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Selected routine laboratory tests in the clinical assessment of patients with obstructive sleep apnea

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Abstract

Introduction, Obstructive sleep apnea (OSA) is a chronic disease characterized by repetitive complete or partial occlusion of the upper airways during sleep with respiratory muscle effort, which leads to consecutive apneas and hypopneas. Obstruction of the upper airways during sleep leads to repetitive episodes of disrupted airflow and consequent changes in blood oxygenation, resulting in hypoxaemia and hypercapnia. Intermittent hypoxaemia induces the production of pro-inflammatory factors and promotes metabolic dysregulation and platelet aggregation.

Objective. The main aim of this study was to determine differences, if any, in selected standard parameters in routine laboratory tests often used in GP practice between patients with obstructive sleep apnea, without comorbidities, and a well-defined control group with the absence of this syndrome proven in polygraphic examination.

Materials and method. Of the 192 clinically assessed persons with suspected OSA and admitted to the Internal Medicine Department in Lublin, 85 were qualified for the study after application of exclusion criteria. Demographic and health behaviour-related data, medical history regarding sleep habits and cardiovascular disease, were collected from each patient.

Results. Apart from significantly higher MCV and MCH among the cpontrol group, no significant differences were found between patients with obstructive sleep apnea and the control group.

Conclusions. The results can be useful for the holistic assessment of the health status of patients with newly-diagnosed OSA.

Key words

C-reactive protein, obstructive sleep apnea, fasting glucose, lipid profile, haematological parameters, NT-proBNP, hypoxia

INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic disease characterized by repetitive complete or partial occlusion of upper airways during sleep with respiratory muscle effort, which leads to consecutive apneas and hypopneas [1]. Latest reports showed that the prevalence of OSA in some countries exceeds 50% of the adult population and it is estimated that OSA affects almost 1 billion people worldwide [2]. The most common risk factor of OSA is obesity. Other risk factors include postmenopausal status among women, craniofacial dysmorphisms and advanced age [3]. Main symptoms are snoring at night, frequent awakening from sleep, followed by somnolence during the day, lack of ability to concentrate, and even mood disorders [4]. It is worth mentioning that OSA is a predisposing factor of hypertension, independently from other factors [5]. The risk of developing cardiovascular disorders, such as ischemic heart disease, heart failure, arrhythmia, stroke, and transient ischemic attack, is relatively high in patients with OSA [6, 7]. OSA may cause cognitive dysfunction as well as accelerate aging processes [8].

The Epworth Sleepiness Scale (ESS) is a questionnaire widely used to determine sleepiness among patients in clinical practice [9]. However, overnight polysomnography is considered to be the first choice diagnostic method in diagnosing obstructive sleep apnea, central sleep apnea, and sleep related hypoxia and hypoventilation [10]. The traditional polysomnogram (PSG) is a diagnostic procedure that consists of pulse oximetry, electroencephalogram, electrocardiogram, electrooculogram, electromyogram, airflow and respiratory effort monitoring. The classification of OSA severity depends on the apnea-hypopnea index (AHI), which is calculated during a diagnostic test. However, the full PSG is a time-consuming and complicated procedure. That is the reason for OSA being frequently diagnosed with more simplified methods, such as polygraphy, which measures the blood oxygen saturation, snoring, leg movements, respiratory effort and airflow [11]. The device measures the respiratory

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disturbance index (RDI), and according to the results, the severity of OSA is assessed.

Obstruction of the upper airways during sleep among patients with OSA leads to repetitive episodes of disrupted airflow, and consequent changes in blood oxygenation, resulting in hypoxaemia and hypercapnia. Intermittent hypoxaemia induces the production of pro-inflammatory factors and promotes metabolic dysregulation and platelet aggregation [12]. Moreover, hypoxia and consequent re-oxygenation induces reactive oxygen species (ROS) which react with different molecules, such as nucleic acids, proteins, and lipids leading to inflammation, cellular damage and DNA alterations [13, 14]. In the light of the facts mentioned above, the question arises whether, and if so, what changes in laboratory test results commonly used in primary care and GP practice may occur in patients with OSA, without additional medical circumstances that may affect the results.

OBJECTIVE

The main aim of this study was to determine differences, if any, in selected standard parameters in routine laboratory tests often used in GP practice between patients with obstructive sleep apnea, without comorbidities, and a well-defined control group with the absence of this syndrome proven in a polygraphic examination.

MATERIALS AND METHOD

Of the 192 clinically assessed persons with suspected OSA and admitted to the Internal Medicine Department in Lublin, 85 were qualified for the study after application of exclusion criteria. The study population consisted of 85 patients divided into a study group – 58 patients, and a control group – 27 patients with excluded OSA. Inclusion criteria were age between 35–65 years old, no comorbidities, except well controlled hypertension. Demographic and health behaviour-related data collected from each patient including age, gender, body mass index (BMI) (Tab. 1), and medical history regarding sleep habits and cardiovascular disease. Morning blood samples were drawn from patients after a 12- hour fasting period. The concentration of LDL cholesterol was calculated by using Friedwald equation, under the condition that triglycerides were below 400 mg/dl, with the formula:

$$\text{LDL (mg/dl)} = \text{TC (mg/dl)} - \text{HDL (mg/dl)} - \text{TG (mg/dl)}/5$$

Table 1. General characteristic of patients. BMI- body-mass index

	Research group (58)	Control group (27)	p
Age	52.7 ±9.5	48.2±7.5	0.09
Female (%/n)	24.1/14	33.3/9	0.63
Male (%/n)	75.9/44	66.7/18	0.44
Weight (kg)	95.8 ± 14.8	97 ± 15.1	0.81
BMI (kg/m2)	31.8 ± 4.3	33 ± 3.4	0.2

Simplified overnight unsupervised polygraphy (Dr Fenyves und Gut Deutschand GmbH) was performed in every case. Based on the apnoea-hypopnoea index (AHI), which is congenial to RDI, patients were grouped into 3 OSA severity categories: mild (AHI ≥ 5/h and <15/h, with accompanying clinical symptoms), moderate (AHI ≥ 15/h and <30/h), and severe (AHI ≥ 30/h). Patients with AHI <5 served as control group. Statistical analysis was conducted using Statistica 10 version. Data were introduced in the form of mean values, standard deviation, minimum and maximum values. Normal distribution of examined variables was tested using the Kolmogorov-Smirnov test. Variables with normal distribution were scanned with parametric tests, otherwise non-parametric tests were performed. The study protocol was approved by the local Ethics Committee, and all patients gave written informed consent to participate.

RESULTS

The vast majority of patients were men (75.9%). Mean BMI in study group was 31.8 ± 4.3 kg/m2, which shows that patients were overweight or obese.

The mean value of AHI among study group was 40.1 ± 21.6, which was significantly higher compared to the control group. The value of mean SpO2 among patients in the study group was 90.3 ± 3.4 %, which was significantly lower than in control group. The difference between AHI and SpO2 between the study and control groups were statistically significant. The vast majority of patients in study group (62.1%) had severe stage of OSA (Tab. 2).

Table 2. Comparison of mean SpO2 and AHI (apnea-hypopnea index) between study and control groups, and obstructive sleep apnea (OSA) severity categories among the studied groups

	Research group (58)	Control group (27)	p
AHI (/h)	40.1 ± 21.6	2.6 ± 1.7	<0.000001
Mean SpO2 (%)	90.3 ± 3.4	92.6 ± 1.9	0.002
OSA severity categories (n/%)	Mild – 9/15.5 Moderate – 13/22.4 Severe – 36/62.1	-	-

Peripheral blood count measurements showed significantly higher mean corpuscular volume (MCV) among the study group compared to controls (90.2 ± 4.3 vs 86.9 ± 3.9 fl) (p= 0.0005). Another parameter, which was elevated among study group compared to controls was mean cell haemoglobin (MCH) (30.5 ± 1.5 vs 29.8 ± 1.4 pg) (p=0.009). Other parameters of peripheral blood count did not significantly differ between the groups (Tab. 3).

Mean triglycerides concentration levels were similar in both groups and within the upper value of normal range. The remaining parameters, such as C-reactive protein (CRP), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), NT-proBNP and fasting glucose levels, did not significantly differ between the groups (Tab. 3).

DISCUSSION

Many recent studies have searched for the dependence between OSA and different complete blood cell count parameters. It has been investigated whether the severity of OSA correlates with the value of various parameters [15–18].

Table 3. Comparison of morphological and biochemical parameters among study and control groups

	Research group (58)	Control group (27)	p
RBC (T/l)	4.8 ± 0.4	4.8 ± 0.5	0.92
Hgb (g/dl)	14.6 ± 1.1	14.4 ± 1.5	0.37
Ht (%)	43.2 ± 3.3	42 ± 4	0.14
WBC (G/l)	6.5 ± 1.4	6.8 ± 1.3	0,2
PLT (G/l)	245.7 ± 60.8	254.4 ± 58.4	0.35
MCV (fl)	90.2 ± 4.3	86.9 ± 3.9	0.0005
MCH (pg)	30.5 ± 1.5	29.8 ± 1.4	0.009
MCHC (g/dl)	34 ± 1.3	34.1 ± 1.1	0.91
CRP (mg/l)	2.6 ± 1.9	3.1 ± 1.8	0.16
Total cholesterol (mg/dl)	196.3 ± 41.7	190.7 ± 41.3	0.56
LDL-C (mg/dl)	117.4 ± 39	121 ± 36.8	0.69
HDL-C(mg/dl)	45.4 ± 13.2	44.7 ± 10.9	0.8
Triglycerides (mg/dl)	163.4 ± 62	142.8 ± 65	0.12
Glucose (mg/dl)	87.4 ± 7.9	86 ± 5.8	0.21
NT-proBNP (pg/ml)	104.8 ± 81.3	78.1 ± 56	0.22

RBC- red blood cells; Hgb- haemoglobin; Ht- haematocrit; WBC- white blood cells; PLT- platelets; MCV- mean cell volume; MCH – mean cell haemoglobin; MCHC – mean corpuscular haemoglobin concentration; CRP – C-reactive protein; LDL – C low-density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; NT-proBNP – N-terminal pro B-type natriuretic peptide.

In the current study, there were no differences in haematocrit and haemoglobin levels in OSA patients, compared to the control group. Literature data are contradictory in this respect. According to Cummins et al., the haemoglobin and haematocrit levels were significantly higher among patients with severe OSA compared to those without OSA, although in every group, values stayed within the normal range [19]. Moreover, the haemoglobin and haematocrit levels were negatively correlated with mean SpO2 as a result of hypoxia, which stimulates the production of erythropoietin and consequent increased erythrocytes production [20]. On the other hand, Ozsu et al. reported that there was no significant difference in haemoglobin levels between OSA and non-OSA patients [21].

In the presented study, the value of MCV and MCH were significantly higher among patients with OSA than among the control group, while the MCHC did not differ between groups. There are only a few data sources which describe the dependence between OSA severity and such parameters as MCV, MCH, or MCHC. There is also a possible influence of other medical conditions which have an impact on red blood cell parameters, such as alcohol intake, and vitamin deficiency [22]. Morell-Garcia et al. reported that parameters such as MCHC significantly differed between moderate and severe OSA groups; thus, this parameter could be used as a marker of severe OSA [23]. However, the study was performed among children with OSA and its comparison with the current study with adults, is therefore limited. Moreover, Cummins et al. reported an inverse correlation between mean SpO2, AHI, and MCV among patients with severe OSA, suggesting that hypoxia among OSA patients induces erythropoiesis and consequent changes in red blood cells parameters, such as MCV [19]. Red blood cell distribution width (RDW) is a measurement, which shows the variability of red blood cells (RBC) circulating in the bloodstream. Medical conditions which influence erythropoiesis or haemolysis are responsible for the heterogeneity of RBC and consequent changes in RDW [24]. Gunbatar et al. presented that there were no significant differences between OSA patients and the control group in RDW values [25]; however, Ozsu et al. presented significantly higher RDW values among OSA patients than in the control group (13.6% vs. 12.9 %) [21], and RDW positively correlated with mean SpO2 [16]. Some data present that the RDW value is correlated with the severity of OSA measured by AHI [18].

In the current study, there was no significant difference in platelet count between the obstructive sleep apnea group and the control group. However, it is reported in many surveys that the increased platelets activation and aggregation are present among patients with OSA [26, 27]. In addition, the greater the platelets activatio, the greater their volume; thus, the mean platelet volume (MPV) and the platelet distribution width (PDW) constitute an easy to check parameter to indirectly assess platelets function. Moreover, larger platelets are more predisposed to aggregate than the smaller ones [28]. According to Fan et al., the MPV and PDW values were correlated with the severity of OSA, assessed with AHI [29]. This has also been confirmed in other studies in which MPV was significantly higher among severe OSA patients, compared to controls and mild and moderate OSA [26, 30]. On the contrary, according to a few studies, the MPV and PDW are not good parameters to assess the OSA severity, while the different shape and volume of platelets are also present among healthy individuals, and the bigger platelets did not show the higher aggregation features in the aggregometer [31].

In this study, no significant differences were observed in the number of peripheral blood leukocytes, depending on the occurrence of OSA. However, the literature in this area is not unambiguous. The most numerous subgroup of leukocytes are the neutrophils, which play an essential role in the first line defence in the inflammation process. They are responsible for proteolytic enzymes and reactive oxygen species production, macrophages activation and inflammatory leukotrienes release [32]. The activity of neutrophils contributes to endothelial dysfunction via various mechanisms, such as increased vascular penetrability caused by ROS, foam cell formation by macrophages activation, and consequent plaques aggregation [33]. According to Geovanini et al., OSA is reported to increase concentration of the neutrophils, with no changes in total WBC count [34]. Fan et al. confirmed the observation that OSA is connected with increased neutrophils level, thus increased an inflammatory state [29]. In addition, the neutrophil count is associated with increased risk of myocardial infarction, heart failure and increased mortality, which confirms the statement that patients with OSA are more predisposed to have cardiovascular disease [35].

However, there are also some reports which present the opposite view, that the concentration of neutrophils does not differ in patients with OSA compared to the healthy population [36, 37]. Interestingly, the increased level of neutrophils has also been found in the sputum of patients with OSA, which confirms the existence of a general increased inflammation state among these patients, including their bronchial tree [38].

Lymphocytes are essential in maintaining the immune defence mechanisms against pathogens. What is more, lymphocytes play an important role in controlling the immune responses, and the disorders in lymphocytes

differentiation are the background of autoimmune diseases, allergic inflammation and cancer development [39, 40]. Lange et al. reported that OSA is connected with enhanced levels of lymphocytes [41]. In addition, there is a positive dependence between the severity of OSA and the level of lymphocytes circulating in the bloodstream [29]. Moreover, OSA has an influence not only on the number of lymphocytes, but also on their differentiation. According to Tan et al., sleep deprivation, which is the basis of OSA pathogenesis, alters lymphocytes Treg function, which induces the endothelial damage and dysfunction and contributes to enhanced cardiovascular diseases risk [42]. The confirmation that sleep fragmentation among OSA patients is responsible for disturbances in lymphocytes number and function may be the fact that implementation of 6-month CPAP treatment decreases the circulating lymphocytes level in patients with OSA [43].

It is reported that eosinophil and basophil levels are enhanced among patients with OSA [19, 29]. Some reports show that asthma, which is the medical condition connected with increased levels of the above-mentioned leukocytes, is commonly present among patients with OSA [44]. Patients with asthma and coexisting obesity are more likely to develop OSA in the future [45]. Moreover, according to some studies, the more severe the asthma, the greater the risk of OSA [46, 47]; Auckley et al., however, presented the opposite point of view [48]. In spite of an enhanced level of basophils, Cummins et al. did not confirm a dependence between asthma and severity of OSA, explaining that the increased level of this subgroup of leukocytes could be a potential effect of rhinitis or dyslipidaemia [49, 50].

Elevation of the monocyte level is present among patients with OSA [29]. Interestingly, the intermittent hypoxia present among patients with OSA upregulates the gene expression of monocyte chemoattractant protein-1 (MCP-1), which is a chemokine located in macrophage-rich atherosclerotic plaque [51]. The connection between the MCP-1 and its receptor results in adhesion and spreading of the monocytes, thus OSA is connected with greater risk of atherosclerosis development.

C-reactive protein is a marker of inflammation which is reported to be elevated among patients with OSA. Moreover, there is a positive correlation between CRP and parameters used as a diagnostic tool in OSA screening tests, such as AHI and SpO2 [52]. In addition, obesity, which commonly coexists among patients with OSA, is related to elevated CRP serum levels, independently from OSA [53]. However, after correction for BMI, data indicates a significant difference in the serum level of CRP in patients without OSA, compared to severe OSA individuals [52]. Contrary to this observation, however, no significant OSA-dependent CRP elevation was observed in the current study.

In the light of the literature, there is an association between OSA and altered lipid profile and lipid metabolism, leading to an enhanced level of lipids in the bloodstream [54]. In the current study, there were no significant differences between the study and control groups; however, the level of triglycerides was in the upper range of normal. According to the literature, triglycerides are mainly stored in adipocytes, and hydrolyzed to free fatty acids by adipocyte triglyceride lipase (ATGL) [55]. The mentioned reactions are altered among patients with OSA: oxidative stress increases activation of ATGL, resulting in an increased level of free fatty acids in the bloodstream [56]. Moreover, intermittent hypoxia, which is a stress factor for the organism, stimulates the adrenal gland with consequent noradrenaline and cortisol release, which also stimulates lipolysis [57]. In addition, the circulating HDL-C level is reported to be decreased among patients with OSA [58, 59]. However, Kollar et al. reported no significant HDL-C level differences between OSA and non-OSA patients [60]. Moreover, in another study, severe OSA induced dysfunction of HDL more than changes in its concentration [61]. These observations, indicating no simple relationship between OSA and lipids, are consistent with the findings of the presented study.

The results of the current study do not indicate an OSA-dependent increase in fasting glucose level. However, according to the literature, OSA is connected with the increased risk of impairment in glucose metabolism, which could result in diabetes development in the future [62]. According to Kim et al., the impact of OSA is more obvious among non-obese patients than in the obese group [63]. Among OSA patients, both the impaired fasting glucose and impaired glucose tolerance are present [64]. Interestingly, the intermittent hypoxia, consequent ROS production and activation of the sympathetic nervous system, induce the fluctuations of blood glucose level among patients with OSA, even with normal glucose metabolism [65]. According to studies performed on animal models, hypoxia induces glycolysis and glycogenolysis with consequent elevation of blood glucose concentration [66]. There is correlation between AHI and glycaemic variability [67]. According to Saito et al., the glycaemic variability is more dependent on the time during sleep spent in hypoxemia (SpO2<90%), rather than on AHI [68]. Even 1-week CPAP treatment implementation significantly improved the glycaemic variability [66].

N-terminal-proBNP (NT-proBNP) is an endogenous peptide hormone which is released from cardiac cells due to increased cardiac wall stress or myocardial ischemia [68]. The assessment of NT-proBNP level in patients with OSA is ambiguous, as this biomarker is reported to be elevated also due to non-cardiac factors, such as age, gender, BMI, and kidney function [69]. Most of the reports, which were conducted among patients with OSA and without cardiac diseases, did not confirm correlation between NT-proBNP and severity of OSA, and the concentration of NT-proBNP was relatively low [70, 71, 72]. This is in line with the results of the current study. However, according to Ljunggren et al., there is one study in which the correlation between enhanced level of BNP and OSA severity was confirmed [73]. The surveys were performed among non-obese patients, thus the effect of OSA on cardiac biomarkers was much clearer. Another study, which did not confirm the effect of OSA on NT-proBNP, was performed among obese individuals, thus the possible BNP-lowering effect of obesity could be present in these reports.

Limitations of the study. There are some limitations which could have an impact on the interpretation of obtained results. 1) The patients in the research group were slightly older than in the control group, but this was not statistically significant. 2) The research group was relatively small. Both factors could therefore have an effect on the statistical analysis; thus, further study on a wider research group should be considered in the future

CONCLUSIONS

Hypoxia in a well-defined group of patients with obstructive sleep apnea without comorbidities is associated with a significantly higher mean red blood cell volume, and mean corpuscular haemoglobin level, but does not affect the lipid profile, C-reactive protein, fasting glucose and NT-pro BNP levels. Hence, an increase in red blood cell volume of unclear origin may be the result of undiagnosed obstructive sleep apnea. There are still only a few data available about the influence of OSA on routine laboratory tests often performed in general practice circumstances; thus, further studies should be undertaken.

Institutional Review Board Statement. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University in Lublin, Poland (Protocol No. KE-0254/115/2012, dated 31 May 2012). Informed consent was obtained from all subjects involved in the study.

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