Neuroendocrinology Letters Volume 41 No. 5 2020
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

A positive correlation between adipocyte fatty acid binding protein and epicardial fat thickness in patients with obstructive sleep apnoea – preliminary data

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Submitted: 2020-01-28 Accepted: 2020-08-28 Published online: 2020-08-28

Key words: **Obstructive sleep apnoea; adipocyte fatty acid binding protein; epicardial fat thickness**

Neuroendocrinol Lett 2020; **41**(5):239–244 **PMID:** 33315335 NEL410520A05

Abstract

BACKGROUND: Obstructive sleep apnoea (OSA) is considered an important risk factor of cardiovascular diseases (CVDs). Epicardial fat (EF) thickness and adipocyte fatty acid-binding protein (A-FABP) may be important links to accelerated atherosclerosis observed in patients with OSA. The aim was to evaluate the relationship between EF thickness and A-FABP levels in patients with OSA.
METHODS: 66 patients (of which, 60 were males) of average age 55.6 ± 8.8 years, with newly diagnosed OSA were enrolled in this study. All patients underwent a sleep study, anthropometric parameters were measured, laboratory analysis and echocardiography with EF thickness measurements were collected. Patients were divided into two groups: Group 1: EF < 1mm; Group 2: EF > 1mm.
RESULTS: Epicardial fat was present in 51 patients (77.3%). A positive correlation was found between A-FABP levels and % of body fat (r=0.452, p=0.0002). After adjusting to % of body fat, there was no significant difference found in A-FABP levels in the two groups divided.
CONCLUSIONS: This study found a positive correlation between serum A-FABP level and % of body fat in patients with moderate to severe obstructive sleep apnoea. No significant difference was found between both groups.

Abbreviations:

A-FABP	- adipocyte fatty acid binding protein
AHI	- apnoea-hypopnoea index
EF	- epicardial fat
OSA	- obstructive sleep apnoea
CVD	– cardiovascular disease

BACKGROUND

Epicardial fat (EF) is the visceral thoracic fat deposition located between the myocardium and the visceral pericardium (Zagaceta *et al.* 2013). Epicardial fat is highly metabolically active, producing many cytokines which for example, play a role in the progression of atherosclerosis (Rosito *et al.* 2008).

Obstructive sleep apnoea (OSA) is characterized by the repetitive closure of the upper airways leading to periods of apnoea or hypopnoea (American Academy of Sleep Medicine. 2014). It is considered to be an important risk factor for the development of CVDs alongside atherosclerosis, arterial hypertension and myocardial infarction (Ludka *et al.* 2014). The precise pathophysiological mechanisms connecting OSA with advanced atherosclerosis observed in these patients is not completely clear and adipose tissue dysfunction may play an important role.

Adipocyte fatty acid-binding protein (A-FABP, also known as FABP4 or aP2) is one of the nine members of the family of fatty acid-binding proteins (FABPs) (Storch & Corsico. 2008). A-FABP may be a promising link between metabolic syndrome and atherosclerosis (Krusinova & Pelikanova. 2008), and a new biomarker for predicting the development of type II diabetes mellitus (Tso *et al.* 2007). In mouse models, a protective effect of A-FABP deficiency on the development of atherosclerosis was demonstrated (Makowski *et al.* 2001). Chow *et al.* showed, in a 12 year prospective study, that an elevated A-FABP level predicts the incidence of cardiovascular events (Chow *et al.* 2013). In another study, Lam *et al.* (Lam *et al.* 2009) reported a positive correlation between serum A-FABP levels and obstructive sleep apnoea parameters. A-FABP levels also correlated with nocturnal hypoxemia and insulin resistance, independent of adiposity.

It is not yet completely clear whether there is a difference in A-FABP production between different types of adipose tissues. Agra *et al.* published an experimental study investigating the expression of genes involved in adipogenesis, including A-FABP, in EF and subcutaneous adipose tissue (Agra *et al.* 2014). They found that epicardial adipocytes expressed significantly lower levels of the adipogenic gene A-FABP than subcutaneous adipocytes. Upregulation of adipogenic genes were observed in obese patients. The enlargement of adipocyte size was related to levels of A-FABP expression in stromal cells. This may show a new mechanism for understanding the relationship between epicardial fat, obesity, and CVD.

There is also data available proving a positive correlation between A-FABP level and EF thickness in overweight patients with left ventricular diastolic dysfunction (Baessler *et al.* 2014), and in overweight patients with a family history of CVD (Sovova *et al.* 2017).

According to available literature, data regarding the correlation between A-FABP levels and EF thickness in patients with obstructive sleep apnoea is missing.

METHODS

66 patients (of which, 60 were males) with an average age of 55.6 ± 8.8 years, were enrolled in this study. These were consecutive patients with newly diagnosed obstructive sleep apnoea. Anthropometric parameters, together with blood pressure measurements, were taken.

In all patients, obstructive sleep apnoea (OSA) was diagnosed during a sleep study (full polysomnography

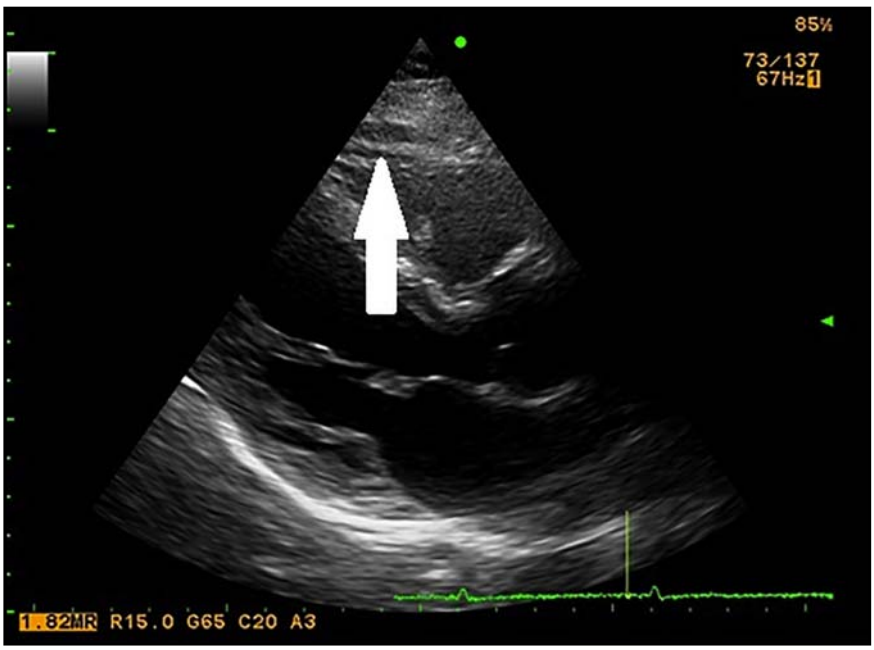

Fig. 1. Epicardial fat – 2-dimensional echocardiography. Arrow depicting epicardial fat

Tab. 1. Basic anthropometric parameters. BMI – body mass index

Parameter	Mean (±SD)	Median (Minimum-Maximum)
Age (years)	55.6±12.0	57.5 (24.0-71.0)
Weight (kg)	107.4±18.1	103.0 (76.0-152.0)
Height (cm)	174.1±8.9	175.0 (153.0-208.0)
BMI	35.4±5.2	35.1 (26.6-48.0)
% of body fat	35.3±6.1	34.6 (26.6-49.0)
Neck circumference (cm)	45.1±3.3	45.0 (40.0-54.0)
Waist circumference (cm)	118.3±13.2	115.0 (94.0-150.0)
Hip circumference (cm)	115.4±7.5	115.0 (101.0-134.0)
A-FABP (g/l)	34.1±19.3	27.7 (10.8-102.1)

– Alice 5, Respironics, USA or respiratory polygraphy – Miniscreen, F+G, Germany). All patients were indicated for positive airway pressure treatment and fell under the following criteria: apnoea-hypopnoea index (AHI) >15, or >30% of the duration of sleep with SpO_2 <90%.

Measuring A-FABP levels: Venous blood was collected after 12 hours of overnight fasting. Plasma levels were measured by enzyme-linked immunosorbent assay (Bio-Vendor Laboratory Medicine Inc., Brno, Czech Republic) according to the manufacturer's instructions. To determine variability, both intra and inter-assay variance was calculated, human plasma was used with 3 different samples being assessed (CV intra-assay <4.8%, CV inter-assay <10%).

Laboratory analyses were blinded i.e. carried out without access to clinical data.

Echocardiography was performed using VIVID 7 GE Medical. EF thickness was measured in the parasternal view (long and short axis), on the right ventricular free wall in diastole as a hypoechoic space under the epicardial surface, using the mean of three consecutive beats (Figure 1) (Bertaso *et al.* 2013). If there was a difference between the measurement in long and short axis the result was taken to be the mean value of these two measurements.

Statistical analysis

IBM SPSS Statistics version 22 (Armonk, NY: IBM Corp.) was used for statistical analysis. Spearman's correlation analysis was carried out to evaluate the relationship between EF and A-FABP, and other baseline variables. The normality of distribution was checked by the Shapiro–Wilk test. $P<0.05$ was considered statistically significant.

The Chi-square test or Fisher's exact test was used to compare two groups (1 and 2) that were divided according to EF thickness parameters (Group 1: EF < 1mm; Group 2: EF > 1mm). The Mann-Whitney U-test was used to compare the differences between groups in quantitative parameters.

RESULTS

Basic anthropometric parameters (mean ±SD, median, minimum, maximum) and A-FABP levels are shown in Table 1. Of the 66 patients: 52 (78.8%) were being treated for arterial hypertension; 22 (33.3%) were diabetic and 7 (10.6%) were current smokers together with 26 (39.4%) ex-smokers.

Epicardial fat was present in 51 patients (77.3%). Sleep study parameters are presented in Table 2. A positive correlation was found between EF thickness and A-FABP level (r=0.334, p=0.006) as well as between EF thickness and waist/hip ratio (r=0.274, p=0.026). No correlation was found between AHI and A-FABP level (r=-0.183, p=0.142).

The results of Spearman's correlation test, between EF thickness and the different clinical parameters are presented in Table 3.

Tab. 2. Sleep study parameters

Parameter	Mean (±SD)	Median (Minimum-Maximum)
Apnoea-hypopnoea index	55.4±19.3	54.7 (6.4-92.2)
Average night blood oxygen saturation	90.0±3.2	91.0 (78.0-94.0)
Oxygen desaturation index	57.7±22.6	60.8 (12.0-106.1)
% of sleep <90% SpO_2	31.1±21.3	26.0 (1.0-92.0)
Epworth sleepiness scale	10.6±4.4	10.0 (3.0-22.0)

Tab. 3. Spearman's correlation coefficients between epicardial fat thickness and different parameters

Parameter	Correlation coefficient	Significance (p)
BMI	0.126	0.315
% of body fat	0.239	0.057
Neck circumference	0.037	0.768
Waist circumference	0.209	0.092
Hip circumference	-0.036	0.776
Waist/hip ratio	**0.274**	**0.026**
Epworth sleepiness scale	-0.012	0.924
Apnoea-hypopnoea index	0.089	0.478
Average night blood oxygen saturation	-0.047	0.710
Oxygen desaturation index	0.138	0.268
% of sleep <90% SpO_2	0.093	0.455
A-FABP (g/l)	**0.334**	**0.006**

For further analysis, we have divided the sample into two groups according to the presence of EF. (Group 1: EF < 1mm; Group 2: EF > 1mm). Table 4 presents the characteristics of both groups.

After adjusting to % of body fat, there was no significant difference found in A-FABP levels between both groups (p=0.155).

DISCUSSION

This study has augmented the current information available regarding a possible correlation between EF thickness and A-FABP levels, in patients with obstructive sleep apnoea indicated for positive airway pressure therapy.

In this cohort, epicardial fat was present in 77.3% of subjects. This is in concordance with a previously published study of patients without known OSA (77.9%) (Sovova *et al.* 2017).

A correlation between OSA parameters and EF/A-FABP was not found; however, this is in contrast to the limited number of current available studies. Derin *et al.* (Derin *et al.* 2018) (62 subjects) described a correlation between AHI and EF in non-obese subjects with OSA with the same being found by Mariani *et al.* (Mariani *et al.* 2013) in a group of 115 obese subjects. However, both of these cohorts are different when compared with the group of patients in this study; there is a need for further, larger, studies to be conducted to shed more light on this.

A significant positive correlation was identified between epicardial fat thickness and A-FABP level, which may play a role in the higher cardiovascular risk of overweight patients with obstructive sleep apnoea.

However, after adjusting to % of body fat, there was no significant difference found between both groups according to the presence of EF. It seems that body composition is the stronger predictor of A-FABP levels, than the presence of EF or OSA itself.

It is well known that obese patients with OSA may have a higher cardiovascular risk; previous studies have shown that higher amounts of epicardial fat was found to be related to the presence of coronary syndromes, and the weakening of atheromatous plaques (Ito *et al.* 2012; Yerramasu *et al.* 2012). There is also data showing that individuals with a higher amount of epicardial fat have more severe coronary plaques, indicating that the thickness of epicardial fat plays a key role in the progression of coronary atherosclerotic disease (Okada *et al.* 2014). EF thickening is thus considered a risk

Tab. 4. Characteristics of group according to epicardial fat thickness

Parameter	Group 1	Group 2
BMI	34.1±6.0	35.8±6.0
% of body fat	33.1±6.9	35.9±5.8
Neck circumference (cm)	44.8±3.1	45.1±3.4
Waist circumference (cm)	114.0±14.7	119.6±12.5
Hip circumference (cm)	115.5±7.1	115.4±7.7
Waist/hip ratio	1.0±0.1	1.0±0.1

factor of coronary plaque formation and their vulnerability (Demircelik *et al.* 2014).

Some studies have also found that epicardial fat thickness decreases following continuous positive airway pressure therapy (Cetin *et al.* 2016). This could potentially reduce cardiovascular risk.

A previous study found that messenger RNA (mRNA) expression of A-FABP was higher in subcutaneous adipocytes, than in epicardial adipocytes (p<0.001), with gene expression in obese patients (BMI >30) being found to be significantly higher in comparison with leaner subjects (Agra *et al.* 2014). This study included subjects that were overweight and obese (median BMI 35.1), where we could expect similar gene overexpression and A-FABP overproduction, with possibly negative cardiovascular outcomes as high serum A-FABP levels are considered to be a negative risk factor of cardiovascular diseases (Chow *et al.* 2013).

In patients with obstructive sleep apnoea, a significant correlation had been previously found between serum A-FABP levels and the duration of sleep desaturation (r=0.293, p=0.001), % of sleep <90% SpO_2 (r=0.004, p=0.001). Similarly, when comparing waist-matched patients with AHI of <34.4 and >34.4, there was significantly higher serum A-FABP level (p=0.036) found in those with more severe OSA (Lam *et al.* 2009).

This study has several limitations. Firstly, the use of echocardiography in the measurement of epicardial fat thickness. The biggest drawback of utilizing this method is the need to identify the pericardium, as this can sometimes be very difficult, especially in an obese individual where good quality images are not usually available. On the other hand, in large population studies where there is a need for economic, safe and fast examinations, this approach for epicardial fat measurement seems justifiable, especially if we consider that results obtained with this method are concordant with results obtained by magnetic resonance imaging (r=0.91, p=0.001) (Iacobellis *et al.* 2003).

Secondly, the simultaneous use of full overnight polysomnography together with respiratory polygraphy creates a possible bias in overestimation or underestimation of OSA severity in some patients. On the other hand, this method is widely used and is considered suitable for OSA diagnosis.

A third limitation is the small percentage of women in the study group. However, according to literature (Akilli *et al.* 2014), there does not seem to be intersex difference in epicardial fat thickness.

CONCLUSION

Body composition, particularly the % of body fat, is the strongest predictor of A-FABP levels in patients with OSA. If we consider that epicardial fat thickness predicts cardiovascular risk, then abdominal type of obesity is perhaps more strongly associated with cardiovascular risk, than OSA severity. Therefore, weight reduction should be the strongest recommendation for obese patients with OSA.

DECLARATIONS

Ethics approval and consent to participate

Informed consent was obtained from all individual participants involved in this study. This study was approved by local Ethics Committee- University Hospital Olomouc Ethic Committee- application number 76/08.

Consent for publication

Consent for publication was part of Informed consent form signed by subjects

Availability of data and material

Data will be available upon request by corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was funded from budget of Department of Respiratory Medicine, University Hospital Olomouc, Czech Republic.

Authors contributions

All authors contributed in equal way in preparation of this manuscript.

Acknowledgments

We would like to thank Dr. Zapletalova for statistical analysis.

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