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Sleep apnoea involves iron homeostasis regulation

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PURPOSE / OBJECTIVES

Syndrome of obstructive sleep apnoea (OSA) represents by symptoms caused by intermittent restriction and/or total obstruction of airflow through upper respiratory tract during sleep. Epidemiologically increased morbidity from OSA is established. Main OSA symptoms are daily drowsiness, disrupted concentration and motivation, difficulties in routine tasks performances, irritability, decreased libido, chronic fatigue, inadequate rest, restless sleep, snoring, and nocturia. During desaturation episodes, organism is subject of chronic stress. These changes leads to increased frequency of occurrence of arterial hypertension, metabolic syndrome, diabetes mellitus type 2, and increased risk of brain-vascular damages. High-sensitivity-CRP (hsCRP) is relevant marker for inflammation in obstructive sleep apnoea patients.

Hepcidin-25 is amino-peptide that regulates iron homeostasis through its duodenal absorption. Hepcidins' main function is performed by its interaction to the only know intracellular iron exporter, named ferroportin. Increased hepcidin concentrations might be a risk of cardio-vascular disorders through iron mobilization in macrophages; iron turns them into atherogenic. Different studies shows role of hepcidin in atherogenesis in dialysis patients.

Homocysteine is exclusively formed from methionine (Met) through the transmethylation pathway. Elevated homocysteine is an independent, modifiable risk factor for atherosclerotic cardio-vascular diseases.

The aim of our study is to assess the connection between iron metabolism dysregulation in OSA and atherosclerotic changes of carotid arteries occurrence.

MATERIALS & METHODS

40 OSA patients with brain-vascular atherosclerotic evidences were included in this study; changes were evaluated by intima-media thickness (IMT) of a. carotis and flow-mediated dilatation (FMD), representing main part of non-invasive measurements of atherosclerosis (NIMA).

Their results were compared to equal number of healthy volunteers without OSA and atherosclerotic changes in carotid arteries.

Complete blood count (CBC), erythrocyte indices (MCV, MCH, MCHC), serum iron and total iron-binding capacity (TIBC), serum transferrin, ferritin and hepcidin were quantified for iron metabolism evaluation.

Homocysteine, hsCRP, vitamin B12, liver enzymes, Lactate dehydrogenase (LDH), fasting glucose and creatinine were measured in included OSA patients and control group.

For hematological, biochemical and immunological parameters analyzers by Siemens Healthineers Diagnostics were used. Hepcidin was quantified by previously validated ELISA method. Average age of included OSA patients was 41.3 ± 5.8 years; for the control group - 42.1 ± 6.1. The study sets on the ethical principles of the Helsinki declaration.

During statistical analysis established results were presented as average value ± SD for parametric distribution.

Pearson's correlation and paired t-test were used for evaluation of significance and correlation between values. Level of P<0.05 was considered as statistically significant.

RESULTS

Benchmarking of serum hepcidin concentration in OSA patients with atherosclerotic changes in carotid arteries **and healthy controls – expressed as average value (in µg/L) and standard deviation.**

	n	$\bar{X}$	± SD
OSA with ATH	40	121.7	11.9
Healthy controls	40	20.4	1.8

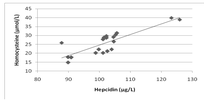
Benchmarking of serum biochemical parameters, IMT and ABI in OSA patients with atherosclerotic changes in carotid arteries **and healthy controls – expressed as average value and standard deviation.**

Group / Parameter	Controls	OSA with ATH	P
Iron (µmol/l)	17.7 ± 2.2	32.7 ± 8.5	P<0.001
Ferritin (ng/ml)	117.4 ± 5.9	279.4 ± 25.7	P<0.001
Homocysteine (µmol/l)	1.1 ± 0.3	29.1 ± 3.6	P<0.001
Vitamin B12 (pmol/l)	449.7 ± 21.4	71.7 ± 9.9	P<0.001
IMT	0.34 ± 0.07	1.22 ± 0.19	P<0.001
ABI	1.11 ± 0.06	1.71 ± 0.14	P<0.01

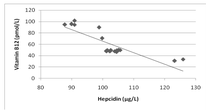
Evaluation of hepcidin is still a novelty in our routine practice although some studies show role of hepcidin in atherogenesis in OSA patients. Our findings contribute to clarification of hepcidin role in atherosclerotic changes in obstructive sleep apnea patients, and might be helpful in right therapeutic choice of accompanying metabolic distortions. We established increased serum hepcidin levels in OSA patients with atherosclerotic changes in carotid arteries (P<0.005). The connection between hepcidin concentration and hepcidin/ferritin ratio with presence of atherosclerotic plaques and ABI, confirms hepcidin role in atherosclerotic process. In our study we found significant positive correlation between serum hepcidin levels and ABI and IMT in OSA patients with atherosclerotic changes in carotid arteries (P<0.01 and P<0.05).

RESULTS

Correlation between serum hepcidin levels and homocysteine in OSA patients with atherosclerotic changes in carotid arteries – level of correlation r=0.902; significance P<0.005



Correlation between serum hepcidin levels and vitamin B12 in OSA patients with atherosclerotic changes in carotid arteries – level of correlation r=-0.911; significance P<0.005



SUMMARY/CONCLUSION

During desaturation episodes, organism is subject of chronic stress, which leads to decreased nitric oxide (NO) levels, increased interleukin-6 and tumour necrotic factor-α secretion. These changes lead to insulin resistance, arterial hypertension, metabolic syndrome, and others diseases occurrence, risk of brain-vascular damages increases.

hcCRP is a relevant marker for inflammation in OSA patients and our study proved it once again. Meta-analysis of 30 studies assessing the relationship between CRP and OSA confirmed that CRP was higher in OSA patients compared with controls (pooled mean difference 1.77). In the study of Shamsuzzaman et sl. 22 otherwise healthy OSA patients and 20 subjects matched for age and body mass index (BMI) without OSA were included. CRP levels were significantly higher among the former (0.33 versus 0.09 mg/d, $P < 0.0003$), and they were independently associated with disease severity. We established increased concentrations of hsCRP in OSA patients with atherosclerotic changes in carotid arteries compared to control group (P<0.001).

Several studies have reported that elevated plasma levels of total homocysteine are related to an increased risk of cardiovascular disease. In our study increased level of serum homocysteine was established in OSA patients with atherosclerotic changes in carotid arteries compared to control group; 1.1 µmol/l vs.29.1 µmol/l; P<0.001.

Vitamin B12 deficiency may increase the risk of carotid atherosclerosis by elevating total homocysteine. Serum vitamin B12 levels was decreased in OSA patients with atherosclerotic changes in carotid arteries compared to controls (449.7 pmol/l ± 21.4 vs. 71.7 pmol/l ± 9.9; P<0.001).

In our study NIMA parametres - IMT and ABI also was increased in OSA patients in comparison to healthy volunteers; P<0.001. Similar results were obtained from Szaboova and al. They found that IMT (max) was increased in subjects with mild to moderate OSA alone (AHI=20.4+/-8.7/h) versus healthy controls (0.83+/-0.14 mm versus 0.63+/-0.08 mm, p<0.01). Other authors reported similar results.