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Research Article

The Relationship Between Disease Severity and Serum Kallikrein Level in Individuals Diagnosed with Obstructive Sleep Apnea Syndrome

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Keywords

- OSAS
- OSAS severity
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Abstract

Introduction and aim: Kallikrein is one of the molecules thought to be effective in the pathophysiology of Obstructive Sleep Apnea Syndrome (OSAS). In this study; "The relationship between kallikrein and OSAS severity groups" was investigated by making a more specific analysis, and the possibility of kallikrein levels to predict the severity of the disease was tried to be evaluated.

Materials and Methods: For the study, 250 patients who were admitted to chest diseases and/or cardiology outpatient clinics were evaluated. Out of these patients, 76 newly diagnosed serum kallikrein levels of the patients were examined by dividing them into groups according to the severity of OSAS.

Results: Of the patients included in the study, 20% (n = 18) were female and 75% (n = 58) were male. Among the mild, moderate, and severe OSAS groups, a significant difference was found in regard to mean monocyte count (p = 0.008). A significant positive weak-moderate correlation between kallikrein levels was detected by using Mean Platalet Volume (MPV), Mean Volume Count (MCV) and Mean Count Hemoglobin (MCH). A significant negative weak-moderate correlation was found between High-Density Lipoproptein (HDL), triglyceride, and kallikrein. Hemoglobin (HGB) value increases 1.5 fold for each unit of kallikrein while Red Blood Count (RBC) value decreases 5.1 fold.

Discussion and conclusion: it can be observed in our study results that, in OSAS, there are still many complex and unanswered questions between specific blood parameters and comorbidities. Although our study results do not clearly reveal the relationship between OSAS disease severity and kallikrein, we think that they contribute to the literature in terms of advanced study plans. The relationship between monocyte count and kallikrein can be predicted using routine evaluation in patients. This is important in terms of determining the cardiovascular and renal risk of a patient in that group. Again, routine MPV, MCV, and MCH parameter evaluations may also provide insight into kallikrein and therefore to the cardiovascular and renal risks of the patients.

INTRODUCTION AND AIM

Obstructive sleep apnea syndrome (OSAS) is one of the diseases with a high prevalence, accompanied by different comorbidities, and is characterized by intermittent episodes of hypoxia and interruption of sleep with apnea attacks. Comorbidities are various diseases such as metabolic syndrome, obesity, Type 2 Diabetes Mellitus (DM). These comorbidities also affect the severity of the disease [1-3].

Polysomnography (PSG) is used to diagnose the disease and to determine the severity. During the PSG, by measuring the decrease in breathing (H = hypopnea) and complete cessation of breathing (A = apnea), the number of Apnea (A) -Hipopnea (H) per hour (I = index) is the determinant. The disease is grouped according to AHI rates (AHI:5-15/hour: Mild OSAS; 16-30/hour: Moderate OSAS; >30/hour: Severe OSAS). The follow-up and treatment of these groups differ [4-6].

Obstructive sleep apnea syndrome (OSAS) is a common public health issue that can have adverse effects on the metabolic and cardiovascular system. Although much has been learned about the pathophysiology and consequences of OSAS in recent years, the molecular mechanisms have not been yet fully determined. Advanced high-throughput proteomics-based technologies have become a fundamental approach to identify new disease mediators as potential diagnostic and therapeutic targets for many diseases, including OSAS [7].

Kallikrein is one of these molecules thought to be effective in the pathophysiology of OSAS. Two main kallikreins are known. These are plasma kallikrein (KLKB1) with only one trypsin sequence and tissue (glandular) kallikrein (KLK). KLKB1 binds to high molecular weight kininogen (KNG) and secretes bradykinin accordingly (BK). KLKB1 also plays a role in digesting plasminogen to plasmin and in surface-dependent activation of blood coagulation, fibrinolysis, and inflammation. Kallikrein converts

prorenin into renin, activating the renin-angiotensin system (RAS). Kinins help protect against cardiac ischemia and play an important role in preconditioning, as well as the cardiovascular and renal protective effects of angiotensin-converting enzyme (ACE) and angiotensin type 1 receptor blockers (ARB). However, the role of kinins in the pathogenesis of hypertension remains controversial [3]. Therefore, kinins play an important role in the regulation of cardiovascular and kidney function, as well as many of the beneficial effects of ACE inhibitors and ARBs on target organ damage in hypertension [3].

In our study, patients diagnosed with OSAS, depending on the severity of the disease, were compared by measuring their serum kallikrein levels. It was seen that studies on "The relationship between Kallikrein and OSAS severity groups" were rare and undetailed. Also, the relationship between kallikrein levels and comorbidity was evaluated in these patient groups.

Materials and Methods

Study population

In the study; Between April, May and June 2020, 232 patients aged 18-80 years who applied to the chest diseases and/or cardiology outpatient clinic with complaints of respiratory arrest, snoring, sleep interruption, difficulty in breathing and chest pain during sleep were evaluated. 43 patients with a history of central sleep apnea, a history of neurological diagnosis such as a history of cerebrovascular accident, a history of recent head trauma or a history of drug use that may cause central sleep apnea, and 32 patients with additional comorbidities other than DM were excluded from the study.

Ultimately, the study was conducted with 76 of these patients who met the inclusion criteria. Out of the OSAS diagnosed patients included in the study, 20% (n=18) were female and 75% (n=58) were male. In the mild, moderate, and severe OSAS groups, the mean age of the patients was 53.7 ± 9.9, 54.5 ± 10.9, and 53.6 ± 10.4, respectively and there was no difference between the groups in terms of mean age.

Serum kallikrein measurement: Polysomniography (PSG) reports were used to determine the disease severity group. Hemogram parameters of the empty stomach, venous blood samples in K2EDTA tubes, taken in the morning from patients and have been studied with an automatic device (Sysmex XN 1000, Japan) within two hours, the biochemistry parameters from the serum obtained by centrifugation of the tubes without anticoagulant have been studied on an autoanalyzer (Cobas 8000, Roche Diagnostics, Germany). For the measurement of kallikrein, serum samples stored at -80°C were studied by a single biochemist using the commercial kit (Elabscience, China) and the ELISA method as recommended by the manufacturer. The cost of the commercial kit has been borne by the researchers. The PSG reports of the patients were also recorded by a single physician and were classified as mild-moderate-severe OSAS according to the Apnea-Hypopnea Index (AHI) criteria. Serum kallikrein levels were examined in groups according to the severity of OSAS.

Polysomnography (PSG)

During an overnight examination, four-channel electroencephalogram (EEG) and two-channel electro-oculography (EOG), submental electromyography (EMG), pulse oximetry, thoracic and abdominal movements, electrocardiogram (ECG), tracheal sound and oronasal airflow were recorded by using a Philips Respironics Polysomnography device (1001 Murry Ridge Lane Murrysville, PA 15668 USA Respironics Deutschland Gewerbestrasse 17 82211 Herrsching, Germany). Interruption of airflow for more than 10 seconds was defined as apnea, 4% decrease in oxygen saturation and > 30% decrease in airflow for more than 10 seconds was defined as hypopnea. OSAS severity was calculated according to AHI. All patients were grouped according to their AHI scores as mild (AHI: 5-15/hour), moderate (AHI: 15-30/hour) and severe (AHI> 30/hour) OSAS.

Statistic analyses

Numerical variables are shown with mean standard deviation, median, minimum and maximum values, while categorical variables are shown with frequency and percentage. The Shapiro-Wilk test was used to determine whether the normality assumption was achieved. Kruskal-Wallis, Mann-Whitney U and Chi-Square tests were used for group comparisons. Spearman Correlation Coefficient was provided to determine the relationship between Kallikrein variable and biochemical parameters. Multiple linear regression model was established to determine the variables affecting the Kallikrein variable, variables significant in group comparisons were included in the model, and the Backward method was used as the variable selection method in the model setup. All analyses were made with SPSS v.21, and $p<0.05$ was considered statistically significant in all analyses.

RESULTS

76 patients newly diagnosed with OSAS were included in the study. Out of the OSAS diagnosed patients included in the study, 20% (n=18) were female and 75% (n=58) were male.

In disease severity groups, which are mild, moderate, severe OSAS, there was no difference in terms of gender, mean age, and presence of Diabetes Mellitus (DM). Since DM is a very common comorbidity, the difference between groups was evaluated. Among the mild, moderate and severe OSAS groups, a significant difference was detected in the mean monocyte count ($p = 0.008$). There was no significant difference in terms of the other variables which are the following; kallikrein, HbA1c, glucose, haemoglobin (HGB), red blood cell count (RBC), white blood cell count (WBC), lymphocyte, neutrophil, platelet, eosinophil, basophil, mean volume count (MVC), mean count haemoglobin (MCH), mean count haemoglobin (MCHC), red blood cell distribution volume (RDW), mean platelet volume (MPV), C-reactive protein (CRP), creatinine, total, low-density lipoprotein (LDL), high-density lipopretin (HDL) cholesterol and triglycerides ($p> 0.05$ for each parameter). (Table 1, 2)

A significant positive weak-moderate relationship was found between Kallikrein, MPV, MCV and MCH. A significant negative weak-moderate correlation was found between High Density Lipoproptein (HDL), triglyceride and Kallikrein. (Table 3). The HGB value increases 1.5 fold for each unit of kallikrein, while the RBC value decreases 5.1 fold (Table 4).

In the subgroup analysis within the groups: There was a

Table 1. Basal demographic characteristics-1 (Distribution of the groups in regard to sex and DM).				
	AHI-1	AHI-2	AHI-3	p
Male	17 (22%)	16 (21%)	25 (32%)	0,503
Female	7 (9%)	6 (8%)	5 (6,5%)	
DM	3 (4%)	8 (10%)	12 (15%)	0,08
Non-DM	21 (27,6%)	14 (18,4 %)	18 (23%)	
.DM: Diabetes mellutus.				

Table 2. Basal demographic and laboratory characteristics-2 (General characteristics of the groups with laboratory and PSG results).

Features and results	OSAS groups (N=76)				Multiple comparisons β, α		
	AHI:5-15 Mild OSAS N= 24	AHI:16-30 Moderate OSAS N= 22	AHI>30 Severe OSAS N= 30	p μ, Ω	Group 1vs.2	Group 1 vs.3	Group 2 vs.3
Age	53,7 ± 9,9	54,5 ± 10,9	53,6 ± 10,4	0,948 μ			
BMI	33,6 ± 6,6	34,5 ± 6,7	32,8 ± 4,7	0,632 μ			
Kallikrein	4,1005 (1,1785-11,976)	8,182 (4,034-13,9)	6,296 (2,258-13,7)	0,184 Ω			
A/H RATIO-INDEX	8,1 (5,6-10,75)	21,15 (19,1-26,8)	55,7 (39,4-69)	<0,0001 Ω	<0,0001	<0,0001	<0,0001
HbA1c	5,91 (5,7-6,27)	6,24 (5,82-7,28)	6,2 (5,92-6,66)	0,081 Ω			
Glucose	98,5 (87-108,5)	109 (91-153)	101 (87-117)	0,100 Ω			
Hgb	14,6 ± 1,5	13,9 ± 2,1	15,4 ± 1,7	0,011 μ	Ns.	Ns.	0,009
RBC	5 ± 0,5	4,8 ± 0,5	5,3 ± 0,7	0,012 μ	Ns.	Ns	0,011
WBC	9,1 ± 2,8	7,7 ± 1,7	8,8 ± 1,9	0,057 μ			
Lymphocytes	2,4 ± 1	2,5 ± 0,5	2,8 ± 0,9	0,218 μ			
Neutrophils	5,6 ± 2,7	4,4 ± 1,4	5 ± 1,9	0,130 μ			
Platelets	280,4 ± 65	288,6 ± 87,7	264,9 ± 55,5	0,463 μ			
Monocytes	0,7 ± 0,2	0,6 ± 0,2	0,7 ± 0,2	0,016 μ	0,025	Ns.	Ns.
Eosinophils	0,195 (0,105-0,345)	0,2 (0,15-0,32)	0,155 (0,11-0,265)	0,542 Ω			
Basophils	0,04 (0,03-0,065)	0,04 (0,03-0,07)	0,05 (0,03-0,06)	0,719 Ω			
MCV	87,15 (84,9-89,6)	86,45 (83,2-91,7)	87,1 (84,8-90,3)	0,970 Ω			
MCH	29,1 (28,25-29,75)	28,8 (27,7-30,2)	29,4 (28,1-30,4)	0,658 Ω			
MCHC	33,25 (32,25-34,15)	32,9 (31,9-33,5)	33,6 (32,8-34,1)	0,887 μ			
RDW	13,15 (12,75-14,05)	13,45 (12,7-14,7)	13,2 (12,7-14)	0,760 Ω			
MPV	10,2 (9,6-10,85)	10,2 (9,6-10,9)	9,9 (9,2-10,5)	0,303 μ			
CRP	0,49 (0,13-0,85)	0,3 (0,1-0,68)	0,37 (0,15-0,79)	0,760 Ω			
Cre	0,9 ± 0,3	0,9 ± 0,2	0,9 ± 0,2	0,944 μ			
TCHOL	200,5 ± 45,4	173,3 ± 50,4	195,3 ± 39,3	0,102 μ			
LDL	120,8 ± 42	98,5 ± 43,7	120,5 ± 36,1	0,113 μ			
HDL	42 ± 9,4	44,1 ± 18,8	40,4 ± 9,2	0,599 μ			
Trg	207,5 (144-272)	155 (111-208)	194 (124-215)	0,298 Ω			
Duration of sleep	251,1 ± 72,1	322,2 ± 65,1	336 ± 67	<0,0001 μ	0,002	<0,0001	Ns.
Sleep activity	61,9 ± 18,7	109,7 ± 155,6	80,1 ± 12,6	0,163 μ			
Apnea count	4 (1-10,5)	14,5 (8-25)	62 (26-190)	<0,0001 Ω	0,012	<0,0001	<0,0001
Hypopnea count	18 (6,5-40,5)	102,5 (85-133)	180,5 (146-252)	<0,0001 Ω	<0,0001	<0,0001	<0,0001
Apnea + Hypopnea count	34 ± 21,3	120,9 ± 30,4	320,1 ± 142,4	<0,0001 μ	<0,0001	<0,0001	<0,0001
Central apnea count	1 (0-4)	3 (1-9)	10 (3-25)	<0,0001 Ω	Ns.	<0,0001	0,004
Obstructive apnea count	1,5 (0-5)	8,5 (4-12)	28 (12-84)	<0,0001 Ω	0,004	<0,0001	<0,0001
Mixed (central + obst.) apnea count	0,5 (0-2,5)	2 (0-5)	8,5 (2-30)	<0,0001 Ω	Ns.	<0,0001	0,002
Non-REM/ratio	97,9 (86,4-100)	89,15 (86,1-100)	96,65 (93,9-100)	0,159 Ω			

Stage1 rate	13,95 (7,8-28,45)	12,25 (6-15,2)	8,45 (5,1-19,7)	0,103 Ω			
Stage 2 rate	53,4 ± 14,2	54,6 ± 14,5	56,9 ± 13,6	0,648 μ			
Stage 3 rate	17,8 (7,35-31,25)	18,4 (12,8-32,3)	26,65 (10,1-42,5)	0,475 Ω			
REM rate	2,05 (0-13,55)	10,85 (0-13,9)	3,3 (0-6)	0,155 Ω			
Non-REM AHI	7,2 ± 4	21,3 ± 4,4	74,4 ± 115,8	0,003 μ	Ns.	Ns.	Ns
REM AHI	0 (0-2,5)	20,6 (0-33,3)	31,55 (0-62,4)	0,001 Ω	0,002	0,001	Ns.
Apnea index	1,15 (0,4-2,35)	2,9 (1,7-4,6)	12,95 (4,7-31,8)	<0,0001 Ω	0,029	<0,0001	<0,0001
Hypopnea index	5,7 ± 4,3	19,3 ± 4,5	36,7 ± 15	<0,0001 μ	<0,0001	<0,0001	<0,0001
Left side AHI	1,55 (0,75-9,1)	12,9 (9,5-18,2)	58,95 (34,9-73,7)	<0,0001 Ω	0,008	<0,0001	<0,0001
Supine AHI	10,2 (5,75-19,2)	34,9 (23,8-57,2)	68,75 (56,2-76,2)	<0,0001 μ	0,003	<0,0001	<0,0001
Right side AHI	0 (0-7,6)	15,85 (10-23)	41,85 (24,1-77,5)	<0,0001 Ω	<0,0001	<0,0001	<0,0001
Left side sleep	86,3 ± 60,4	107,6 ± 72	88,2 ± 63,7	0,483 μ			
Left side deep sleep	5,5 (1-28,25)	15,5 (0-40)	15 (4,2-37)	0,560 Ω			
Supine sleep	106,1 (22,55-166,85)	81,95 (33-147,4)	97,65 (58,3-202)	0,401 Ω			
Supine deep sleep	8,15 (0,75-33,75)	6,75 (0,6-24,9)	17,5 (3,6-32,8)	0,381 Ω			

μ: ANOVA, Ω: Kruskal-Wallis Test, β: Tamhane Multiple comparisons, α: Mann-Whitney U test. Ns.: Non-significant

Table 3. Correlations of biochemical parameters with the Kallikrein variable.

Variable	r	p
HbA1c	0,042	0,721
Glucose	0,03	0,799
Hgb	0,008	0,948
Rbc	-0,11	0,346
Wbc	-0,057	0,628
Lymphocytes	-0,034	0,775
Neutrophils	0,043	0,712
Platelets	-0,031	0,79
Monocytes	-0,074	0,527
Eosinophils	-0,022	0,851
Basophils	-0,065	0,582
MCV	0,231	0,046
MCH	0,281	0,015
MCHC	0,113	0,332
RDW	-0,193	0,097
MPV	0,261	0,024
CRP	-0,076	0,526
Cre	0,219	0,059
TCHOL	-0,009	0,937
LDL	0,002	0,987
HDL	-0,292	0,012
Trg	0,299	0,012

Hgb: Hemoglobulin, Rbc: Red blood cell, Wbc: White blood cell, MVC: Mean corpuscular volume, MCH: Mean corpuscular Hemoglobin, MCHC: Mean corpuscular Hemoglobin concentration, RDW: Red cell distribution width, MPV: Mean platelets volume Cre: Creatinine: T Chol: Total Cholesterol LDL: LDL cholesterol HDL: HDL cholesterol Trg:Triglycerides

Table 4. Results of multiple linear regression analysis.

Variables	β	Standard Error (β)	p value	95% Confidence Interval for β	
				Lower Limit	Upper limit
Fixed	11,288	6,033	0,065	-0,739	23,315
HGB	1,581	0,659	0,019	0,266	2,895
RBC	-5,197	2,034	0,013	-9,251	-1,142

The RBC value decreases 5.1 fold. HGB: Hemoglobin, RBC: red blood cell.

significant difference between mild, moderate and severe OSAS groups in terms of supine, right side, left side AHI, hypopnea index, apnea count, hypopnea count, the total number of apnea and hypopnea, obstructive apnea count, A/H ratio. There were differences between some groups in terms of HGB, RBC, monocyte count, sleep duration, central apnea, mixed type apnea count, Non-REM AHI, REM AHI.

DISCUSSION AND CONCLUSION

Kallikrein is one of the molecules thought to be effective in the pathophysiology of Obstructive Sleep Apnea Syndrome (OSAS). In this study, the relationship between OSAS disease severity and kallikrein was evaluated.

The application of chromatography and/or MS methods to detect biomarkers has helped to understand the mechanisms of OSAS. Further proteomic and metabolomic studies are warranted to develop potential diagnostic and clinical monitoring methods for OSAS (2). For this purpose, in our study, the measurement of kallikrein was carried out with the kit using the ELISA method.

Kinins are oligopeptides containing the amino acid sequence of bradykinin. They are produced from precursors known as kininogens by enzymes such as tissue (glandular) and plasma kallikrein. Some of the effects of kinins are mediated by autocoids such as eicosanoids, nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF) and/or tissue plasminogen activator († PA). Kinins appear to play a role in the pathogenesis of arthritis and inflammatory diseases of the skin; They act on innate immunity as inflammatory mediators by promoting the maturation of dendritic cells, which in turn activates the body's adaptive immune system and thus stimulates mechanisms that promote inflammation. On the other hand, kinins acting through NO contribute to the vascular protective effect of ACE inhibitors during neointima formation. In myocardial infarction produced by ischemia/reperfusion, kinins help reduce infarction size following preconditioning or treatment with ACE inhibitors. In heart failure secondary to infarction, the therapeutic effects of ACE inhibitors are mediated in part by kinins. NO release, drugs that activate the angiotensin type 2 receptor partially act through kinins and NO [3].

A number of proteins involved in coagulation, inflammation, and lipid metabolism can actually interact in the context of OSAS to affect lipid and vascular pathways, in a study suggesting that OSAS can facilitate the onset and progression of atherogenesis. Jurado Gámez et al. concluded that protein expression is associated with disease severity, but it also provides relevant mechanical information [8]. A significant negative weak-moderate correlation was found between HDL, triglyceride and kallikrein. This result shows that as the severity of the disease increases, lipid profile deteriorates and kallikrein decreases. The deterioration in the lipid profile can be interpreted as the decrease in kallikrein as the disease severity increases. The fact that we did not evaluate the protein profile in our study can be considered as one of the limitations of the study. The relationship between kallikrein, protein and lipid profiles in OSAS severity groups can be considered as a separate study topic.

Another study demonstrated a relationship between glucose metabolism parameters and triglycerides, which underlie the complexity of the process leading to cardiovascular/metabolic complications, and OSAS severity. In addition, homocysteine, glycemic and lipidic profiles changed significantly after 6 months of PAP treatment in OSAS, supporting its cardiovascular and metabolic protective effect [9]. Our study results support these study results. In our study, there was no difference in terms of kallikrein in OSAS severity groups that did not differ in terms of DM. In our study where comorbidities other than DM were excluded, the relationship between coagulation values, cardiac markers and d-dimer kallikrein was not evaluated. However, the platelet (PLT) and kallikrein relationship may give an idea about this issue. No significant results were obtained between platelet and kallikrein between the groups. The same is true for renal risk assessment, and in our study population without chronic renal disease, no significant relationship was found between creatinine and kallikrein between the OSAS groups.

In our study, the pediatric group was excluded. But in a study in children, after semi-rapid maxillary expansion (SRME), a significant decrease in kallikrein level was observed [10]. The relationship between disease severity and kallikrein in the pediatric patient population can also be considered as a study topic. Because in this group, the lipid and protein profile is completely different.

In our study, no significant relationship was found between OSAS groups and kallikrein value. This could be because of that our study population had no additional comorbidities other than DM and there was no difference between the groups in terms of DM. That is to say, only one comorbidity that did not differ between groups was evaluated in our study. In fact, with this data, it can be concluded that there is a strong relationship between disease severity and glucose and kallikrein. Kinins have a renal and cardiovascular protective effect [3]. A significant result can be obtained between the kallikrein level in OSAS groups with cardiovascular and/or renal chronic disease. The reason for that is the way these chronic diseases affect OSAS.

One of the most important results of our study is; between kallikrein and OSAS groups, there was a significant difference in the mean monocyte count (p=0,008), and another was a significant positive weak-moderate relationship between kallikrein and MPV, MCV and MCH parameters. In patients in whom kallikrein cannot be evaluated, the relationship between monocyte count and kallikrein can be predicted with routine evaluation. This is important in determining the cardiovascular and renal risk of a patient in that group. It is also important that routine MPV, MCV and MCH parameter evaluations give clues about the cardiovascular and renal risks of the patients.

As a result, it can be observed in our study results that, in OSAS, there are still many complex and unanswered questions between specific blood parameters and comorbidities. Although our study results do not clearly reveal the relationship between OSAS disease severity and kallikrein, we think that they contribute to the literature in terms of advanced study plans. On this subject, in double, triple or more comorbidity groups, in which glucose and lipid profiles are also evaluated, the kallikrein level relationship can be evaluated. Therefore, in daily practice, a more objective idea can be formulated about the relationship between the number of comorbidities and kallikrein level of patients in the

same OSAS group, and especially the progression of renal and/or cardiovascular disease. This is just a hypothesis we made with our study results. For the evaluation of the hypothesis, well-classified patient groups, in terms of comorbidities, with a large patient population are needed.

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