DOI: 10.7860/JCDR/2020/43021.13450

Original Article

Pathology Section

Study to Evaluate the Role of Inflammatory Biomarker- IL-6 in Obstructive Sleep Apnea in Correlation with Apnea-Hypopnea Index

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ABSTRACT

Introduction: Many biomarkers are associated with the Apnea-Hypopnea Index (AHI) in the majority of the studies, but most of the explored approaches were not able to identify definitive biomarkers of Obstructive Sleep Apnea (OSA) morbidity.

Aim: To evaluate the correlation of AHI with inflammatory biomarker-Interleukin-6 (IL-6).

Materials and Methods: Adult patients above 18 years of age, and suffering from OSA or had history suggestive of OSA were included in the study. IL-6 was measured by ELISA kit and immunoassay equipment. Polysomnography (PSG) study was done which included sleep stages, Heart rhythm monitoring, Leg movements recording, Breathing monitoring. Obstructive apnea was taken as cessation of airflow for at least 10 seconds with persistent respiratory effort. Descriptive statistical methods were used such as computing percentage, mean, standard deviation, pivot tables, and correlation.

Results: A total number of 46 patients with OSA were evaluated. Out of 46 patients, 9 (19.57%), 6 (13.04%) and 31 (67.39%) patients belonged into mild, moderate and severe AHI, respectively. ELISA for IL-6 was done in 41 patients. The value ranged from 20.92 to 4145.23 pg/mL with SD±1769.32 and with mean of 1427.94. Average values of biomarker IL-6 was 675.26 pg/mL, 1261.19 pg/mL, 1658.58 pg/mL in mild, moderate and severe OSA respectively. There was a positive correlation between AHI severity and IL-6 with correlation value.

Conclusion: In this study, IL-6 appeared to exhibit a favourable profile for a biomarker aiming to discriminate OSA in adult patients. However more large scale studies are required to establish a definitive correlation between OSA and IL-6.

Keywords: Enzyme linked immunosorbent assay, Inflammation, Polysomnography

INTRODUCTION

An OSA is by far the most common sleep disorder and estimated to occur in 34% of men and 17% of women, afflicting more than 100 million adults worldwide [1-3]. It involves a reduce or complete halt in airflow due to collapse of upper airways during sleep. Moreover, OSA is a well-known risk factor for work related and motor vehicle accidents and when left untreated, it has been associated with increased health morbidity, and mood deficits that reduces the work efficiency and productivity. Consequently, healthcare costs are substantially increased for patients with OSA, accounting either directly or via its associated morbidities for a considerable proportion of all medical related expenses. To prevent the health consequences of OSA, early identification and optimal treatment of OSA is necessary. Currently, the role of co-morbidities in OSA is a major topic in clinical research as is shown by the rising number of publications on this subject [4,5]. Several recent epidemiologic studies reported a high prevalence of co-morbidities in OSA, some more prevalent than the others [6-9]. The severity of OSA is most often reported in terms of AHI. A patient diagnosed with OSA should have AHI more than five episodes per hour of cessation of breathing for at least 10 seconds on overnight PSG. The severity of sleep apnoea is categorised as Mild OSAS: 5<AHI<15, Moderate OSAS: 15<AHI<30 and Severe OSAS: AHI >30. Oxygen desaturation accompanying apneic events, negative intrathoracic pressure, arousals induced by upper airway obstruction and repeated activation of the sympathetic system may cause abnormal activation of neural, hormonal, thrombotic, metabolic, and inflammatory responses [10,11]. The potential aetiological mechanisms may include endothelial dysfunction, oxidative stress, inflammation, and disorders of coagulation and lipid metabolism [12]. Throughout the most recent 14 years, a few diverse OSA biomarkers have been proposed. Despite the fact that the legitimacy of biomarkers in the determination of OSA stays vague, however in grown-ups IL-6 appears to have a positive potential to turn into a decent biomarker to distinguish OSA [13]. So, present study was conducted to evaluate the correlation of AHI with Inflammatory biomarker- IL-6.

MATERIALS AND METHODS

Present cross-sectional study was carried out from 1st October 2017 to 31st March 2019 (18 Months) at the Department of Respiratory Medicine in collaboration of Department of Pathology at Institute of Medical Sciences, Banaras Hindu University, after getting approval from the ethical committee (IEC- Dean/2017/EC/204).

Inclusion Criteria

Patients willing and able to participate in the study, adult patients above 18 years of age, and suffering from OSA or had history suggestive of OSA were included in the study.

Exclusion Criteria

Unstable medical or psychiatric conditions that would interfere in performing the study. Chronic respiratory failure or insufficiency, recent myocardial infarction, exacerbation of obstructive airway diseases, Patients having a history of upper airway surgery, disorders of a craniofacial abnormality like Marfan's syndrome, Down's syndrome, Pierre-Robin syndrome.

Detailed history and physical examination with special attention to risk factors of OSA was done. Patients' height, weight, neck

circumference, neck length, abdominal and waist circumference were measured. Body Mass Index (BMI)- BMI >30 kg/m^2 was considered as obese. Neck Circumference (NC) >37 cm in men and >34 cm in women was set as the upper limit of overweight/obesity. Neck Length (NL) or Mentohyoid distance of less than 3 finger-width was considered as a strong association with OSA. Abdominal Circumference (AC) and Waist Circumference (WC): AC in Men: >102 cm; in Women: >88 cm taken as central obesity. WC Men: ≥90 cm; women: ≥80 cm and Waist Height Ratio (WHtR) 0.5 was taken as a cut-off for central obesity. Blood tests-Haematocrit, Glucose Fasting and Post-prandial, Lipid Profile-cholesterol, triglycerides, DHL, LDL, VLDL Thyrotropin (TSH), ELISA for IL-6 Normal range of haematocrit - 45% to 52% for men and 37% to 48% for women. Patients with blood glucose ≥110 mg/dL were considered diabetic. Patients with normal sugar values on medication were taken as a diabetic patient. Patients with triglycerides ≥150 mg/dL and HDL cholesterol <40 mg/dL in men and <50 mg/dL in ladies were delegated patient of dyslipidaemia. Diagnosis of metabolic syndrome was made in the presence of at least 3 of the 5 significant clinical signs i.e., Obesity, Hypertension, Diabetes mellitus, Hypertriglyceridaemia, Hypercholesterolaemia. IL-6 was measured by ELISA kit (Immunoshop India Pvt., Ltd.,) and immunoassay equipment. PSG study was done which included sleep stages, Heart rhythm monitoring, Leg movements recording, Breathing monitoring. Obstructive apnea was taken as cessation of airflow for at least 10 seconds with persistent respiratory effort. Following parameter were noted- AHI - Categorised as Mild OSAS: 5<AHI<15, Moderate OSAS: 15<AHI<30 and Severe OSAS: AHI >30.

STATISTICAL ANALYSIS

Data collected for the sample was analysed using Microsoft Excel 2016. In present study, we used descriptive statistical methods such as computing percentage, mean, standard deviation, pivot tables, and correlation. SPSS Inc. (233 South Wacker Drive, 11th Floor Chicago, IL 60606-6412) software was used and appropriate tests were employed for categorical, parametric or non-parametric data. Wherever necessary, the results of the study are depicted in the form of charts, tables, graphs and percentages.

RESULTS

A total number of 46 patients with OSA were evaluated, out of which 21 (46%) were females and 25 (54%) were males. Maximum number of male 7 (15%) and female 10 (22%) patients belonged to age group 50-59 and 60-69 years, respectively [Table/Fig-1]. The study showed that the average age of female and male patients was almost similar (58.8 yrs. Vs. 58 yrs.). In the study, 24% of males were smokers followed by the history of alcohol intake and tobacco chewing in 8% each. No female patient was having a history of smoking or tobacco chewing but 38% of females was exposed to biomass/kerosene fuel smoke at home. The severity of OSA was divided into Mild, Moderate and Severe AHI according to the number of apnoea episodes/hr. on Polysomnography (PSG) study. Mild, Moderate and Severe AHI is shown in [Table/Fig-2]. Due to financial issue, ELISA for IL-6 (Inflammatory Biomarker) was done in 41 patients only. The value ranged from 20.92 to 4145.23 pg/mL with SD±1769.32 pg/mL and Mean of 1427.94 pg/mL [Table/Fig-3,4]. Average values of biomarker IL-6 was estimated 675.26 pg/mL in mild OSA, 1261.19 pg/mL in Moderate ODA and 1658.58 pg/mL in severe OSA. There was a Positive correlation between AHI severity and IL-6 with Correlation Value (CV) of +0.369867430051592, means if the severity of OSA increases the IL-6 value will also increase and vice versa. It is also represented in [Table/Fig-5].

DISCUSSION

OSA is characterised by a recurrent partial or complete collapse of upper airways during sleep. In a survey from northern part of India, the prevalence of OSA Syndrome is estimated as 3.6% and separately for males and females it was 4.9% and 2.1%, respectively [14]. In this study, we included 21 (46%) female and 25 (54%) male patients who clinically had symptoms suggestive of OSA and underwent PSG to access severity of AHI. Present study showed that the average age of female and male patients was almost similar (58.8 yrs vs. 58 yrs), which was higher as compared to other study. The sex distribution of the patients was similar in the both studies [15].

Patients with OSAS are always exposed to intermittent hypoxia and re-oxygenation from the cycles of apnoea/arousals. It is suggested that sustained hypoxia leads to oxidative stress and activation of a systemic inflammatory response with increase in general blood antioxidant activity and in production of pro-inflammatory cytokines, including Tumour Necrosis Factor TNF-α

	Age (years)													
	30-39		40-49		50-59		60-69		70-79		80-89		Total %	Total No.
Sex	%	No	%	No	%	No	%	No	%	No	%	No		
Female	2%	1	2%	1	20%	9	22%	10	0%	0	0%	0	46%	21
Male	4%	2	11%	5	15%	7	11%	5	7%	3	7%	3	54%	25
Grand total	7%	3	13%	6	35%	16	33%	15	7%	3	7%	3	100%	46

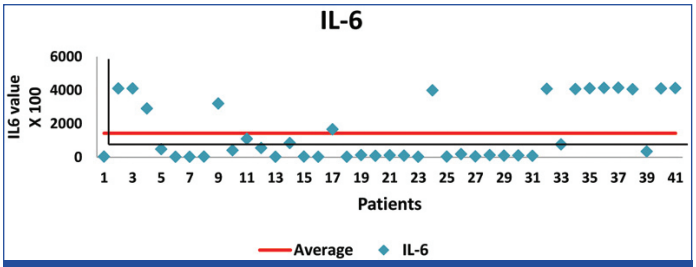
[Table/Fig-1]: Age-Sex distribution of patients with OSA.

AHI grade		
Mild (5<AHI<15)	9	19.57%
Moderate (15<AHI<30)	6	13.04%
Severe (AHI>30)	31	67.39%
Grand total	46	100%
AHI		
Mean	44.3	
Median	41.3	
Mode	80.4	
Standard deviation	26.9	
Range	90	
Minimum	5	
Maximum	95	

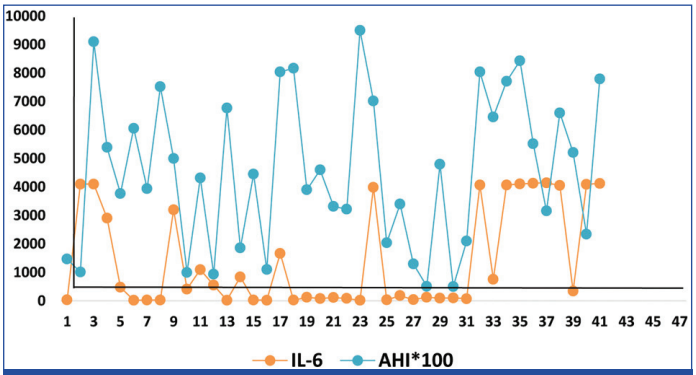
[Table/Fig-2]: Severity of OSA and mean, mode and standard deviation of AHI.

IL-6 (Pg./mL)	
Mean	1427.94
Median	341.6666
Mode	21.87254
Standard deviation	1769.326
Minimum	20.9292
Maximum	4145.235
Sum	58545.56
Count	41

[Table/Fig-3]: Showing mean, mode, median and standard deviation in 41 patients with OSA.



[Table/Fig-4]: Shows IL-6 value in 41 patients with OSA (AHI value scaled by 100).



[Table/Fig-5]: Shows positive correlation value between AHI and IL-6.
(*IL-6 values shown are multiplied by 100)

and interleukin-6 [16]. In the present study, we had selected IL-6 as a biomarker to evaluate its levels in 41 patients with OSA. We correlated IL-6 levels with AHI. The average value of IL-6 was 1427.94 pg/mL, ranging from 20.9292 to 4145.235 pg/mL. Average values of IL-6 were estimated by Immunoassay (ELISA) as 675.26 pg/mL in mild OSA, 1261.19 pg/ml in Moderate OSA and 1658.58 pg/mL in severe OSA. A study was conducted by Podkówka R et al., to estimate IL-6 levels in 29 healthy young adults (27.0±4.2 years) and 30 healthy elderly (71.1±5.5 years). The level of interleukin-6 was five times higher in the patient's who belonged to the older age group, but it was not statistically significant [17]. The findings in present study are also in support of some other studies [18-22]. PSG is a poor predictor of OSA-associated morbidities. Two patients with similar OSA severity may behave with markedly different clinical phenotypes. That's why such studies have importance to enable incorporation of morbidity biomarkers into well-defined and validated clinical guidelines or algorithms [23].

The searching out of an important biomarker for OSA associated morbidity has the potential to provide knowledge related to prognosis and response to therapy. Blood-based biomarkers were accounted in the majority of the studies, and most of the explored approaches did not identify definitive biomarkers of OSA morbidity. Studies showed that interleukin-6 can be considered as a biomarker to differentiate the patients with OSA with different co-morbidities [24]. Furthermore, in the present study, the average value of IL-6 was significantly higher than general young and elderly population thus, we can presume that high levels were because of OSA but, cannot confirm that these levels were because of OSA or associated comorbidities, or both.

Limitation(s)

First limitation is a small sample size, and the second is that we did not rely on a control group, comprising individuals without OSA, to establish correlation with the associated morbidities.

CONCLUSION(S)

Blood-based biomarkers accounted for the majority of the studies, but most of the studies did not identify a reliable biomarker of OSA morbidity.

In present study IL-6 levels have shown positive correlation with AHI. However, more large scale studies are required to establish a definitive correlation between OSA and IL-6. These findings warrant further research with case-control studies and standard statistical analyses to have a better understanding of interrelationships of these cytokines.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 17, 2019
- Manual Googling: Dec 18, 2019
- iThenticate Software: Dec 30, 2019 (16%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: No
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 16, 2019**
Date of Peer Review: **Nov 08, 2019**
Date of Acceptance: **Dec 18, 2019**
Date of Publishing: **Jan 01, 2020**