Study of Haematocrit Level in Obstructive Sleep Apnea Syndrome

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Abstract

Obstructive Sleep Apnea Syndrome can lead to oxyhaemoglobin desaturation and has the possibility of stimulating erythropoiesis, leading to an increased haematocrit (HCT). The aim of this study is to identify the level of HCT in obstructive sleep apnea syndrome (OSAS) patients and to determine the correlation between HCT levels and the severity of obstructive sleep apnea syndrome (OSAS). This is a cross-sectional study at Hospital Universiti Sains Malaysia. All consented patients were interviewed and underwent a polysomnography (PSG) study. The severity of OSAS was based on the apnea–hypopnea index (AHI) and average oxygen desaturation. The blood HCT level was also obtained. Thirty-six OSAS patients were in the study group, and 17 patients were in the control group. The mean HCT level in the control group was 41.6 (2.5 SD), whereas in the study group the mean HCT level was 44.0 (3.27 SD). Pearson correlation analysis showed there was weak correlation between AHI and HCT level (p-value: 0.392), however, there was a fair correlation between HCT levels and average oxygen saturation level (P-value: 0.022). The independent t-test between mean HCT level between OSAS group and control group showed that there was a significant difference between the mean HCT level among the control and OSAS groups. The increased level of HCT is significantly correlated with average oxygen desaturation but not with AHI in OSAS patient. Average oxygen desaturation can be considered as a parameter to assess severity and hypoxic stress in OSAS patients.

Keywords
Obstructive sleep apnea syndrome, HCT, Apnea-hypopnea Index, oxygen desaturation

Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is characterised by repetitive upper airway obstruction during sleep and associated with intermittent hypoxic stress, characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, leading to intermittent hypoxia and sleep fragmentation [1]. The prevalence of OSAS varies depending on the population being studied. According to recent references, the prevalence of OSAS in the general population is approximately 13% for men and 6% for women [2]. In OSAS middle-aged men and women, the prevalence was 57.7% and 41.7% respectively [3].
OSAS is strongly related to cardiovascular disease, which comprises pulmonary hypertension (20–30%), coronary heart disease (20–30%), congestive heart disease (5–10%), systemic arterial hypertension (40–60%), and cardiac arrhythmia (50–60%) [4,5]. OSAS patients have prolonged upper airway collapse, resulting in a reduction in their oxygen saturation level while the carbon dioxide level in their lungs rises. This condition can lead to oxyhaemoglobin desaturation and has the possibility of stimulating erythropoiesis, leading to an increase in haematocrit (HCT). High HCT levels are associated with the incidence of hypertension regardless of other risk factors in men [6]. The pathogenesis of HCT increments in OSAS contributing to hypertension is not fully understood but several mechanisms have been proposed. Among the mechanism proposed is that patients with OSAS demonstrate cyclical increases in pulmonary arterial pressure coinciding with apnoeic episodes, which has been largely attributed to acute hypoxic pulmonary vasoconstriction (HPV). Intermittent hypoxia (IH) causes oxidative stress which in turn increases endothelin-1 (ET-1) and angiotensin II (Ang II), which plays a role in the increased blood pressure [7]. This study was aimed at identifying the level of HCT in OSAS patients and determining the correlation between HCT levels and the severity of obstructive sleep apnea syndrome (OSAS) based on an apnea-hypopnea index (AHI) and average oxygen desaturation level on polysomnography. Apnea is the complete absence of airflow through the nose and mouth during sleep, whereas hypopnea is a partial collapse of the airway, leading to limited breathing during sleep. The AHI is an index used to indicate the severity of sleep apnea. It represents the average number of apnea and hypopnea events per hour of sleep. The AHI is calculated by dividing the number of apnea and hypopnea events by the number of hours of sleep.

This study on the HCT level in OSAS could provide insights into the pathogenesis of hypertension in OSAS and the effectiveness of CPAP treatment in reducing HCT levels. Additionally, such a study could help identify the potential biomarkers for the diagnosis and management of OSAS.

Methodology
This is a cross-sectional study of patients attending the Sleep Clinic at the Hospital Universiti Sains Malaysia, from 2015 to 2016. Only male patients were recruited for the study, as no female patients were available to participate for unclear reasons. The sampling method used was convenience sampling where all patients who fulfilled the inclusion criteria over the study period were included in the study.

Sample size was designed and calculated according to the objectives of the study. Each variable was tested individually using their means and standard deviations from reference [8]. To compare the HCT level in obstructive sleep apnea patient and non-obstructive sleep apnea patient, based on the calculation and after considering all aspects of the study, the number of subjects was 17 (14 plus 10% drop-out) for each group. In determining the relation of HCT level with apnea/hypopnea index (AHI) from polysomnography in obstructive sleep apnea patient and the relation of HCT level with average oxygen desaturation from polysomnography in obstructive sleep apnea patient, the calculation uses Pearson Correlation to estimate the sample size, whereby the number of subjects was 36 (n=29.0123 ~ 30 + 10% drop out) [8]. Sample size was determined based on comparison of two mean using Power and Sample Size Calculation Software version 3.1.6 with parameters of level of significance of 0.05, power of 80%, ratio of 0.5, SD of 0.05 and expected difference of mean of 0.042. The minimum required sample size with 10% dropout was 58 [8, 9].

The inclusion criteria were male patients aged 18 to 60 who had symptoms of OSA. Patients with underlying medical illness that has the possibility of interfering with the HCT level, such as chronic renal failure, chronic liver failure, anaemia, chronic lung disease, malignancy, malnutrition, a previous major operation, or smoking, were excluded from the study. The consented patients were interviewed, and demographic data such as body mass index (BMI) and blood pressure were collected. The WHO classification of BMI was used to diagnose and assess the severity of obesity. The subjects were then categorized into underweight (BMI 18.5 kg/m²), normal (18.5 kg/m²-24.9 kg/m²), preobese (25 kg/m²-29.9 kg/m²), obese (30 kg/m²-
34.9 kg/m²), and morbidly obese (> 35 kg/m²). The patients’ blood HCT level was obtained and all of them were subjected to overnight polysomnography. Based on the polysomnography results, the patients will be divided into two groups. The patients with an apnea-hypopnea index greater than 5 will be in the OSAS group, while those with an index less than 5 will be in the control group. The severity of OSAS was based on AHI and average oxygen desaturation. The study protocol was reviewed and approved by Research Ethics Committee (Human), Universiti Sains Malaysia (Reference no. USMKK/PPP/JEPeM 232.3[02]).

Data entry and all analyses were performed with SPSS version 22.0 software. A descriptive analysis was performed, in which categorical variables were presented as frequencies (percentages), while numerical variables were presented as mean standard deviation (SD). For the independent t, the dependent variables are HCT, and the independent variables is OSAS group. As for the correlation, all tested variables are dependent variables. Independent sample t test was used to compare mean the HCT level between OSAS group and non-OSAS group. Pearson’ correlation to determine the correlation of HCT with age, BMI, SBP, DBP, AHI and average oxygen desaturation.

Results
A total of 53 male patients were included in this study, with 36 OSAS patients in the study group and 17 patients in the control group. The mean (SD) age in the OSAS group was 40.97 (11.27) years old, and in the control group, it was 36.65 (12.01) years old. The mean (SD) BMI in the OSAS group was 31.38 (3.51), and for the control group it was 27.17 (2.29) (Table 1). The frequency of hypertension in the OSAS group was 22.2%, and none of the participants in the control group were hypertensive. Out of 36 OSAS patients, 75.0% were diagnosed as having severe OSAS, 19.4% had moderate OSAS, and about 5.6% had mild OSAS. The mean (SD)O₂ desaturation was 9.15 (4.29) in the OSA group.

The mean (SD) HCT level in the control group was 41.59 (2.53), whereas in the study group the mean HCT level was 44.04 (3.27 SD). (Table 2). Pearson correlation analysis showed a significant fair correlation between HCT levels and average oxygen desaturation level with the coefficient value ($r$) = 0.30, and the $p$-value =0.022 (Table 3), however the correlation between AHI and HCT level with the coefficient value ($r$) = 0.15 showed a weak correlation and $p$-value of 0.392 (Table 3).

The mean HCT level in OSAS is higher compared to the mean HCT in the control group. The independent t-test between mean HCT level between OSAS group and control group showed that there is a significant difference between the mean HCT level among control and OSAS group with the $p$-value of 0.029. There was no or weak correlation of HCT level with age, BMI, SBP, DBP and lowest oxygen saturation n (Table 3).

Discussion
The mean age of the OSAS group is higher compared to the control group. The prevalence of OSA increases with age in adults which is similar to our study [10]. This age-related increase in prevalence may be attributable to parapharyngeal fat deposition, lengthening of the soft palate, and changes in other anatomic parapharyngeal structures [11]. According to Santaolalla et al., the risk of developing OSA increases 3.8 times in the older group (> 52 years old) compared to the younger age group [12].

BMI
The mean BMI in the OSAS group was higher compared to the control group. (Table 1) A study by Jehan et al., concluded that a higher BMI is associated with a higher risk of OSAS in patients [13]. Lopez et al. found that the prevalence of OSA in the severely obese group (BMI 35–39.9 kg/m²) was 71 % and the incidence of OSA in patients that came for weight loss surgery was more than 70% [14]. A systematic review and meta-analysis concluded that OSAS patients with higher BMI and obesity have an increased risk of developing resistant hypertension. Another study compared individuals with mild to moderate OSAS to those with
severe OSAS and found that individuals with severe OSAS had higher BMI and respiratory-disturbance scores. \[15,16\]. Overall, these studies suggest that higher BMI is associated with an increased risk of OSAS.

**Hypertension**

The prevalence of hypertension in the OSAS group varies according to different studies. Patel et al., showed that the prevalence of hypertension in OSAS patients is estimated to be between 30% and 70%, whereas Khamsai et al., showed that the average prevalence of OSAS in cases of hypertension is around 50% \[17,18\]. However, it is important to note that the prevalence can vary depending on the population studied and the criteria used to diagnose OSAS as seen in a study in Japan that showed a lower prevalence of hypertension with OSAS which was around 10%, and from an epidemiological study by Karim et al., that show prevalence of OSA in patients with hypertension varies from 14% to 75% \[19,20\]. In this study, the prevalence of hypertension in the OSAS group was 22.2% and none in the control group. Recent evidence supports the notion that OSA represents the most prevalent secondary contributor to elevated blood pressure (BP) in patients with resistant hypertension \[13,21\]. Previously published population-based studies identified an independent correlation between a greater AHI and increasing BP, both at baseline and when measured over long-term follow-up \[21\]. The prevalence levels for hypertension were 36.5%, 46%, and 53.6% in subjects with mild, moderate, and severe OSAS, respectively \[23\]. Severe OSAS patients were more associated with co-morbid diseases \[24,25,26,27\]. From the results, most of the patients in the OSAS group were in a severe level (AHI > 30).

**Haematocrit level**

OSAS is characterised by recurrent, transient hypoxemia. It is thought that this mechanism can lead to hypoxic stress. Hypoxic stress is frequently associated with erythrocytosis and increased HCT levels. In this study, the HCT level was higher in the OSAS group compared to the control group. A study by Choi et al. also found that the HCT level is higher in severe OSAS patients as compared to mild, moderate, or non-OSAS patients \[28\]. The higher level of HCT in OSAS patients can be due to erythropoiesis, which is driven by oxygen desaturation, a situation found in people living at high altitudes or in patients with severe Chronic Obstructive Pulmonary Disease (COPD) \[29,30\]. It had been recently reported that erythropoiesis increased only in patients with severe OSAS \[31\]. Thus, erythropoiesis could be playing a role in the higher HCT level seen in severe OSAS, which is supported by Zhang et al., that noted a significantly higher erythropoiesis levels found in patients with body mass index <30 kg/m2, cardiovascular complications and in sleep apnea patients \[32\]. From our study, the HCT level did not significantly correlate with AHI, even though the HCT level was high in the OSAS group. There was a possibility that the hypoxic stress effect was likely modified by other factors, which were not controlled in this study. Even though AHI is used to assess the severity of OSAS, it does not indicate the percentage of oxygen desaturation events. Apnea and hypopnea are not always associated with oxygen desaturation \[33\]. A study by Rosa et al., found that compared to the AHI, pulse oximetry had lower sensitivity and specificity in diagnosing OSAS \[34\]. There was a significant association between oxygen desaturation and HCT levels, such as study by Martelli et al, which found a relationship between HCT level and nocturnal oxygen desaturation \[30\].

Our study did not directly investigate the erythropoiesis mechanism responsible for increased HCT levels in OSAS. Serum erythropoietin could serve as a more informative parameter in this context. Another limitation is the exclusion of patients with lung diseases based solely on history and physical examination, without conducting pulmonary function tests. However, none of the subjects had an awake resting oxygen saturation below 90%, reducing the likelihood of significant, severe, and silent lung disease coexistence. Furthermore, the study population being predominantly Malay hinders the generalization of results to the wider multi-ethnic population in Malaysia. The study should be conducted in the larger size of both OSAS and non-OSAS population so that we can compare the accurate value of variables and parameter.
Conclusion

HCT levels hold potential as an additional tool for managing OSAS, offering early detection and risk assessment. Tracking changes in HCT levels can help gauge the effectiveness of treatments, particularly weight loss. The increased level of HCT is significantly correlated with average oxygen desaturation but not with AHI in OSAS patients. Average oxygen desaturation can be considered a parameter to assess severity and hypoxic stress in OSA patients.

Declaration of Competing Interests

This research was held by the author cost and there was no relevant conflict of interest in this research.

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