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Original Article

Internal Medicine Section

Utility of Serum Markers in Obstructive Sleep Apnoea Syndrome: A Case-control Study

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ABSTRACT

Introduction: Obstructive Sleep Apnoea Syndrome (OSAS) consists of cessation of breathing for atleast 10 seconds during sleep inspite of inspiratory efforts. The OSAS is an independent risk factor for a number of cardiovascular diseases and cerebrovascular events. The OSAS is diagnosed and assessed by polysomnography which is time consuming and expensive. C-Reactive Protein (CRP) and Creatine Phosphokinase (CPK) are markers of systemic inflammation. Inflammatory component is present in OSA. Biomarkers like CRP and CPK may serve as diagnostic tools which are simpler, cheaper and quicker alternatives.

Aim: To study the role of serum markers CRP and CPK in the diagnosis of sleep disordered breathing.

Materials and Methods: This was a case-control study, conducted from May 2021 to October 2021, in the Department of Pulmonary Medicine, NRI Medical College, Guntur, Andhra Pradesh, India. Total 50 patients were studied for their various symptoms suggestive of OSAS and confirmed by polysomnography were selected for the study. Total 40 age and weight matched controls were included in the study. The association of serum CRP and CPK with OSA was assessed. The Z-test of difference between two proportions was used to compare gender and smoking status of study participants of the two groups. The p-value <0.05 was reported as statistically significant.

Results: The mean CRP in those suffering from obstructive sleep apnoea was 12.075±7 mg/dL with 13.89 in moderate to severe OSAS group and 10.26 in mild cases. The CRP showed statistically significant association (p-value=0.00344) with OSA whereas CPK levels in OSA subjects showed no statistically significant association with OSAS. Sensitivity of CRP and CPK compared to the Apnoea Hypopnea Index (AHI) in the diagnosis of OSAS was 66% and 34%, respectively. Specificity of CRP and CPK was 87.5% for both. Positive predictive value for CRP and CPK was 86.8% and 77.2%, respectively.

Conclusion: C-reactive protein, a systemic inflammatory marker has a potential role in the diagnosis of OSAS.

Keywords: C-reactive protein, Cardiovascular diseases, Creatine kinase, Polysomnography

INTRODUCTION

Sleep Disordered Breathing (SDB) is characterised by abnormal respiratory pattern during sleep mostly associated with repetitive episodes of transient oxygen desaturation. It affects 4-9% of adult population and 3% of children [1]. The SDB includes Obstructive Sleep Apnoea Syndrome (OSAS) which consists of cessation of breathing for atleast 10 seconds during sleep inspite of inspiratory efforts [2]. OSAS is an independent risk factor for a number of cardiovascular diseases and cerebrovascular events [3]. The OSA is diagnosed and assessed using polysomnography, which is a time-consuming and expensive tool.

The OSAS is associated with both inflammatory aetiology and repetitive episodes of upper airway obstruction. Inflammatory markers are elevated in OSAS. Hence serum markers like CRP [4], Creatine Phosphokinase (CPK) [5], homocysteine [6], Lipoprotein-A [7], fibrinogen [8], C-Reactive Protein (CRP), serum amyloid A, leptin may serve as biomarkers in detecting the presence of OSA. These markers are simpler, cheaper and quicker alternatives in the diagnosis of OSAS.

CRP is an important inflammatory marker synthesised in the liver in response to Interleukin-6 (IL-6). Adipose tissue is a potent source of IL-6. Nocturnal hypoxemia and sleep disturbances lead to increased CRP in OSA patients [4]. An elevated CRP level is a strong predictor of cardiovascular risk [9]. CPK is an energy transfer enzyme and is elevated in conditions associated with increased muscle activity. Repeated attacks of hypoxemia and its effects on respiratory and skeletal muscles in OSA leads to elevated levels of CPK [5]. The elevation of CPK is either due to distintegration of muscle cells or due to leakage from muscle membranes [10,11].

Several studies have shown that CRP was significantly elevated in OSA [12-14]. Bhattacharjee R et al., have also found an association between CRP and OSA in children. However, other diseases with increased CRP levels like, asthma, and allergic rhinitis, were not ruled out [15]. Similarly, serum CPK was found to be associated with OSA. CPAP therapy in OSAS patients resulted in a significant decrease in CPK level [16]. Hence, this study was undertaken to evaluate the utility of these markers in the diagnosis of OSAS.

MATERIALS AND METHODS

This was a case-control study, conducted from May 2021 to October 2021, in the Department of Pulmonary Medicine, NRI Medical College, Guntur, Andhra Pradesh, India. The study was carried out after approval from Institutional Ethics Committee (IEC NRIMC365).

Inclusion criteria:

- Patients with symptoms suggestive of OSAS and Apnoea Hypopnea Index (AHI) >5/hr.
- All those above the age of 18 years.
- Those who gave the informed consent.

Exclusion criteria:

- Patients with cardiac illness, chronic obstructive pulmonary disease, recent trauma, neuromuscular diseases or other systemic illnesses.
- Patients who were on medications.

Procedure

Cases: Fifty OSA patients were selected based on their symptoms like snoring, apnoeic spells during sleep, excessive daytime sleepiness, fatigue and Apnoea Hypopnea Index (AHI) of >5/hour on polysomnography. Body Mass Index (BMI) (kg/m^2) and neck circumference (cm) was measured. All the patients were evaluated for thyroid dysfunction. Epworth Sleepiness Scale (ESS) [17] scoring was done for the cases. All the cases underwent Polysomnography (PSG)

in sleep laboratory using Alice-5, 54 channel PSG. AHI is the total number of respiratory events per hour of sleep:

- AHI >5 [18] on PSG diagnostic of OSA,
- AHI= 5-15/hour were considered as mild
- AHI >15/hour as moderate to severe.

Lowest oxygen saturation (SpO_2) was measured on PSG, with pulse oximetry.

Controls: Total 40 weight and age-matched controls were selected for the comparison. Attenders of the patients and hospital staff of NRI Medical College with no systemic illnesses were included in the control group. None of the subjects did not exercise on the day of the study, because exercise may alter the values of CRP and CPK.

Serum samples of all the subjects were taken by venepuncture from antecubital fossa by standard method and sent for laboratory for CRP and CPK measurements. Cut-off value for CRP was taken as <0.6 mg/dL (RHELAX-CRP slide agglutination test). The standardisation of detection limit of the test is traceable to the international reference standard [19]. CPK was measured on VITROS analyser and <200 IU/L was taken as cut-off value [20].

STATISTICAL ANALYSIS

The baseline characteristics of the subjects and CRP and CPK levels are expressed as mean±SD. t-test of difference between two means was used to compare mean age, BMI, CRP and CPK of cases and controls (MedCalc statistical software). Z-test of difference between two proportions was used to compare gender and smoking status of study participants of the two groups. The p-value <0.05 was reported as statistically significant.

RESULTS

The total number of cases diagnosed as OSA were 50, out of which 42 were males and 8 were females. The number of controls matched for age and weight were 40, out of which 30 were males and 10 were females. Out of the 42 male patients, 35 were smokers [Table/Fig-1].

Parameters	Cases	Controls	p-value
Age (years) (mean±SD)	42±4	40±8	0.1261
Body Mass Index (kg/m^2) (mean±SD)	36±2	35±7	0.338
Sex (Male:Female) (n)	42:8	30:10	0.34212
Smoking (smokers:non smokers) (n)	35:15	30:10	0.65272

[Table/Fig-1]: Baseline characteristics of the study participants.

The OSA patients were divided into two groups based on AHI (apnoea hypopnea index), those with 5-15/hour as 'mild', and those above >15/hour as 'moderate to severe'. The mean and SD of ESS score was 8±3.6 in OSA patients. The ESS score was significantly higher in moderate to severe OSAS group compared to mild group. However, the neck circumference was not significantly different between the two groups. The AHI was significantly higher in the moderate to severe OSAS group. The lowest oxygen saturation was significantly lower in the moderate-severe group (p-value <0.0001) [Table/Fig-2].

Parameters	Mild OSA (Mean±SD)	Moderate-Severe OSA (Mean±SD)	Total (N=50)	p-value (mild vs moderate-severe
Epworth sleepiness scale Score	6±2.2	11±3.1	8±3.6	0.0001
Neck circumference (cm)	38.84±2.4	40.62±5.41	39±2.6	0.114
Apnoea hypopnea index (events/hr)	10±4	60±2	37±4.6	<0.0001
Lowest oxygen saturation (%)	78±3	65±3	72±2.8	<0.0001

[Table/Fig-2]: Obstructive Sleep Apnoea (OSA) severity {Mild OSA (n=34), moderate OSA (n=16)} with clinical and polysomnography findings.

The mean CRP in those suffering from obstructive sleep apnoea was significantly higher compared to control group (p-value=0.00344). The CPK values were however similar in both the groups [Table/Fig-3].

Serum markers	Cases (Mean±SD)	Controls (Mean±SD)	p-value (t-test)
C-reactive protein (<0.6 mg/dL)	12.075±7	5±1	0.00344
Creatine phosphokinase (<200 U/L)	146.45±12	138±6	0.50521

[Table/Fig-3]: Mean values of serum markers.
p-value <0.05 considered significant

The mean CRP was significantly higher in moderate to severe OSAS group compared to mild cases. The CRP levels were proportionate to the severity of OSA [Table/Fig-4].

Parameters	Mild OSA (Mean±SD)	Moderate to severe OSA (Mean±SD)	p-value (t-test)
C-reactive protein (mg/dL)	10.26±2.8	13.89±4.2	0.0029

[Table/Fig-4]: Comparison of CRP with respect to severity of OSA.
p-value <0.05 considered significant

The sensitivity and specificity of CRP was 66% and 87.5%, respectively. Sensitivity of CPK was 34% and specificity of CPK was 87.5%. Positive predictive value of CRP and CPK was 86.8%, and 77.2%, respectively. Negative predictive value of CRP and CPK was 67.3% and 51.4%, respectively [Table/Fig-5].

Parameters	Controls (N=40)	Cases (N=50)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CRP <0.6 mg/dL	35	17	66%	87.5%	86.8%	67.3%
CRP ≥0.6 mg/dL	05	33				
CPK <200 U/l	35	33	34%	87.5%	77.2%	51.4%
CPK ≥200 U/l	05	17				

[Table/Fig-5]: Sensitivity, specificity, positive predictive value and negative predictive value of serum markers.

DISCUSSION

This study shows that patients with OSA had statistically significant elevated levels of CRP when compared to age and weight matched control individuals. Similar findings were found in several other studies [21,22]. Bhushan B et al., have found that OSAS patients have elevated CRP irrespective of BMI [21]. However, few studies have not found this association [23,24]. In a study by Barceló A et al., the CRP levels were significantly elevated in OSAS patients who were obese in comparison to non obese OSA patients and controls; the probable reason could be association of CRP with obesity rather than nocturnal hypoxemia [23].

In the present study, the controls had no cardiac disorders, thereby strengthening the association of CRP with OSA. In a study by Drager LF et al., they have concluded that elevated CRP is independently associated with OSAS [25]. The CRP elevation is proportional with the severity of OSA [26]. The mean CRP was elevated in moderate to severe OSA compared to mild cases in the present study, similar to a study done by Shamsuzzaman AS et al., and Sharma SK et al., have concluded that obesity is associated with hs-CRP, and there is no association between OSAS and elevated levels of high sensitivity CRP (hs-CRP) [27,28]. However in the present study, most of the patients were obese and CRP elevation was observed in obese OSAS patients. In a study by Taheri S et al., they have concluded that CRP levels and sleep duration were not associated significantly. The primary contributing factor attributing to relationship between CRP and sleep disordered breathing may be obesity [29].

The present study was done after close matching of cases and controls and none of them had other systemic illnesses, which further substantiates the finding that CRP is significantly increased in OSAS patients. It was also established that there was proportionate increase in CRP with severity of OSAS. Several studies reported a strong association between CRP and cardiovascular diseases

[9,10]. Thereby, measuring CRP in OSAS patients also becomes an important biomarker for cardiovascular risk.

The CPK was however not significantly associated with OSA in the present study. The probable reason for the result could be small sample size. In contrast, Lentini S et al., found that one third of study population showed mild-to-moderate elevation in CPK level, which was highly predictive of OSAS and application of positive pressure in those patients reduced CRP significantly [16]. The mechanism suggested was increased activity of upper airway muscles. In a study by Sakellaropoulou A et al., they observed that a relationship exists between hypoxia and CPK concentration [30]. In a study by Shah N et al., OSAS patients had lower CPK compared to non apnoeic patients [31]. Further studies are needed to establish the strong association of CPK and OSAS and whether treatment of OSA lowers CPK values.

Thus, this study recommends CRP as diagnostic marker in OSA patients however it should be used in conjunction with clinical manifestations. CPK levels were not significantly elevated in OSAS patients and further studies are needed to establish it as a strong predictor.

Limitation(s)

The study is constrained by its small sample size. Another limitation is majority of OSAS patients were obese and association of CRP was not studied in relation to obesity.

CONCLUSION(S)

Elevated CRP is a useful marker and can be used as a screening test to identify patients who require PSG, on a priority basis to diagnose OSA. As there is a strong association between CRP and cardiovascular disease, monitoring CRP levels also determines the patients who are at increased risk of cardiovascular complications. Further studies are needed to determine whether OSAS will improve with treatment targeted at reducing CRP.

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