Treatment of obstructive sleep apnea with continuous positive airway pressure decreases adipocyte fatty acid-binding protein levels

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Aim. Obstructive sleep apnea (OSA) can be associated with the metabolic syndrome. Adipocyte fatty acid-binding protein (A-FABP) may play a role in OSA. The aim of this study was to determine whether continuous positive airway pressure (CPAP) treatment results in decreased serum A-FABP levels.

Subjects and methods. 81 patients (70 males, a mean age of 53.9±10.3 years) were evaluated by polysomnography, diagnosed with OSA and indicated for CPAP treatment. Anthropometric, clinical and laboratory investigations were carried out and repeated after 1 month/ 1 year of CPAP treatment. The data were analyzed using the SPSS Statistics 15 software (SPSS Inc., Chicago, USA).

Results. Patients had significantly decreased A-FABP levels (34.4 ng/ml; 31.2 ng/ml; 24.8 ng/ml; P=0.048; P=0.001) and improved OSA parameters: AHI (53.9; 5.0; 5.6; P<0.0001), mean nocturnal oxygen saturation (91%; 93%; 94%, P<0.0001), ODI (55; 9; 8, P<0.0001), and percentage of sleep time with oxygen saturation below 90% (28.2; 0.2; 0, P<0.0001). BMI, waist, neck circumference, and blood pressure did not statistically significantly change.

Conclusion. CPAP therapy in OSA patients has a positive effect on A-FABP levels. Decreased A-FABP levels play an important role in regulating glucose metabolism and affect the regulation of lipid metabolism and thus may contribute to decrease in the cardiovascular complications of OSA.

Key words: obstructive sleep apnoea, adipocyte fatty acid-binding protein, continuous positive airway pressure

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INTRODUCTION

Obstructive sleep apnea (OSA) syndrome is a global problem affecting 2-4% of middle-aged adults[1]. OSA may activate pathological pathways leading to insulin resistance, atherosclerosis and hypertension[2]. The Sleep Heart Health Study Authors showed that OSA is associated with impaired glucose tolerance and insulin resistance and thus may result in the development of type 2 diabetes mellitus (DM) (ref. [3]). According to Coughlin et al.[4], the risk of the metabolic syndrome is as much as 9.1 times higher in OSA patients than in controls.

Adipocyte fatty-acid binding protein (A-FABP), also known as FABP4 or aP2, is a member of a family of 9 fatty acid-binding proteins (FABPs). It is produced by adipocytes and macrophages and accounts for approximately 1.8-8.1% of all proteins produced by these cells[5].

A-FABP plays an important role in regulating glucose metabolism. Patients with a polymorphism at the A-FABP aP2 locus have significantly reduced risk for diabetes and cardiovascular disease (CVD) (ref.[6]). It seems that A-FABP could be a new biomarker for predicting the development of type 2 diabetes mellitus[7] and play a role in integrating stress and inflammatory responses with metabolic homeostasis[8].

A-FABP influences the regulation of lipid metabolism. It is highly expressed in both murine and human foam cells found in atherosclerotic plaques. There, A-FABP acts mainly through increased expression of anti-inflammatory cytokines by macrophages[8]. In mouse models, a protective effect of A-FABP deficit on the development of atherosclerosis was shown[9]. Several studies found a correlation between serum A-FABP levels and coronary artery disease[10,11], with CVD patients having significantly higher A-FABP levels. Hsu et al.[12] demonstrated that fasting levels of A-FABP positively correlated with the diagnostic criteria of metabolic syndrome. According to another study, A-FABP suppresses cardiomyocyte contraction, suggesting a new link between obesity and heart disease[13]. Thus, A-FABP may be a promising link between the metabolic syndrome and atherosclerosis[14].

In a recent study, Lam et al.[15] reported a positive correlation between serum A-FABP levels and OSA parameters. A-FABP levels also correlated with nocturnal hypoxemia and insulin resistance independent of adiposity. The results support the hypothesis that A-FABP could

be a link in the association between OSA and cardiometabolic dysfunction.

Continuous positive airway pressure (CPAP) is one of the most effective methods for treating OSA, significantly normalizing (decreasing) the apnea-hypopnea index (AHI), improving oxygenation, shortening sleep time with oxygen saturation below 90% and thus preventing micro-awakenings. To be effective, the therapy must be prolonged[16]. Some authors reported a positive effect of CPAP on insulin resistance[17].

The objective of the present study was to verify the hypothesis that CPAP treatment improves OSA parameters (AHI, sleep time with oxygen saturation below 90%, oxygen desaturation index [ODI], mean nocturnal oxygen saturation) and decreases serum A-FABP levels.

SUBJECTS AND METHODS

Consecutive (aged >18 years) patients were evaluated by polysomnography at the Sleep Laboratory of the Department of Respiratory Medicine, University Hospital Olomouc in 2007-2010. OSA patients were defined as those with the AHI >5 per hour of sleep and meeting the valid criteria for OSA clinical signs.

The exclusion criteria were severe chronic obstructive pulmonary disease (class III or IV), severe pulmonary hypertension, severe heart valve disease, heart failure, ejection fraction below 50%, and non-compliance with CPAP treatment.

All subjects gave written informed consent. The study protocol was approved by the Institutional Review Board of the Faculty of Medicine and Dentistry, Palacky University Olomouc.

Anthropometric measurements and physical examination (body height, body weight, waist circumference, neck circumference, body mass index (BMI), casual blood pressure), and laboratory assessment of A-FABP levels were carried out in the subjects at the beginning, after one month and after one year of CPAP treatment. Body fat percentage was measured by the bioelectrical impedance analysis using the Omron BS 306 analyzer. All subjects filled in the Epworth Sleepiness Scale questionnaire. Polysomnography was performed using the Alice computerized diagnostic system (Respironics, USA). The following parameters were assessed: AHI, mean nocturnal oxygen saturation and sleep time with oxygen saturation below 90%. The records were checked and manually rescored[18].

A-FABP measurement. The blood samples were drawn under aseptic conditions from the cubital vein after 12 h fasting. The human A-FABP ELISA kits were obtained from the Bio-Vendor Laboratory Medicine, Inc. (Brno, Czech Republic). The assay was conducted according to the manufacturer's instructions. The intra- and inter-assay variations were evaluated by measuring 3 different samples in replicates of 8 (CV intra-assay <4.8%, CV inter-assay <10%).

The patients were treated by CPAP. For each patient, the pressure was set individually using autotitrating CPAP (autoCPAP) and 3-night mean records.

Statistics. The data were analyzed using the SPSS Statistics 15 software (SPSS Inc., Chicago, USA). The normal distribution was checked by the Shapiro-Wilk test. Either the Friedman test and post-hoc analysis using the Wilcoxon paired test with the Bonferroni correction or ANOVA (analysis of variance) with the Bonferroni post-hoc analysis were used to compare the paired data. The data were expressed as the median or mean ± SD. A P-value <0.05 was considered statistically significant.

RESULTS

A total of 81 patients (70 males) with a mean age of 53.9±10.3 years were recruited.

The demographic and clinical parameters of the patients: 67 patients (82.7%) with hypertension, 20 patients (20.69%) with diabetes mellitus, 8 patients (9.8%) with coronary artery disease, 7 patients (8.64%) were smokers and 33 patients (40.7%) exsmokers

The studied parameters (median/mean±SD) (baseline, after 1 month of CPAP treatment, and after 1 year of CPAP treatment) are shown in (Table 1). To compare repeated measurements, the Wilcoxon paired test with the Bonferroni correction was used (see results in Table 2).

The anthropometric parameters (i.e. body weight, BMI, body fat percentage, waist circumference, neck circumference, and waist-to-hip ratio) did not statistically significantly change after 1 month or 1 year.

The OSA parameters (i.e. Epworth Sleepiness Scale, AHI, ODI, sleep time with oxygen saturation below 90%) were significantly reduced after both 1 month and 1 year as compared with the baseline values. The mean nocturnal oxygen saturation increased significantly. The differences between values measured after 1 month and after 1 year were not significant in any of the parameters.

As compared with the baseline data, the A-FABP levels were significantly decreased after both 1 month and

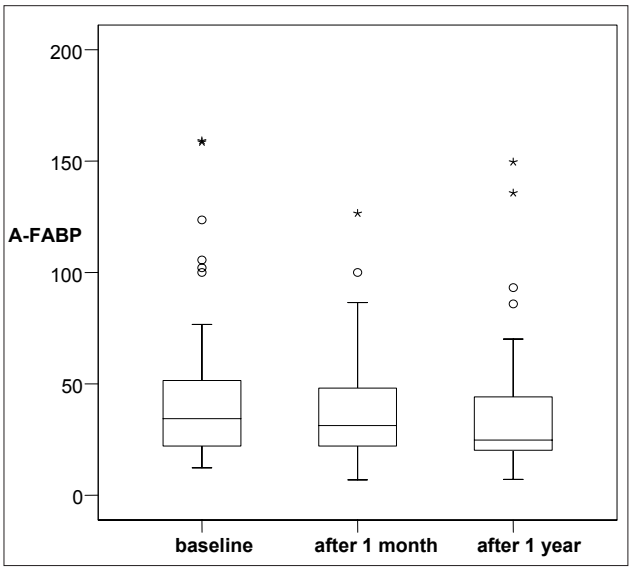

Fig. 1. Changes in serum A-FABP levels.

Table 1. Changes in the studied parameters.

Parameter	Baseline (N=81) mean±SD median	After 1 month of CPAP (N=81) mean±SD median	After 1 year of CPAP (N=81) mean±SD median	Significance
Weight (kg)	109.7±19.2 104.5	110.3±20.6 104.5	108.6±21.1 103.0	0.425[a]
BMI	36.1±6.3 35.1	36.2±6.4 35.4	35.6±6.1 34.7	0.318[a]
Body fat percentage	35.9±6.7 34.8	35.7±6.4 34.7	35.5±6.7 35.1	0.743[b]
Neck circumference (cm)	45.1±3.6 45.0	44.7±3.5 44.0	44.6±3.2 44.0	0.483[a]
Waist circumference (cm)	119.0±13.2 115.0	118.5±14.0 116.0	117.7±13.1 116.00	0.283[a]
Hip circumference (cm)	117.2±11.0 115.0	117.6±11.5 115.0	116.4±10.0 114.0	0.286[a]
Waist-to-hip ratio	1.016±0.065 1.0	1.008±0.066 1.0	1.011±0.071 1.0	0.757[b]
Systolic BP (mm Hg)	135±13 140	132±15 130	129±18 130	0.116[a]
Diastolic BP (mm Hg)	**82**±11 80	**80**±9 80	**79**±7 80	**0.006**[a]
Epworth Sleepiness Scale	**10.7**±5.1 10.0	**6.4**±3.8 5.5	**6.3**±4.1 6.0	**< 0.0001**[a]
AHI	**54.4**±21.6 53.9	**8.5**±11.3 5.0	**7.6**±9.8 5.6	**< 0.0001**[a]
Mean nocturnal oxygen saturation (%)	**89.1**±4.4 91.0	**93.0**±2.4 93.0	**93.2**±2.4 94.0	**< 0.0001**[a]
ODI	**55.9**±23.3 55.0	**14.1**±17.5 9.0	**11.9**±12.9 8.0	**< 0.0001**[a]
Sleep time with oxygen saturation below 90% (%)	**35.3**±25.4 28.2	**7.9**±19.0 0.2	**7.6**±18.5 0	**< 0.0001**[a]
A-FABP (ng/mL)	**42.1**±29.2 34.4	**37.7**±21.6 31.2	**34.2**±24.5 24.8	**0.001**[a]

[a] Friedman test, [b]ANOVA
BMI body mass index, BP blood pressure, AHI apnea-hypopnea index, ODI oxygen desaturation index, A-FABP adipocyte fatty acid-binding protein

Table 2. Changes in selected parameters after CPAP treatment.

Parameter	Baseline	After 1 month	After 1 year	Significance		
				Baseline vs. 1 month	Baseline vs. 1 year	1 month vs. 1 year
Diastolic BP (mm Hg)	80	80	80	0.507	0.102	1.000
Epworth Sleepiness Scale	10.0	5.5	6.0	**< 0.0001**	**< 0.0001**	1.000
AHI	53.9	5.0	5.6	**< 0.0001**	**< 0.0001**	1.000
Mean nocturnal oxygen saturation (%)	91	93	94	**< 0.0001**	**< 0.0001**	1.000
ODI	55	9	8	**< 0.0001**	**< 0.0001**	1.000
Sleep time with oxygen saturation below 90% (%)	28.2	0.2	0	**< 0.0001**	**< 0.0001**	1.000
A-FABP (ng/mL)	34.4	31.2	24.8	**0.048**	**0.0001**	0.108

Median values are shown in the table. BP blood pressure, AHI apnea-hypopnea index, ODI oxygen desaturation index, A-FABP adipocyte fatty acid-binding protein

1 year (34.4 ng/ml, 31.2 ng/ml, and 24.8 ng/ml, respectively), as seen from (Fig. 1).

DISCUSSION

The present study showed that CPAP treatment of OSA markedly normalizes parameters of significance for sleep apnea as well as A-FABP levels.

The findings are consistent with the study by Lam et al.[15] who showed a positive association between serum A-FABP levels and OSA parameters (duration of oxygen desaturation, AHI). The authors excluded patients with hypertension, diabetes mellitus, cardiovascular disease and those regularly taking medications. By contrast, patients with hypertension, diabetes mellitus or a history of ischemic heart disease were included in the present study. This is also reflected in baseline A-FABP levels in high-risk patients in this study which were higher than those reported by Lam et al. In the group studied by Miyoshi et al.[10], the A-FABP cut-off value for the risk of CVD was 20.1 ng/ml (76% specificity and 65% sensitivity). Patients in the reported study had A-FABP levels more than twice as high as that, suggesting a high risk of CVD in these patients with OSA.

A-FABP levels significantly correlate with waist circumference and BMI (ref.[15,19]). In this study, CPAP treatment of OSA did not lead to statistically significant decreases in BMI or waist circumference but A-FABP levels decreased. This may be explained by the fact that improved oxygenation is a protective factor and decreases A-FABP expression. Similar findings were noted in *in vitro* studies[20]. This also confirms the conclusion by Lam et al.[15] that different intensity of intermittent hypoxia in OSA subjects results in different degrees of heightened expression of A-FABP. More research is needed on the dependence of A-FABP on various clinical situations. Although Engl et al.[21] found a positive correlation between A-FABP and BMI and body fat percentage, A-FABP levels in patients who lost weight over one year did not decrease as had been expected. On the other hand, Stejskal et al.[22] reported that A-FABP dynamic could be an important prognostic marker for predicting weight loss and weight maintenance.

Lower AFABP levels in OSA patients may improve insulin resistance and response of macrophages and decrease the risk of CVD. Thus, studies of A-FABP levels in OSA patients may contribute to better understanding of the pathological relations between these nosological entities.

CPAP is a very important approach to OSA treatment. In a group of 449 subjects, Buchner et al.[23] showed that CPAP treatment of OSA patients decreased their risk of cardiovascular events (non-fatal myocardial infarction [MI], stroke, revascularization for acute coronary syndrome, death from MI or stroke) by 64%, independent of age and current cardiovascular comorbidities. Similarly, Marin et al.[24] reported an increase in fatal (OD 2.87) and non-fatal events in OSA patients receiving no therapy. Few studies have focused on the effect of CPAP treatment on early signs of atherosclerosis. In patients treated with CPAP, Drager et al.[25] found improvements in carotid intima-media thickness and pulse wave, and decreased C-reactive protein and catecholamine levels. CPAP treatment may result in improved endothelial vasomotor tone and decreased inflammatory parameters[26]. From the literature, no study was found on the effect of CPAP therapy on A-FABP levels.

Lower A-FABP levels were observed as early as after 1 month of therapy, with another decrease after 1-year treatment (although the difference between 1-month and 1-year treatment was not statistically significant), suggesting that long-term OSA therapy is effective. Excluded were patients without adequate compliance with CPAP treatment. This aside, CPAP treatment did not result in completely normalized A-FABP levels.

CONCLUSION

In patients with OSA, long-term CPAP treatment led to a statistically significant decrease in A-FABP levels. Lower AFABP levels in OSA patients may improve insulin resistance, response of macrophages and decrease the risk of CVD. Thus, studies of A-FABP levels in OSA patients may contribute to better understanding of pathological relations between these nosological entities.

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