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Research Article

COMPARATIVE STUDIES TO EVALUATE SERUM LEVELS OF C-REACTIVE PROTEIN IN OBSTRUCTIVE SLEEP APNEA AND HEALTHY CONTROLS

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A B S T R A C T

Aims

1. To evaluate the correlation between elevated levels of C-Reactiveprotein (CRP) and obstructive sleep apnea.
2. To compare the levels of CRP with normal controls matched for age, sex, BMI, Occupation.

Methods

Study group consisted 80 subjects. Polysomnography was done for all subjects on the basis of which 30 subjects were taken normal controls {Apnea Hypopnea Index (AHI) <5 and Respiratory Disturbance Index(RDI)<5}. Rest of the 50 subjects were cases. (AHI >5 and RDI >5).Various clinical and polysomnographic data {viz their neck circumferences, blood pressure, Arterial pCO2, Epworth Sleepiness Scale, AHI, and the Oxygen desaturation index(ODI)} along with serum quantitative CRP were recorded and compared between the two groups.

Results: we found positive correlation between:

1. AHI and CRP independent of BMI. R value: 0.815, P value: <0.001.
2. RDI and CRP. R value: 0.815, P value <0.001
3. ODI and CRP. R value: 0.835, P value: <0.001

Area under ROC (receiver operating characteristic) curve for AHI was 1.000 with cutoff value: 5.15 to differentiate cases from controls. P value was <0.001 Area under ROC curve for CRP was 0.878 which is considered good to differentiate cases from controls with cutoff value: 0.655.

Conclusions: CRP value is marker of inflammation and cardiovascular risk was raised in cases independent of BMI. Its association with AHI shows that severity of OSA is positively correlated to CRP levels. CRP levels are also positively correlated to the ODI implying Hypoxia as one of the mechanisms by which OSA induces systemic inflammation.

INTRODUCTION

An obstructive hypopnea/apnea is characterized by a transient reduction in, or complete cessation of breathing due to upper airway occlusion. According to standard definitions, an apnea is a period of cessation (or near cessation) of airflow lasting at least 10 seconds. Hypopnoea is characterised by polysomnographic (PSG) variables as any one of the three, namely, decrease in nasal airflow by more than 50% for more than 10 sec, decrease in nasal airflow by less than 50% with a more than 4% fall in oxygen saturation or a decrease in nasal airflow by less than 50% with electroencephalographic (EEG) evidence of arousal. [AASM task force, 1999].

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According to the American Academy of Sleep Medicine [1999, AASM], the diagnostic criteria for the Obstructive Sleep Apnea-Hypopnea syndrome (in the following text called Obstructive Sleep Apnea Syndrome, OSAS) are:

1. Five or more obstructive breathing events per hour of sleep during overnight monitoring and
2. Excessive daytime sleepiness not better explained by other factors, or
3. III) At least two of the following: choking or gasping during sleep; recurrent awakenings during sleep; unrefreshing sleep; daytime fatigue; impaired concentration.

Data from the Wisconsin Sleep Cohort Study [Young T *et al*,1993] suggest that approximately 4% of women and 9% of men in the United States (ages 40 to 65 years) have moderate OSA, defined as an AHI of 15 or more events per hour during sleep. Similar estimates of OSA prevalence have also been reported by Bixler *et al* [2001] in a sample of 1741 individuals recruited from the general population.

Sleep apnea as a condition is not a life threatening situation but the risk factors and complications such as cardiovascular (Systemic hypertension, Myocardial Infarction), Uncontrolled Type 2 diabetes mellitus and cerebrovascular diseases (CVA) are the serious problems associated with sleep apnea. Inflammatory cytokines (tumour necrosis factor-α, and interleukin-6,) have been found to be elevated in sleep apnea patients independently of obesity and correlated to sleepiness and fatigue. These cytokines are somnogenic and also involved in sleep regulation. It remains inconclusive whether the changes in circulating inflammatory biomarker levels are due to OSA per se or to some other underlying factors such as excess weight and co-morbidities. Hence, current study aims to study the correlation of serum C- Reactive protein with OSA by comparing various polysomnographic parameters, independent of other co morbidities.

MATERIALS AND METHODS

The study took place in Chest Ward of Department of T.B.& Respiratory Diseases,Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi during July 2015 to July 2017.

Patient selection

Patients with sleep disordered breathing were motivated to participate in the study. Data on demographic characteristics, sleep, medical history, medication use, and habits were obtained with the use of a modified standardized questionnaire and Epworth Sleepiness Scale, before the initiation of overnight polysomnography (PSG). Each patient's height and weight was recorded at the time of polysomnography and used to calculate the body mass index. Sleep history data included a validated measure of daytime sleepiness (Epworth sleepiness scale) and self reported habitual reporting snoring, which was defined as loud snoring occurring " frequently" or "constantly" (most of the interviewers were attended by the patient spouses or a close relative staying at home).

Inclusion and Exclusion Criteria

Inclusion criteria

1. Patients with newly diagnosed OSA.
2. Both male and female included.
3. Control group match for age, sex and body mass index (BMI).
4. Never treated OSA and taking no medication.

Exclusion criteria

1. Any chronic systemic disease.
2. Chronic respiratory failure or insufficiency with suspected or known neuromuscular diseases, moderate or severe COPD or other pulmonary disorders, or participants qualifying for oxygen therapy (arterial saturation 88% for more than five minutes.)
3. Consumption of ethanol more than 4 nights per week (CAGE criteria)
4. Use of recreational drug within the past 12 months.
5. Woman who are pregnant or currently lactating.

Study Group

Study group consisted of 80 subjects. Polysomnography was done for all the subjects on the basis of which 30 subjects were taken as normal controls(AHI <5 and RDI<5). Rest of the 50 subjects were cases. (AHI >5 and RDI >5).Cases and controls were matched in terms of Demographics (age, sex, BMI). All the initial laboratory investigations assessment included CBC, LFT, RFT, ABG, Thyroid profile, Serum Lipid Profile, Blood Sugar level were done.

For CRP measurement, protocol included

- Venous blood collection just after awakening and processing within the next 60 minutes.
- Patient were fasted since 7:00 PM the previous night.
- CRP was measured using a nephelometric (antigen-antibody complex with aggregation) technique (abnormal level ≥ 0.8 mg/dL).
- CRP was measured in these patients and the ones matched for age and body mass index,in whom occult OSA was excluded i.e controls.

Materials

1. Epworth Sleepiness Scale form.
2. Alice PDX portable polysomnography machine.
3. Auto analyzer machine for liver function test, renal function test, complete blood count, blood sugar and serum lipid profile.
4. Sphygmomanometer for B.P. measurement.
5. Weighing machine and measuring tape to calculate patient's BMI and neck circumference.

Statistical methods

- The statistical analysis was done using statistical software SPSS for windows (Version 16).
- Chi-square test was used for non-parametric variables.
- Student's t test was used for comparing two groups and one-way ANOVA test was used for multiple group comparison.
- P-value <0.05 was stated as statistically significant. The ROC curve was used as a tool for diagnostic test evaluation.
- In the ROC Curve, the true positive rate (Sensitivity) was plotted in function of the false positive rate (100-Specificity) for different cut-off points of a parameter.

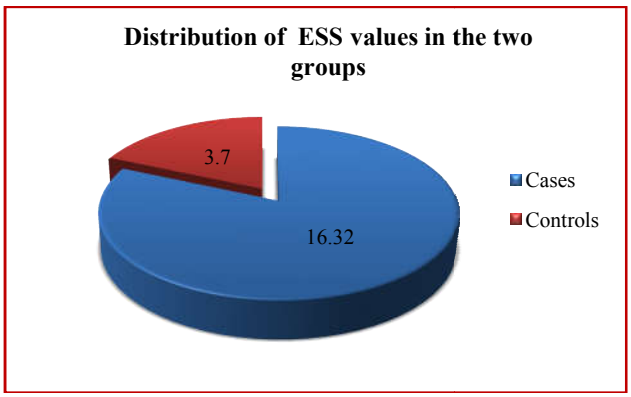
OBSERVATIONS AND RESULTS

- The mean age of cases was 47.08±10.057 and in controls was 50.30±9.491 with male : female ratio was 2.8:1
- In our study, cases and controls were matched regarding demographic features (age, sex, BMI).
- Smoking is a risk factor for the development of OSA. In our study, 16% of the cases and 13.3% of the controls were smokers.
- 48% of the cases and 43.3% of controls were businessmen, followed by Housewives (H/W) 30% in cases and 23.3% in controls.

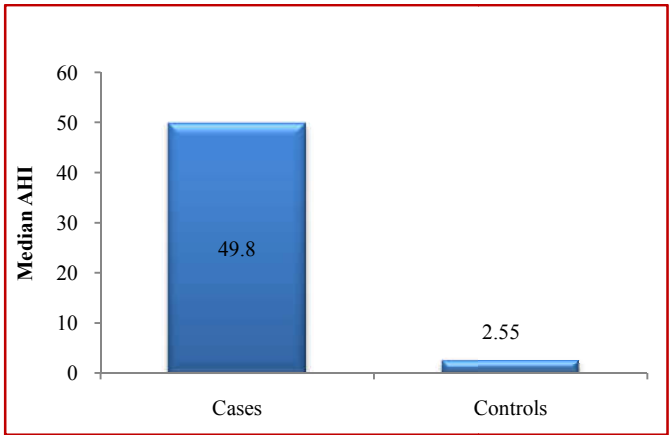
- 14% of the patients were having craniofacial defects in cases and none of the patients in controls which was statistically significant.

The mean level of SBP, DBP, Waist:Hip ratio, weight, pCO_2, LDL, FBS, PPBS were comparable in both the groups.

- Mean Epworth Sleepiness Scale score in cases was 16.32±2.882 while that for controls was 3.70±1.418. (P value <0.001)

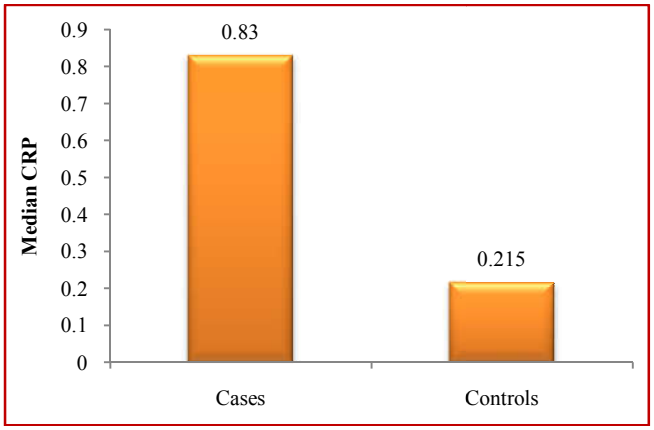


Comparison of AHI in cases and controls:



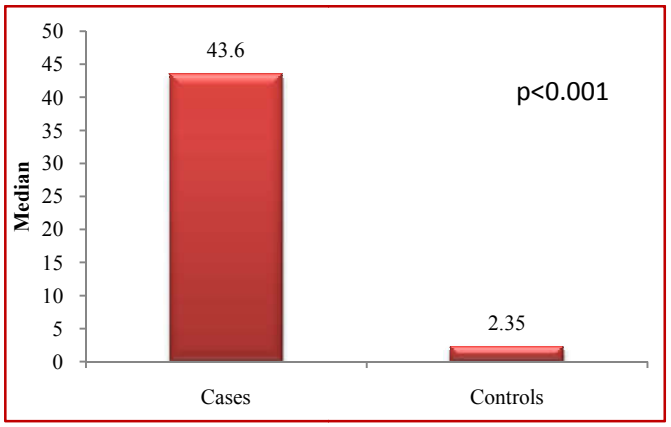
Median AHI for cases was 49.8 which was in the severe range as compared to the AHI of 2.55 in controls.

Comparison of C Reactive Protein in cases and controls:



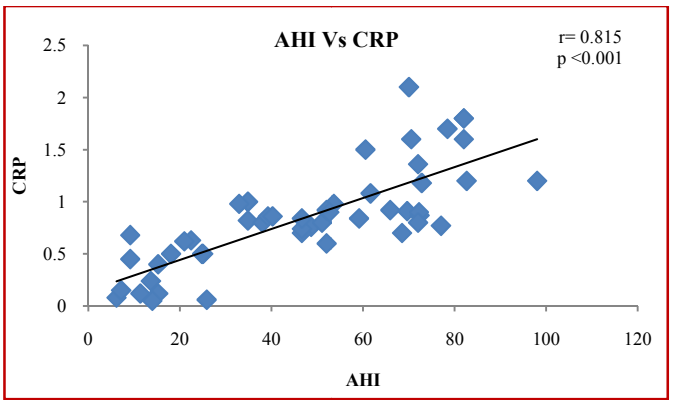
The comparison of CRP among the two groups revealed median CRP in cases to be 0.83 mg/dl (normal <0.8 mg/dl) and the corresponding value in matched controls was 0.215.

Comparison of Oxygen Desaturation Index in cases and controls:



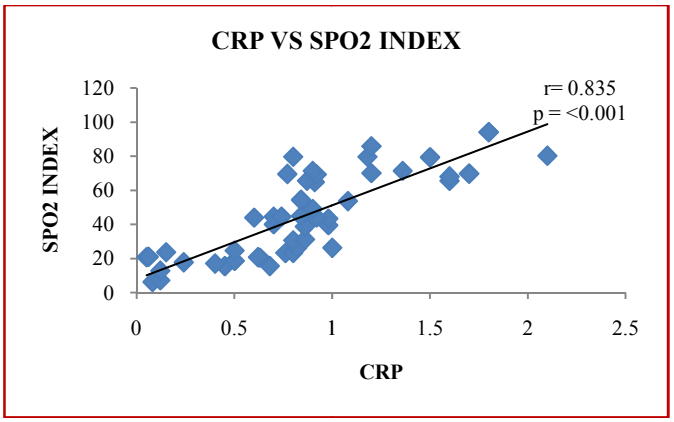
Comparison of ODI between cases and controls revealed a median ODI of 43.6 among the cases against 2.35 among controls.

Correlation between AHI and C Reactive Protein



There was clear cut strong positive correlation between AHI and CRP values with an R value of 0.815.

Correlation between C Reactive protein and Oxygen desaturation Index



Strong correlation was also observed between serum CRP and that of Oxygen Desaturation Index with an R value of 0.835.

Values for the ROC curves are as follows:

1. Area under the ROC curve for RDI was 1.000 with the cutoff value of RDI differentiating cases and controls is 5.80. P value is very significant at <0.001
2. Area under the ROC curve is 1.000 with the cut off value for AHI differentiating cases from controls is 5.15. P value is very significant at <0.001.

3. Area under the ROC curve for CRP is 0.878 with a cutoff value of 0.655 which can be considered good in separating cases from controls. Sensitivity: 70% and specificity: 100%. With a significant P value of <0.001.
4. Area under the ROC curve is 1.000 with the cutoff value for ESS being 8.50 to differentiate cases from controls. P value is very significant <0.001.
5. Area under the ROC curve for Oxygen Desaturation Index was 1.000 with the cutoff value 5.40 differentiating cases from controls. P value was very significant <0.001.

Variable	Area	P-value	Cut- off value	Sensitivity	Specificity
RDI	1.000	<0.001	5.80	100%	100%
AHI	1.000	<0.001	5.15	100%	100%
CRP	.878	<0.001	0.655	70%	100%
ESS	1.000	<0.001	8.50	100%	100%
Oxygen desaturation Index	1.000	<0.001	5.40	100%	100%

DISCUSSION

- Our study was mainly focussed on the association between C-Reactive Protein and Obstructive sleep Apnea in newly diagnosed cases and their comparison to matched controls (for age, sex, BMI) without OSA. Conflicting results have been found in all of the biomarkers of inflammation which have been studied in previous studies:

  1. Both reports of increased levels of TNF-α, IL-6 and CRP independent of body weight (Vgontzas *et al*.,1997; Shamsuzzaman *et al*.,2002; Yokoe *et al*.,2003) and
  2. Papers reporting that the increase in these biomarkers, if found, is mostly dependent on excess weight (or the groups were not matched for body weight) have been published (Vgontzas *et al*.,1997; Steiropoulos *et al*.,2010).
- Another study conducted on Indian population in Delhi concluded that obesity, and not obstructive sleep apnea, is associated with elevated serum levels of hs-CRP. No independent correlation was found between severity of OSA and hs-CRP.(SK Sharma *et al*., 2008)
- Thus, in the wake of ambiguous results regarding relationship between inflammatory markers and severity of OSA our study was done and the study group included Indian population hailing from rural background.
- In our study, the mean CRP in cases was 0.6254±0.48729(mg/dl). The median CRP in cases was 0.8300 (0.5750-1.0200) and in matched controls, was 0.2150 (0.1200-0.3400) with a highly significant P value of <0.001.
- Mean AHI in cases was 30.6188±29.70483. Median AHI in cases was 49.8000 (24.2000-70.8750) and for matched controls was 2.5500 (2.5500-3.2500) with a very significant P value of <0.001.
- Oxygen Desaturation Index is associated with the severity of sleep apnea as proven in previous studies. (Fietze I *et al*., 2004).The mean ODI in cases was 28.8450±28.64806. In our studies we found that the median ODI for cases was 43.6000 (20.8500-69.2750) and for controls was 2.3500 (1.3750-3.5000) with a very significant p value of <0.001.

In our study we found positive correlation between Apnea Hypopnea Index and C Reactive Protein independent of BMI. R value: 0.815 and P value: <0.001 indicative of strong positive relationship between the two. It was consistent with previous studies. {Guilleminault *et al* (2004)} Positive correlation was also found between Oxygen Desaturation Index and C Reactive Protein. R value: 0.835 and P value: <0.001.

ROC curve analysis: the true positive rate (Sensitivity) was plotted in function of the false positive rate (100-Specificity) for different cut-off points of various study parameters.

1. Area under the ROC curve for AHI was 1.000 with a cutoff value of 5.15 to differentiate cases with OSA from controls. P value was <0.001. AHI cut off commonly used is 5 events / hr. Thus in our study for Indian population, AHI cutoff was 5.15.
2. Similarly for CRP, area under the ROC curve was 0.878 which can be considered good to differentiate cases from controls with a cutoff value of 0.655. Commonly considered normal value for CRP is <0.8 mg/dl. Our study gave the value at 0.655 with a sensitivity of 70% and specificity of 100% with P value <0.001.
3. Area under the ROC curve for ODI was 1.000 with a cutoff value of 5.40 to differentiate cases with OSA from controls. P value was <0.001. ODI cutoff commonly used is 5 events / hr. Thus in our study for Indian population, ODI cutoff was 5.40.

SUMMARY AND CONCLUSIONS

In accordance with the criteria formulated for patient selection, Study group consisted of 80 subjects. Polysomnography was done for all the subjects on the basis of which 30 subjects were taken as normal controls (AHI <5 and RDI<5). Rest of the 50 subjects were cases. (AHI >5 and RDI >5). Cases and controls were matched in terms of demographics (age, sex, BMI).

Patients having any chronic systemic disease or Chronic respiratory failure or insufficiency with suspected or known neuromuscular diseases, moderate or severe COPD or other pulmonary disorders, or participants qualifying for oxygen therapy (arterial saturation 88% for more than five minutes.), pregnant and lactating women were excluded from the study. C Reactive protein value, which is a marker of inflammation and cardiovascular risk was raised in cases with OSA independent of the BMI.

Its association with AHI shows that severity of OSA is positively correlated to CRP levels. CRP levels are also positively correlated to the Oxygen Desaturation Index implying Hypoxia as one of the mechanisms by which OSA induces systemic inflammation. Serum CRP levels in patients of OSA can thus be interpreted as markers of systemic inflammation and to gauge the extent of cardiovascular complications involved.

Plus its levels after initiation of therapy can also give us an idea of effectiveness of therapy instituted for OSA. Nonetheless more studies are needed to effectively establish it.

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