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Differences Between Overlap Syndrome and Severe Sleep Apnea Syndrome In BIA/ BIVA, Adiponectin Serum Levels and in Pro-Atherogenic Indices

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ABSTRACT

Introduction: The aim of the study was a comparison of body composition, adiponectin serum levels, and pro-atherogenic indices in overlap syndrome and severe sleep apnea syndrome.
Methods: 33 patients with overlap syndrome (severe OSAS and COPD), 80 patients with severe OSAS and 50 persons from control group were examined. All subjects underwent polygraphy and bioelectrical impedance analysis of body composition. The adiponectin serum levels were measured using a ELISA kit.
Results: To the major findings belong lower phase angle ($p<0.001$) and lower muscle mass percentage ($p=0.005$) in overlap syndrome than in OSAS patients. We showed that overlap patients had lower oxygen saturation and higher BMI and fat mass percentage than OSAS. C-reactive protein increased from control group to overlap syndrome . FEV1% correlated positive with phase angle ($p<0.001$) and MM% ($p<0.001$).
Conclusions: The study showed differences between these two related syndromes, especially in body composition, oxygen saturation and in proinflammatory indices, but we didn't observe differences in adiponectin serum levels.

KEYWORDS adiponectin, body composition, OSAS ,overlap syndrome, phase angle,

INTRODUCTION

Many studies indicate on the relationship between obstructive sleep apnea syndrome (OSAS) and metabolic disorders. OSAS could be associated with higher risk of insulin resistance, obesity, dyslipidemia and metabolic syndrome. Moreover OSAS is independent risk factor of hypertension, myocardial infarction, stroke and increased mortality [1]. OSAS and metabolic disorders seem to share the same pathogenic pathways[2]. Especially increased levels of different inflammatory markers and enhanced oxidative stress could accelerate progression of atherosclerosis and lead to the development of cardiovascular disorders associated with OSAS [2-3].

The term overlap syndrome (OS) was introduced by Flenley in 1985 to describe coincidence of chronic obstructive pulmonary disease (COPD) and sleep apnea syndrome [4]. This co-existence seems to be rather the result of chance than a pathophysiological linkage [5].In a very large study, including 5 954 participants Sanders et al. didn't reveal differences in the prevalence of OSAS among COPD patients and subjects without COPD [6].

Bioelectrical impedance analysis (BIA) consists a simple, non-invasive, infallible and useful method for measuring body composition [7-8]. BIA has been validated for the assessment of body composition and nutritional status in different groups of patients, from healthy persons, COPD patients to cancer patients [8,9,10]. In BIA analysis are used electric properties of the body and differences in current flow connected with changes in body composition. BIA determines the overall electrical resistance of the body [7-8].

BIA analysis could be complemented by bioelectrical impedance vector analysis (BIVA), which is independent of hydration status. BIVA is a pattern analysis of resistance and reactance plotted as a vector in a coordinate system [8].

Adiponectin, an adipocyte-derived cytokine, plays a role in glucose and lipid homeostasis, in addition to antiatherogenic and anti-diabetic effects [11-12]. Hypoadiponectinemia is treated as an independent risk factor for endothelial dysfunction, hypertension, ischemic heart disease and other cardiovascular complications [13].

We hypothesize that in overlap syndrome could be present more pro-atherogenic indices and adiponectin levels could be lower than in patients with OSAS.

The aim of the study was a comparison of body composition (especially phase angle), adiponectin serum levels and pro-atherogenic indices as C-reactive protein and cholesterol fractions in overlap syndrome and severe sleep apnea syndrome.

METHODS

Patients

Although the term overlap syndrome describes the coexistence of COPD and OSAS independently of severity, we decided to include only patients with severe OSAS into both examined groups (with an apnea-hypopnea index AHI> 30). We examinated 33 patients with overlap syndrome (severe OSAS and COPD), 80 patients with severe OSAS and 50 persons from control group. In OSAS group were 18 women, in overlap group 5 and in control group 19. We didn't reveal statistical differences in gender either between control group and all patients (Chi2 Yatesa 2.55; $p=0.110$) or between OSAS and overlap patients (Chi2 Yatesa 0.22; $p=0.636$). The control consisted healthy persons. In both examined groups were patients with many comorbidities. The most common health problem in both groups consisted hypertension. In overlap patients were 28 persons and in OSAS 57 with hypertension. Moreover in overlap syndrome group 13 patients had diabetes and 12 ischemic heart disease, and in OSAS patients 24 were with diabetes and 21 with ischemic heart disease. We didn't reveal statistical significant differences in incidence of hypertension, diabetes or ischemic heart disease. The patient characteristic of the all groups is summarized in the Table 1.

Polygraphy
All subjects underwent nocturnal respiratory polygraphy using a Grass Aura PSG Lite. During 8 hours of nocturnal sleep the following parameters were evaluated: apnoe/hypopnoe index – AHI, desaturation index-DI, mean SaO2 and minimal SaO_2 at the end of the sleep apneas/hypopneas. Apnea was defined as cessation of airflow for >10s and hypopnea as a >50% reduction in airflow from its value during quiet wakefulness for at least 10s followed by 4% or more decrease in oxyhemoglobin saturation.

Lung function measurements and COPD stages
Pulmonary function tests were performed in all examinated patients. Spirometry was performed with a Lungtest 1000 system from MES company (Cracow, Poland) according to the guidelines recommended by the American Thoracic Society. To the variables recorded belong forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and FEV1/FVC ratio. The lung function variables were expressed in the absolute values and as the percentage of predicted value.

In OSAS group and in control group were included only patients without any lung function abnormalities.

In overlap syndrome majority of patients were in stage II of COPD according to GOLD (the Global initiative for chronic Obstructive Lung Disease) guidelines (19 patients). 8 were in stage III, 5 in I and 1 patient in stage IV. All patients received standard treatment for COPD during our examinations. Mean forced expiratory volume in 1 s (FEV 1) was 2.00 + 0.72 l, and mean percentage of FEV1 predicted value was 64.64 + 17.09 %. We didn't observed respiratory failure during daytime.

Body composition
Body composition was evaluated with a single-frequency bioimpedance analyser (Model BIA 101, AKERN-RJL, Italy). All measurements were performed in the morning with standard tetrapolar technique. BIA analysis was complemented by bioelectrical impedance vector analysis (BIVA). Body composition parameters were calculated using manufacturer software BODYGRAM 1.31.

Adiponectin
Blood samples were collected from fasting subjects in the morning. Centrifugation was performed for 10 minutes at 1467 RCF. The serum was removed and stored at -80°C.The adiponectin serum level was measured using a sandwich ELISA kit: Human Adiponectin/Acrp30 Immunoassay Quantikine (R&D Systems, Minneapolis, USA). The microplate reader ELISA MRXe Dynex Technologies was used. Additionally, in the same serum samples CRP, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were measured.

Statistical analysis
Statistical analysis was performed using the CSS Statistica for Windows (version 5.0) .

Our first step was the comparison of selected parameters in 3 groups (control, OSAS and ovelap), we performed this using ANOVA Kruskal-Wallis test. Next we compared the same parameters between OSAS patients and overlap syndrome patients, this time with U Mann-Whitney test. Differences between samples were considered significant at $p<0.05$.

The work has been approved by the appropriate ethical committees related to the institution: Commission of Bioethics at Wroclaw Medical University.

RESULTS
Average oxygen saturation, mean minimum oxygen saturation and minimum oxygen saturation were lower in overlap syndrome patients than in OSAS, although in both groups were patients with severe OSAS and without differences in AHI (apnea hypopnea index) (Table 1).

Many statistical significant changes in body composition between control group, OSAS and overlap patients were observed. Moreover we showed a few important differences in body composition between OSAS and overlap syndrome patients. To the major findings belong lower phase angle and lower muscle mass percentage (MM%) in overlap syndrome than in OSAS patients. Phase angle was smaller in OSAS and overlap than in control group , but also much smaller in overlap than in OSAS only(5.87 vs 5.63 vs 4.79 $p<0.001$).

MM% was lower in OSAS and overlap than in control group , but also much lower in overlap than in OSAS only(43.62% vs 41.21 vs 38.59%; p=0.005). FM% (fat mass percentage) was higher in overlap syndrome than in OSAS (46.21% vs 35.44%, p=0.041).

BMI (body mass index) increased from control group to overlap syndrome and was higher in OS than in OSAS. In addition ECW % (extracellular water percentage) was also higher in OSAS and in overlap comparing with control and also higher in overlap than in OSAS. We observed also a trend, that FFM% (fat free mass percentage) decreased from control group to overlap syndrome (p=0.065). Detailed results of body composition parameters are presented in Table 2 and Figure 1.

CRP (C-reactive protein) increased from control group to overlap syndrome (3.74 vs 6.29 vs 10.21; p=0.001) and CRP was significant higher in overlap patients than in OSAS patients (p=0.042). CRP (C-reactive protein) showed a negative correlation with MM% (muscle mass percentage) in Spearman test (r_s= -0.425, $p<0.001$).

In our study overlap patients were elder than OSAS patients (p=0.038).

We didn't reveal any changes in adiponectin serum levels in examined groups (p=0.663).

We analyzed also total cholesterol, triglycerides and cholesterol fractions LDL (low density) and HDL (high density) in examined groups , but there were no differences in the level of cholesterol and its fractions among the groups (Table 1).

In all patients we evaluated also correlations between FEV1% (percentage of predicted forced expiratory volume in 1s) and selected parameters. FEV1% correlated positive with phase angle ($p<0.001$) and MM% ($p<0.001$). The negative correlations were between FEV1% and CRP and BMI. (Table 3).

DISCUSSION
Many studies indicate on differences between OSAS (obstructive sleep apnea syndrome) and overlap syndrome patients [4-5]. Our observations that overlap syndrome patients had more and deeper desaturations during sleep than patients with OSAS only, confirm many studies. It has been showed, that overlap patients present more important nocturnal desaturations than patients with either OSAS or COPD (chronic obstructive pulmonary disease)[4-5]. We demonstrated also as previous authors that overlap patients were elder than OSAS patients [4].

The changes in body composition and adiponectin levels in overlap syndrome are not good enough described . We didn't find any publications either about body composition changes or adiponectin levels in overlap syndrome.

Our research confirmed described in many previous studies correlations between OSAS and obesity [14]. We showed higher BMI (body mass index) in OSAS patients than in control group, but we demonstrated also higher BMI in overlap patients than in OSAS. Higher BMI in overlap patients could be disputable, because some authors suggest that overlap patients are less obese [4]. However our detailed analysis of body composition parameters revealed many important changes, what indicates that BMI only is not enough valuable

in better understanding of differences between both groups of patients. We observed that FFM% (percentage of fat free mass) decreased and FM% (percentage of fat mass) increased from control group to overlap syndrome. Moreover MM% (percentage of muscle mass) decreased from control group to overlap syndrome.

It seems to be especially interesting , that position of the measurement point in the BIVA (bioelectrical impedance vector analysis) normogram (in majority of cases of OS) was in lower quadrant between 75th and 95th . This could indicate a suspicion of malnutrition although higher BMI as suggest some authors [8].

Previous studies in COPD suggest that body composition could be an important non-pulmonary impairment that modulates the risk of functional limitation in COPD [15]. Low fat free mass in COPD is treated as predictor of mortality [16]. Nishimura showed, that muscle strength was closely associated with lean body mass in COPD patients [17]. Eisner et al. suggested even that in COPD greater fat mass could be the most important predictor of more functional limitation and lean mass is only predictive in relation to fat mass [15]. The correlations between body composition parameters and emphysema have been also demonstrated. Rutten et al. showed, that percentage of low attenuation areas inversely correlated with BMI, FFMI (fat free mass index) and FMI (fat mass index)[18]. We had similar observations, FEV1% (percentage of predicted forced expiratory volume in 1 s) correlated negative with BMI and positive with MM%.

Phase angle can be treated as a marker of nutritional status. It is higher in athletic constitutional type and good nutritional status and lower in poor training status and poor nutritional status [8]. Lower phase angle has been demonstrated in COPD patients [19]. In addition in lung cancer patients lower phase angle could be associated with poorer survival [10]. Recent studies suggest that low phase angle could be also recognized as a new cardiovascular risk factor. De Luis and co-workers revealed , that obese women with low phase angle had high fat mass and high level of glucose, interleukin-6 (IL-6) and leptin. [20]. We showed that phase angle was lower in OSAS patients than in control and also lower in overlap than in OSAS. However some authors suggested that phase angle could positive correlate with BMI [21] and in our study overlap patients were more obese.

So the phase angle could be helpful together with increased CRP in better understanding of higher risk of cardiovasculary complications in OSAS and especially in overlap syndrome patients. It has been confirmed, that OSAS and COPD are independent risk factors for cardiovascular events and some authors indicate that coexistence of these both diseases increases this risk [5,22].

We revealed that muscle mass percentage (MM%) decreased and CRP increased from control group to overlap syndrome. Spearman test confirmed also negative correlation between MM% and CRP. CRP showed also negative correlation with FEV1%. There are many evidences, that in both diseases: OSAS and COPD the persistent systemic inflammation plays important role. In both diseases elevation of many inflammatory markers has been described, including CRP (C-reactive protein), fibrinogen, leucocytes and tumor necrosis factor alpha [3,4]. Moreover activation of inflammatory reaction could lead to muscle wasting. Presence of many inflammatory cytokines (sometimes called catabolic cytokines) as interleukin-1 and 6 or tumor necrosis factor alpha increases muscle proteolysis [22-23].

We didn't find any differences in adiponectin serum levels in examined groups, but these topic is disputable. Some authors indicated on negative correlations between AHI (apnea hypopnea index) and adiponectin and in addition showed the influence of CPAP treatment on adiponectin levels[24]. Other didn't demonstrate differences in adiponectin levels in OSAS or even showed higher adiponectin levels in OSAS patients [11,25]. Newest data suggested, that adiponectin could be promising serum marker in COPD. Yoon et al. demonstrated, that adiponectin was associated with decreased risk of cardiovascular complications, but were related to increased bronchial reactivity and an accelerated decline in lung function[26].

We realize that our study has a few limitations. One of them is coincidence of other diseases in both examinated groups. Some of this diseases could have influence on adiponectin levels and on differences in body composition. As mentioned before, lower adiponectin levels were described in hypertension, ischemic heart disease and diabetes [12,13].

Although this limitations, we didn't decide for exclusion of patients with comorbidities. A growing number of studies confirms high prevalence of many diseases and the association between OSAS and these diseases. The link between OSAS and the most common diseases in our examined groups (hypertension, diabetes and ischemic heart disease) was well established [27-28] .

Differences in BMI between control group and OSAS and overlap patients could also consist a problem in the interpretation of the data. Population studies showed that phase angle increased with BMI, decreased with age, was smaller in women and inversely associated with fat percentage [21]. Moreover newest studies indicate, that obesity could be treated as separate process and obesity itself leads to activation of inflammatory process. The metabolic inflammatory state is termed metaflammation and defined as low-grade, chronic inflammation orchestrated by metabolic cells in response to excess nutrients and energy [29].

We hope that our detailed work in relative homogenous group of patients will help in better understanding of differences between overlap syndrome and OSAS. We tried to compare patients with similar AHI to emphasize changes connected with COPD.

Conclusion

The study points to differences between these two related syndromes, especially in body composition, oxygen saturation and in proinflammatory indices, but we didn't observe differences in adiponectin serum levels.

Competing interests:

The authors declare that they have no competing interests.

Author's contributions

MK and PP collected informations about patients. MK carried out bioelectrical impedance analysis and collected serum samples. MK performed statistical analysis and drafted manuscript. RJ coordinated the study and improved manuscript. All authors read and approved the final manuscript.

Table 1. Comparison of selected parameters in the examinated groups

	Control group n=50	OSAS n=80	OVERLAP Syndrome n=33	ANOVA Kruskal-Wallis test (p)	OVERLAP vs OSAS (U Mann-Whitney test (p)
Age (years)	50.32± 13.62	54.72± 9.41	57.81± 5.24	0.004	0.038
AHI/hr	2.15± 1.85	50.07± 15.00	50.4± 22.30	<0.001	0.693
DI/hr	2.66± 1.55	43.14± 20.68	49.44± 23.12	<0.001	0.250
Average oxygen saturation(%)	94.0± 2.15	88.69± 5.21	86.26± 6.41	<0.001	0.047
Minimum oxygen Saturation(%)	85.74± 6.38	69.16± 11.08	64.44± 11.71	<0.001	0.040

Average min. oxygen saturation(%)	90.62± 2.14	82.74± 7.21	78.60± 8.24	<0.001	0.011
Total cholesterol (mmol/L)	5.5± 1.17	5.55± 1.37	5.02± 0.81	0.106	0.067
Triglicerids (mmol/L)	2.11± 1.46	2.19± 1.11	2.04± 1.25	0.278	0.298
LDL-cholesterol (mmol/L)	3.38± 0.96	3.49± 1.24	3.22± 0.83	0.252	0.326
HDL cholesterol (mmol/L)	1.21± 0.34	1.17± 0.47	1.08± 0.34	0.803	0.817
CRP	3.74± 2.73	6.29± 5.43	10.21± 9.27	0.001	0.042
Adiponectin ng/ml	6131.54± 4179	6480.11± 4886.75	6017.56± 4144.0	0.663	0.633

Abbreviations: AHI apnea hypopnea index, CRP C-reactive protein, DI desaturation index, LDL low density cholesterol, HDL high density cholesterol.

Table 2. The comparison of body composition parameters in examined groups.

	Control group	OSAS	OVERLAP syndrome	ANOVA Kruskal-Wallis test (p)	OVERLAP vs OSAS (U Mann-Whitney test (p)
BMI	29.25±5.45	36.01±7.49	39.78±6.83	<0.001	<0.001
Phase Angle	5.87±0.81	5.63±1.3	4.79±0.90	<0.001	<0.001
TBW%	49.24±6.46	48.22±5.32	48.14±11.47	0.156	0.103
ECW%	46.62±4.32	47.85±7.09	52.56±6.16	<0.001	<0.001
ICW%	53.37±4.32	51.31±6.96	47.43±6.16	<0.001	<0.001
FM%	33.46±9.55	35.44±8.03	46.21±14.12	0.239	0.041
FFM%	66.53±9.55	64.57±8.03	61.63±7.67	0.431	0.065
MM%	43.62±8.27	41.21±7.30	38.59±13.54	<0.001	0.005

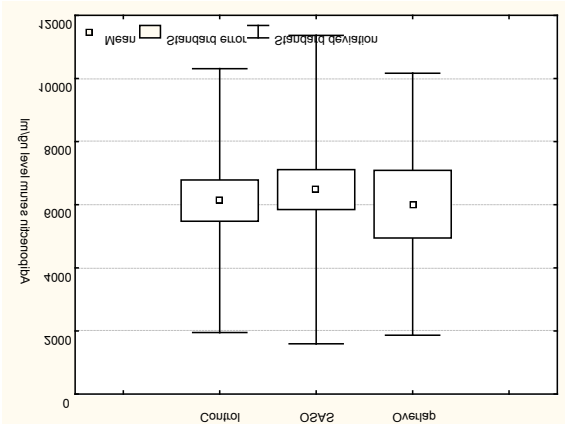
Abbreviations: BMI body mass index, ECW%- percentage of extracellular water , FFM%- percentage of fat free mass, FM%- percentage of fat mass, ICW%- percentage of intra-cellular water, MM%- percentage of muscle mass, TBW% - percentage of total body water.

Table 3. The correlations between FEV1% and selected parameters.

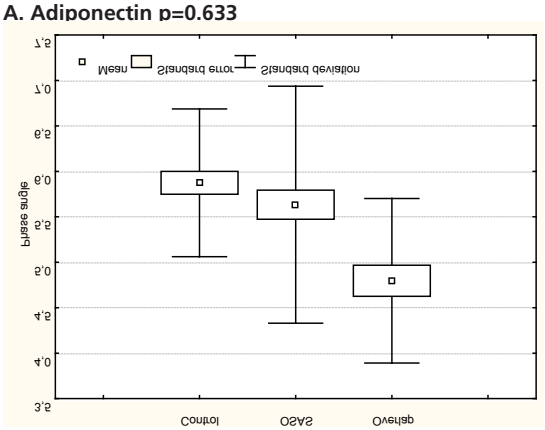
	FEV1% (predicted value of FEV1)	
	r_s	p
Adiponectin ng/ml	0.021	0.830
CRP	-0.343	<0.001
BMI	-0.337	<0.001
Phase Angle	0.474	<0.001
TBW%	0.061	0.496
MM%	0.322	<0.001

Abbreviations: BMI body mass index, CRP C-reactive protein, FEV1 % percentage of predicted forced expiratory volume in 1 second, MM%- percentage of muscle mass, TBW% - percentage of total body water.

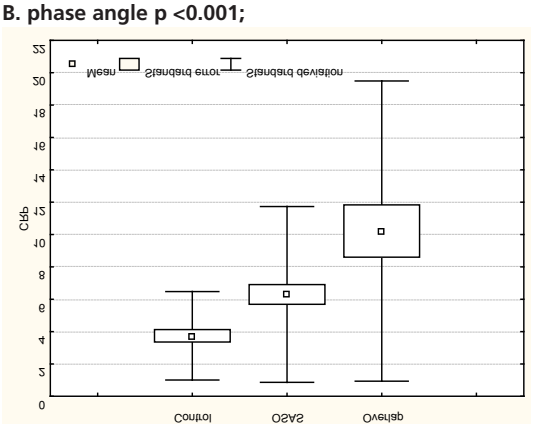
Figure 1.
Differences in selected parameters in examined groups:



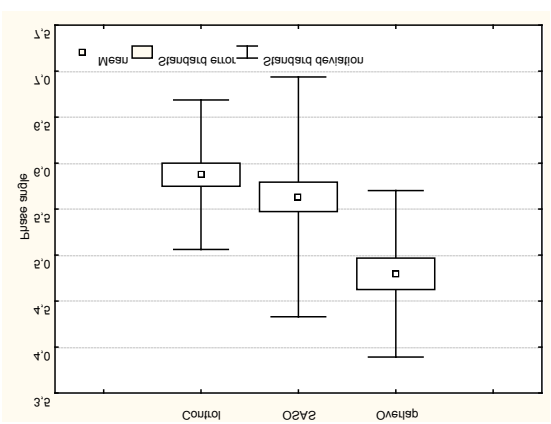
A. Adiponectin p=0.633



B. phase angle p <0.001;



C. CRP (C-reactive protein) p=0.042



D. MM % (percentage of muscle mass) p=0.005

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