Neuroendocrinology Letters Volume 40 No. 2 2019
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Biomarkers - a possibility for monitoring of obstructive sleep apnea syndrome

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Submitted: 2019-03-30 Accepted: 2019-08-10 Published online: 2019-09-02

Key words: **Obstructive sleep apnea syndrome; monitoring; biomarker; blood level; pentraxin-3s**

Neuroendocrinol Lett 2019; **40**(2):85–92 **PMID:** 31785215 NEL400219A07

Abstract

OBJECTIVES: Sleep apnea syndrome affects approximately 4% of adult males and 2% of adult females. It is associated with significant cardio-, cerebrovascular, metabolic and hormonal comorbidities and ranks among the more expensive medical specialties due to the requirement of high-quality technical diagnostic and therapeutic equipment as well as well-educated and experienced personnel. The aim of this study is to detect the relationship between C-reactive protein (CRP), pentraxin-3 (PTX-3), interleukin 6 (IL6), high-sensitivity troponin I (hsTnI), brain natriuretic protein (BNP) and galectin-3 serum levels and obstructive sleep apnea syndrome.

DESIGN: Prospective cohort study.

MATERIAL AND METHODS: A group of 146 patients with middle to severe obstructive sleep apnea syndrome (OSAS) were monitored, and the results were compared with the results from a control group of healthy individuals.

RESULTS: We assessed serum levels of the following biomarkers: CRP, PTX-3, IL6, hsTnI, BNP, and galectin-3. PTX-3 serum levels were statistically significantly higher ($p<0.0001$) in patients with OSAS, compared to controls. Statistical results related to the other biomarkers did not suggest any clinical value. ROC analysis showed that PTX-3 might be able to distinguish patients with OSAS from healthy individuals (AUC=7438).

CONCLUSION: The elevation of PTX-3 serum levels is significantly associated with middle to severe obstructive sleep apnea syndrome. The PTX-3 biomarker appears to be a promising alternative method for sleep apnea syndrome investigations.

Abbreviations:

AUC	- area under the curve
BNP	- brain natriuretic peptide
CRP	- C-reactive protein
hsTnI	- high-sensitive troponin I
IL-6	- interleukin-6
OSAS	- obstructive sleep apnea syndrome
PAP	- positive airway pressure
PG	- polygraphy
PSG	- polysomnography
PTX-3	- pentraxin-3
ROC	- receiver operating characteristic
SAS	- sleep apnea syndrome

INTRODUCTION

Sleep apnea syndrome (SAS) is defined as repeated pauses in breathing during sleep, also referred to as apnea, with each pause lasting more than ten seconds. According to available studies, this disease occurs in approximately 4% of men and 2% of women (Hobzova *et al.* 2016). Depending on the mechanism of origin, there are three forms of sleep apnea: obstructive, central, and mixed. The incidence of obstructive sleep apnea syndrome (OSAS) is 80%, with the central and mixed forms occurring in ap-proximately 10% of cases each (Lojander *et al.* 1996). Sleep architecture disorder and desaturation rank among the basic problems associated with repeated apnea episodes. Obesity is the most common risk factor for OSAS (Braunerova & Hainer, 2010; Ernst *et al.* 2015). The issues related to OSAS are very complex and multi-disciplinary. During the apnea episode, obstruction of the upper airways causes de-saturation of arterial blood, increased negative intrathoracic pressure, and wake-up reactions in connection with activation of the sympathetic nervous system followed by an abnormal reaction of the cardio-vascular, nervous, hormonal and metabolic systems (Monahan & Redline, 2011). Therefore, OSAS is inseparably associated with cardiovascular (e.g., hypertension or arrhythmia), metabolic (diabetes mellitus), or cerebrovascular diseases (e.g., thromboembolic disease) (Kasai, 2012). Studies have shown an association between OSAS and potentiation of atherosclerosis, oxidative stress, endothelial dysfunction, and lipid metabolism (Epstein *et al.* 2009).

Above all, a diagnosis of OSAS is based on cooperation between otorhinolaryngologists (examination of the upper airways) and somnologists/sleep specialists (examination of patients and sleep monitoring). Additionally, pneumology, stomatology, internal medicine, psychology, dietology/nutritionists, as well as bariatric surgery may also be part of the diagnostic and/or treatment process (Aguiar *et al.* 2014). The result of night monitoring is the basis for further management. Treatment for OSAS is always complex, and therapy of all types have common basic goals. There are some common steps for all stages, such as weight reduction, regimen precautions, as well as pursuing a healthy lifestyle. Patients with mild types of OSAS usually undergo surgery. Those ones who suffer from medium to severe OSAS are mainly treated using conservative methods such as positive airway pressure (PAP) into the upper airways (Epstein *et al.* 2009).

Polysomnography (PSG) is still the gold standard diagnostic test for sleep monitoring, although simpler investigation monitoring versions of home polygraphy (PG) and screening are also used in clinical praxis. All of the methods have advantages as well as disadvantages. Polysomnography is definitely the most complex investigation and provides information on all important markers of SAS including a hypnogram. On the other hand, this investigation must be performed during hospitalization, which is connected with a considerable burden related to staff and equipment (well-educated personnel, expensive monitoring devices, and high-quality computers) as well as patient hospitalization-associated stress. Polygraphy provides substantially less information, but it is performed on patients who are not hospitalized, i.e., in their home environment. Basic screening only provides information on whether the patients suffer from apnea. If there is suspicion of SAS, the result is just an indicator for a required "higher-level" investigation. PG facilitates a complete diagnosis of SAS in patients with "non-complicated" disease. If there is any doubt about the diagnosis, PSG (the highest level investigation) is indicated.

Despite current broad-range diagnostic and treatment methods and considerably better expert awareness, compared to previous years, SAS is still an underdiagnosed disease, and some people are unaware of their problems (Young, 1993; Redline *et al.* 1994). This is partially caused by unhealthy, fast-paced lifestyles but is also related to the time-consuming diagnostic process. A solution to this problem could take the form of a validated marker that simply divides patients into two groups – those with SAS and those without SAS.

The intensively developing field of medical biomarkers may provide the solution. At present, biomarkers play an irreplaceable role in some indications (Kretchmer & Tilki, 2017). Nevertheless, this high-potential field has not yet been fully explored as it relates to sleep medicine.

In our case, we define a biomarker as an objectively quantifiable factor of a biological process that is able to distinguish physiological conditions from pathological status on the basis of biomarker serum-levels. For the purpose of this study, we selected six serum biomarkers: C-reactive protein (CRP), pentraxin-3 (PTX-3), interleukin-6 (IL-6), troponin I (hsTnI), brain natriuretic protein (BNP), and galectin-3.

CRP is a well-known biomarker that has been used in a variety of indications for many years. It is one of the most significant "acute-phase" mediators. It is produced by the liver and, to a lesser extent, by the kidneys and vascular walls (Ridker et l. 1998). CRP, which is a short pentraxin, shares some structural properties with PTX-3. Unlike CRP, PTX-3 is not produced by the

Tab. 1. Age characteristics of the compared groups

	Number	Age (years)			
		Average	Minimum	Maximum	P-value
Patients with OSAS	146	58.7	26.0	87.0	0.443
Control group	100	56.7	37.0	82.0	

liver but directly by damaged tissue. PTX-3, which is also a basic component of congenital immunity (Lu *et al.* 2018), has only recently come into use in immunodiagnostics. IL-6 is a well-known cytokine produced by macrophag-es; it influences the metabolism of muscle, adipose, and bone tissues and stimulates "acute-phase" protein synthesis. Troponins are part of the tropomyosin-complex of monocytes in striated muscles. High-sensitivity troponin I, released from the myocardium, is considered to be one of the most sensitive biomarkers for indicating damage to the myocardium (Maeder *et al.* 2015). Brain natriuretic peptide (BNP) is a polypeptide secreted by cardiomyocytes in the heart ventricles, particularly, in patients with acute or chronic heart failure (Kohno & Kataoka, 2017). Galectin-3 is a member of the lectin family. It is produced by activated macrophages and is involved in cell adhesion, proliferation, angiogenesis, and apoptosis.(Pusuroglu *et al.* 2017)

The optimal serum marker for OSAS would be able to detect the presence of OSAS and its stage as well as being able to evaluate the patient's response to suitable therapy on the basis of its plasma level, assuming that the test is sufficiently sensitive and specific. If the marker is easily assessed (i.e., collecting a blood sample followed by a laboratory evaluation), the test might eliminate technical, staff, and time requirements of the current diagnostic, management, and care of OSAS patients.

MATERIAL AND METHODS

Methods

From 2015 to 2017, an observational, analytical, cohort study dealing with patients with diagnosed middle and severe obstructive sleep apnea syndrome was performed. The classification criteria included: OSAS indi-

Tab. 2. Biomarker levels in the OSAS group vs. the control group

Biomarker	Status	Mean	Median (Min – Max)	Lower Quartile	Upper Quartile	Wilcoxon test *p*-Value
CRP (mg/l)	**OSAS**	**6.99**	**3.53** (0.19 – 6.27)	**1.38**	**7.66**	**<0.0001**
	Controls	**2.82**	**1.19** (0.13 – 44.1)	**0.56**	**2.98**	
PTX-3 (pg/ml)	**OSAS**	**5629**	**5216** (588 - 12776)	**3708**	**7050**	**<0.0001**
	Controls	**3524**	**2872** (708 - 12673)	**1727**	**4813**	
IL-6 (pg/ml)	**OSAS**	**3.67**	**2.01** (0.11 – 63.1)	**1.23**	**3.57**	**0.0007**
	Controls	**2.03**	**1.32** (0.18 – 18.4)	**0.88**	**18.4**	
hsTnI (ng/l)	**OSAS**	**5.56**	**3.50** (0.70 - 51.1)	**2.20**	**6.30**	**<0.0001**
	Controls	**3.26**	**2.25** (0.40 - 37.3)	**1.40**	**3.35**	
BNP (pg/ml)	**OSAS**	**29.0**	**10.0** (6.9 - 705)	**10.0**	**23.1**	**0.7235**
	Controls	**18.5**	**10.8** (10.0 - 138)	**10.7**	**14.7**	
Galectin-3 (ng/ml)	**OSAS**	**14.8**	**13.8** (6.90 – 39.2)	**11.6**	**39.2**	**0.0442**
	Controls	**13.2**	**12.9** (5.6 - 27.1)	**10.7**	**14.7**	

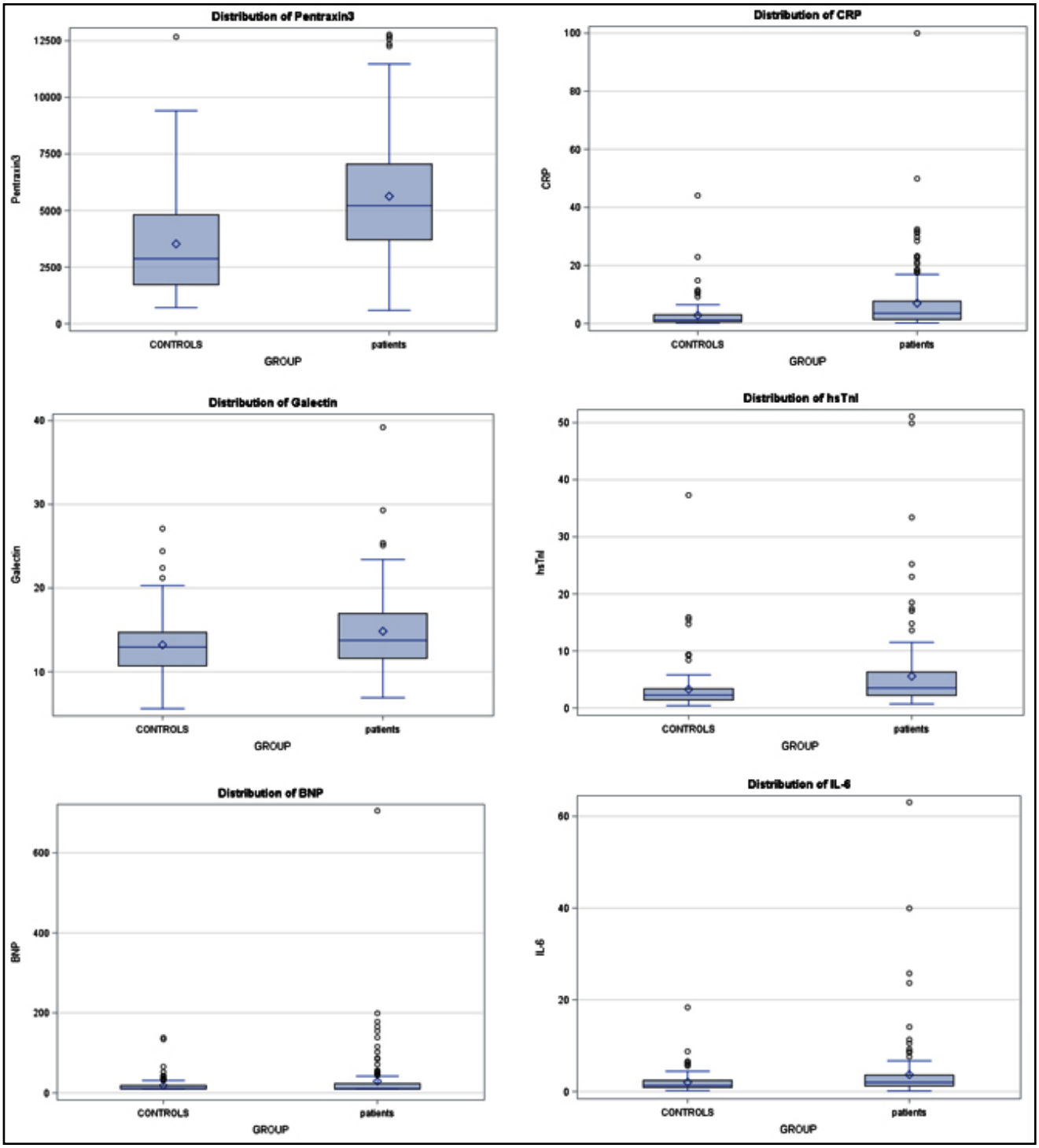

Fig. 1. Comparison of serum levels of biomarkers monitored in OSAS patients vs. healthy controls

cated for treatment with PAP (apnea-hypopnea index, AHI ≥ 15), OSAS without any previous conservative therapy, OSAS without any previous surgical therapy related to the upper airways (except endoscopic adenotomy in childhood), and complete results from sleep monitoring. The AHI marker was defined as the average number of apnea and hypopnea events per hour of sleep. The exclusion criteria included incomplete data from sleep monitoring, chronic bronchopulmonary disease (CHOPN), previous OSAS treatment, previous upper airways surgery, and the potential for poor patient cooperation. The study was made with the approval of the Ethics Committee, University Hospital and Faculty of Medicine, Charles University, Pilsen.

Group of patients

The criteria were met by 146 patients. We assessed the monitored group of patients with OSAS as well as

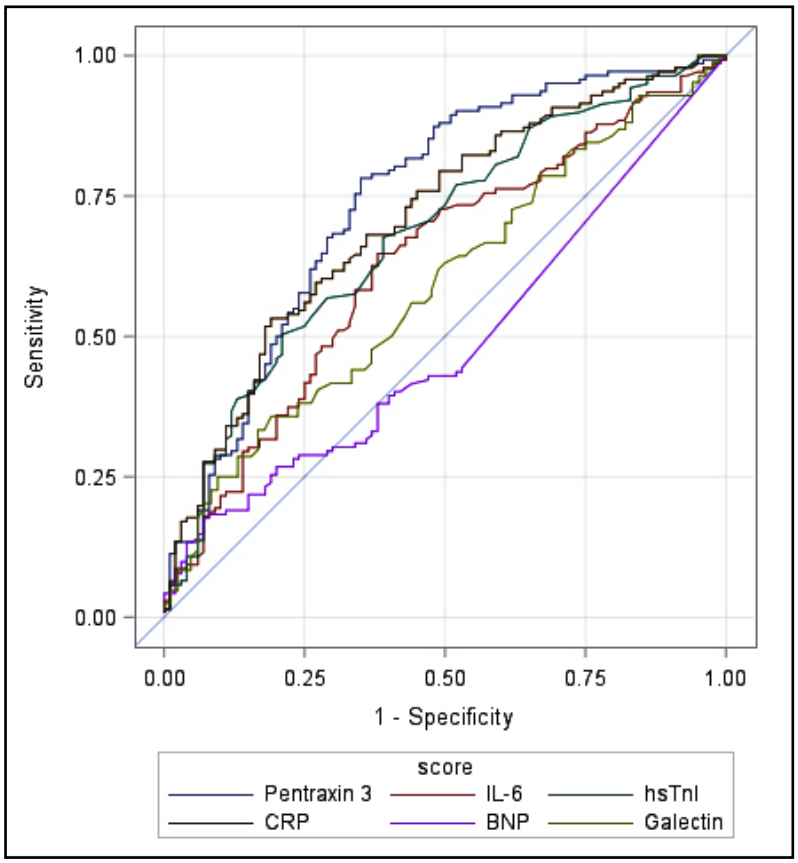

Fig. 2. ROC analysis of the OSAS group vs. the control group

results from a control group containing 100 healthy people participating in regular preventive check-ups at the University Hospital. The comparison between both groups is presented in Table 1 and Figure 1. There was no statistically significant age difference between groups (p=0.1443).

Serum samples

Peripheral blood was drawn by using VACUETTE® Z Serum Sep tubes (Greiner Bio-One, Kremsmünster, Austria) and allowed to clot. Serum was separated within 3 hours of collection by centrifugation at 1700 ×g for 10 min, and all samples were immediately aliquoted and frozen at −80 °C. Samples were stored with 24 h temperature monitoring. Serum samples were thawed only once, just prior to the analysis. Serum levels of CRP, PTX-3, IL-6, hsTnI, BNP, and galectin-3 were measured for each sample.

Sample analysis

Serum levels of CRP were measured by using a chemiluminescent assay using a Maglumi Instrument (Snibe Co., Shenzhen, China), pentraxin-3 was measured using a Simple Plex assay using the Ella System (ProteinSimple, San Jose, CA, USA), IL-6 and hsTnI were measured using chemiluminescent ACCESS assays using a UniCel DxI 800 Instrument (Beckman Coulter, Brea, CA, USA), galectin-3 and BNP were measured using chemiluminescent assays using the Architect 1000i System (Abbott, Libertyville, IL, USA).

Tab. 3. AUC values

Parameter	AUC	95% Confidence Limit	
PTX-3	0.7438	0.6791	0.8085
CRP	0.7099	0.6441	0.7757
hsTnI	0.6822	0.6140	0.7504
IL-6	0.6310	0.5595	0.7025
Galectin-3	0.5906	0.5045	0.6767
BNP	0.4876	0.4195	0.5556

RESULTS

PTX-3 serum levels were statistically much higher ($p < 0.0001$) in OSAS patients compared to controls. CRP and hsTnI serum levels were also statistically much higher ($p < 0.0001$). We detected statistically significant increases in IL-6 levels ($p < 0.0007$), but without any clinical usability. Serum levels for galectin-3 were at the edge of statistical significance and for BNP unaffected. Results are presented in Table Nr.2 and Figure 1.

After performing a ROC analysis, we found a ROC curve showing a relatively high AUC value (0.7438) for PTX-3. However, the ROC analysis of CRP and hsTn1 yielded less promising results related to the AUC (0.7099, 0.6822) and without any suspected clinical usability. The AUC values for IL-6, BNP, and galectin-3 were very low (0.6310, 0.5906, and 0.4876). The AUC values are presented in Table Nr.3. The results of the ROC analyses are shown in Figure 2.

DISCUSSION

Sleep apnea syndrome is not a disease involving a single organ. It is a set of problems requiring a multidisciplinary approach by physicians, hospital staff, and nurses (Costa, 2017). The diagnostic and therapeutic procedures are considered to be professionally, personally, and technically demanding, which is why sleep medicine also ranks among the more financially demanding medical specialties. The socioeconomic burden on society is currently enormous. This will no doubt only increase as sleep medicine investigations and treatment options improve. Currently, we can see huge pressure on preventive healthcare and recognize that many comorbidities are associated with sleep apnea syndrome. Hypertension and other cardiovascular complications, cerebrovascular accidents, metabolic connections as well as the less well-known obstetric complications can all have an OSAS component and collectively have a significant socio-economic impact (Benedetto *et al.* 2017).

The diagnostic role of biomarkers in sleep medicine is not a new idea, with early works by Vgontzas *et al.* (1997) or Ohga *et al.* (1999) research. Hotamisligil *et al.* (1995) and Bruun *et al.* (2000) works dealt with tumor necrosis factor-α, interleukin 8, although neither substance proved to have any clinical utility for OSAS. Factors influencing adhesion abilities of leukocytes related to the endothelium, ICAM-1 (intracellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) were examined in connection with the initiation of atherosclerosis. The works of Ursavas *et al.* (2007) and Ohga *et al.* (1999) also examined their possible association with OSAS. They are considered promising OSAS markers, however, this has not yet been confirmed. Studies dealing with markers of oxidative stress, such as isoprostanes or malondialdehyde, detect an assumed pathophysiological association between OSAS and oxidative stress, but don't appear to have any other diagnostic benefit. Metabolic markers similar to leptin and adiponectin were examined in studies by Tokuda *et al.* (2000) and Zhang *et al.* (2007). Nevertheless, these markers maybe associated with obesity, insulin resistance, and metabolic syndrome to a greater extent than with OSAS.

Given the close connection between OSAS and cardio- and cerebrovascular complications, a group of biomarkers was selected so that the metabolism and serum levels of these biomarkers (besides CRP and IL-6) could also be related to myocardial damage. HsTnI, BNP and galectin-3 belong in this group to poorly studied substances. PTX-3 has so far devoted little space to the available literature. CRP (can be called pentraxin-1) was selected as another pentraxins molecule with a different mechanism action (from PTX-3 mentioned above) and IL-6 as a cofactor of CRP pathway.

A considerable increase in C-reactive protein is detected in patients with bacterial inflammation, while a lesser increase occurs in people with viral inflammation. Relative to OSAS, its low specificity is a serious disadvantage, since it can be elevated in patients with inflammation, myocardial infarction, autoimmune diseases, some malignant diseases, and after surgery. The potential use of C-reactive protein, relative to OSAS, was studied by Sahlman et l. (2010) and Shamsuzzaman *et al.* (2012). Although these authors detected a statistical relationship to OSAS, they found no clear benefits due to the low specificity, as mentioned above. These results correspond to our conclusions ($p < 0.0001$).

PTX-3, a glycoprotein, is a pentraxin that not secreted by the liver like CRP, but instead, is produced directly by damaged tissue cells such as monocytes, macrophages, dendritic cells, endothelial cells, and fibroblasts in response to stimulation, as such, we consider this to be a very promising indicator. PTX-3 plays a key role in inflammation and apoptosis, supports cell proliferation, angiogenesis, and vascular remodeling, and is a fundamental part of congenital immunity (Lu, 2018). Taking into consideration the relatively short history of PTX-3, there are not many studies dealing with this topic. The usefulness of CRP and PTX-3 were previously assessed by Kanbay *et al.* (2015) a Kobukai & Koyama (2014). They focused on the relationship between CRP, PTX-3, endothelial dysfunction and OSAS. Kanbay found a correlation between OSAS severity (AHI marker) and PTX-3 serum levels as well as a statistical clinical correlation with CRP. Kobukai only found a clinical correlation with PTX-3, but no correlation with CRP. Our study (in bigger group of respondents, n=146) is in accordance with Kanbays work, but we suppose a clinical use only for PTX-3 ($p < 0.0001$).

We also studied cytokine IL-6, however, there was no direct relationship to the cardio- or cerebrovascu-

lar system. Cytokine IL-6 participates in the activated "acute phase" of protein synthesis in the liver and in neutrophil and lymphocyte proliferation. Elevated levels of cytokine IL-6 are detected in patients with acute infections or with activated immune systems (chronic infections, operations, or trau-ma). Like Liu *et al.* (2000) research work we found only statistical connection between IL-6 and AHI in our study ($p < 0.0007$) but without the possibility of being used in clinical medicine.

A new generation of high-sensitive kits to determinate troponin I allowed extended indications for detection of myocardial infarction as well as, to a lesser extent, monitoring myocardial cell damage, especially in association with certain chronic diseases. Maeder (2015), who focused on hsTnI and BNP in connection with OSAS, found no significant elevation in serum levels related to either marker, which agrees with our results only for BPN. Our results for hsTnI were different to Maeder results; we found a statistical connection between hsTnI and AHI ($p < 0.0001$) but (in accordance in CRP case) with no potential for clinical use.

Galectin-3 is used for monitoring chronic heart failure on the basis of its attributes and properties. Unlike our results, Pusuroglu *et al.* research work (2017), the only comparable study found, detected a positive correlation between galectin-3serum levels and OSAS. A possible interpretation was offered by Singh & Hanis (2018) in his work dealing with galectin-3 levels in connection with OSAS and gender. In contrast to men, levels of this marker were only elevated in women with OSAS. Serum levels for galectin-3 in our sample were at the edge of statistical significance ($p < 0.0442$).

Results of our study show a clear positive correlation between PTX-3 levels and OSAS. The comparison with results of different studies is relatively difficult because apart from Kanbay *et al.* (2015) and Kobukai & Koyama (2014) works mentioned above, there are few studies dealing with the relationship between PTX-3 and OSAS. Nevertheless, it is necessary to say that the results of our study are very hopeful, both in relation to the two studies mentioned above but also the possibility that plasma levels might also correlate with the severity of OSAS (AHI levels). Our study is a part of an expanding body of research related to sleep medicine. The detected relationship between PTX-3 levels and OSAS might lead to the inclusion of PTX-3 into a larger group of parameters or markers. By integrating them into the diagnostic routine, we may find a technically simple screening, with sufficient specificity and sensitivity, such that it can serve as an alternative to sleep monitoring.

CONCLUSION

PTX-3 serum levels in OSAS patients indicated for PAP-treatment (AHI ≥15) are statistically significantly increased compared to the group of healthy controls. There is a prerequisite for clinical use of PTX-3. A clinical benefit for OSAS was not found for the other biomarkers monitored (i.e., CRP, IL-6, hsTnI, BNP, and galectin-3). The ROC analysis showed that PTX-3 may be able to differentiate patients with OSAS from healthy individuals (AUC=7438). Even if this fact is encouraging, it will have to be verified in a larger number of patients.

STATISTICAL ANALYSIS

Statistical Analysis Software release 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Basic descriptive statistics are presented as the mean, median, minimum and maximum, and lower quartile and upper quartile. The Wilcoxon test was used to compare distributions of biomarker levels in the OSAS group and the control group. P-values less than 0.05 indicated statistical significance. Receiver Operating Characteristic (ROC) curves and the Area Under the Curve (AUC) are presented to aid in the assessment of the usefulness of the selected biomarkers, relative to an OSAS diagnosis.

ACKNOWLEDGMENT

This study was supported by a project of the Ministry of Health of conceptual development of research organization 00669806 – University Hospital in Pilsen.

REFERENCES

1 Aguiar IC, Freitas WR, Santos IR (2014). Obstructive sleep apnea and pulmonary function in patients with severe obesity before and after bariatric surgery: a randomized clinical trial. Multidiscip Respir Med. **9**(1): 143–149.
2 Benedetto M, Garbarino S, Sanna A (2017). Obtructive sleep apnea (OSA): healthcare and social costs. Med Lav. **108**(4): 310–313
3 Braunerova R, Hainer V (2010). Obesity. Diagnostics and treatment. Med Pro Praxi. **7**(1): 19–22.
4 Bruun JM, Pedersen SB, Richelsen B (2000). Regulation of interleukin 8 production and gene expression in human adipose tissue in vitro. J Clin Endocr Metabolism. **3**: 1267–1273.
5 Costa G (2017). The obstructive sleep apnea syndrome (OSAS): implications for work and Occupational Health Med Lav. **108**(4): 251–259.
6 Epstein LJ, Kristo D, Strollo P (2009). Clinical guideline for the evaluation, management and longterm care of obstructive sleep apnea in adults. J Clin Sleep Med. **5**(3): 263–276.
7 Ernst G, Bosio M, Salvado A (2015). Difference between apnea-hypopnea index (AHI) and oxygen desaturation index (ODI): proportional increase associated with degree of obesity. Sleep Breath. **4**: 245–249.
8 Hobzova M, Salzman R, Stejskal D (2016). Serum adiponectin level in obstructive sleep apnea: Relation of adiponectin to obesity and long-term continuous positive airway pressure therapy. Adv Med Sci. **61**(1): 130–134.
9 Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM (1998). Increased adipose issue expression of tumor necrosis factor-α in human obesity and insulin resistance. J Clin Investigation. **5**: 2409–2415.

10 Kanbay A, Kaya E, Tutar N (2015). Correlation between pentraxin-3 and endothelial dysfunc-tion in obstructive sleep apnea syndrome. Am Thorac Med. **10**(3): 199–203.
11 Kasai T (2012). Sleep apnea and heart failure. J Cardiol. **60**(2): 78–85.
12 Kobukai Y, Koyama T (2014). Morning pentraxin 3 levels reflect obstructive sleep apnea–related acute inflammation. J Appl Physiol. **117**(10): 1141–114.
13 Kohno T, Kataoka M (2017). Moderate-to-severe obstructive sleep apnea is associated with subclinical myocardial injury and impaired hemodynamics in pulmonary hypertension patients. Sleep Med. **30**: 121–127.
14 Kretschmer A, Tilki D (2017). Biomarkers in prostate cancer - Current clinical utility and future perspectives. Crit Rev Onc Hematol. **120**: 180–193.
15 Liu H, Liu J, Xiong S, Shen G, Zhang Z (2000). The change of interleukin-6 and tumor necrosis factor in patients with obstructive sleep apnea syndrome. J Med Univ. **20**(3): 200–202.
16 Lojander J, Maasilta P, Partinen M (1996). Nasal-CPAP, surgery, and conservative management for treatment of obstructive sleep apnea syndrome. Chest. **110**: 114–119.
17 Lu J, Mold C, Clos T (2018). Pentraxins and Fc Receptor-Mediated Immune Responses. Front Immunol. **9**: 26–37.
18 Maeder M, Strobel W, Christ M (2015). Comprehensive biomarker profiling in patients with obstructive sleep apnea. Clin Bioch. **48**(4): 340–6.
19 Monahan K, Redline S (2011). Role of obstructive sleep apnea in cardiovascular disease. Curr Opin Cardiol. **26**(6): 541–547.
20 Ohga T, Nagase T, Tomita J (1999). Increased levels of circulating ICAM-1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome. J App Physiology. **11**: 10–14.
21 Pusuroglu H, Rothlein R, Hugdes B (2017). Galectin-3 is associated with coronary plaque burden and obstructive sleep apnea syndrome severity. Kardiol. **75**(4): 351–359.
22 Redline S, Kump K, Tishler P (1994). Gender differences in sleep disordered breathing in a community-based sample. Am J Respir Crit Care Med. **149**: 722–726.
23 Ridker M, Buring J, Shih J (1998). Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation. **98**: 731–733.
24 Sahlman K, Miettinen K, Peuhkurinen H (2010). The activation of the in inflammatory cytokines in overweight patients with mild obstructive sleep apnea: Sleep apnea and inflammation. J S Research. **19**(2): 341–348.
25 Shamsuzzaman M, Winnicki P, Lanfranchi D (2011). Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation. **105**(21): 2462–2464
26 Sinhg M, Hanis C (2018). Sleep apneaq and galectin-3 possible sex-specific relationship. Sleep Breath. **75**: 527–532.
27 Tokuda Y, Sando H, Matsui H (2000). Serum levels of adipocytokines, adiponectin and leptin, in patients with obstructive sleep apnea syndrome. Int Medicine. **47**(21): 1843–1849.
28 Ursavas M, Karadag E, Rodoplu A (2007). Circulating ICAM-1 and VCAM-1 levels in patients with obstructive sleep apnea syndrome. Respiration. **74**(5): 525–532.
29 Vgontzas D, Papanicolaou A, Bixler E (1997). Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocr Metabolism. **82**(5): 1313–1316.
30 Young T (1993). Analytic epidemiology studies of sleep disordered breathing--what explains the gender difference in sleep disordered breathing. Sleep. **16**(8): 121–124.
31 Zhang L, Yin K, Li C (2007). Effect of continuous positive airway pressure treatment on serum adiponectin level and mean arterial pressure in male patients with obstructive sleep apnea syndrome. Chin Med J. **120**(17): 1477–1481.