Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 3, 2024

ORIGINAL RESEARCH

Study to investigate the association between obstructive sleep apnea (OSA) and laryngopharyngeal reflux (LPR) through oropharyngeal pH-monitoring and pepsin saliva measurements

[1]Dr. Harkanwal Preet Singh, [2]Dr. Rachna Dhingra, [3]Dr. Shamim Monga, [4]Dr. Tabish Uzair Saify

[1]Professor and Head, Department of Oral Pathology, Dasmesh Institute of Research and Dental Sciences, Faridkot, Punjab, India
[2]Associate Professor, Department of ENT, GGS Medical College &Hospital, Faridkot, Punjab, India
[3]Associate Professor, Department of Community Medicine, GGS Medical College & Hospital, Faridkot, Punjab, India
[4]Lecturer, Department Of Oral Pathology, Dasmesh Institute Of Research And Dental Sciences, Faridkot, Punjab, India

Corresponding Author
Dr. Shamim Monga
Associate Professor, Department of Community Medicine, GGS Medical College & Hospital, Faridkot, Punjab, India

Received date: 10 February 2024 Acceptance date: 2 March 2024

Abstract
Objective- This study aimed to explore the relationship between obstructive sleep apnea syndrome (OSA) and laryngopharyngeal reflux (LPR) in patients with OSA, utilizing oropharyngeal pH-monitoring and detecting pepsin in saliva samples. **Materials and Methods-** A total of 55 adult patients experiencing primary patient-reported sleep disturbances alongside symptoms indicative of laryngopharyngeal reflux (LPR), were recruited included in this study.Pepsin concentration in saliva was measured using autoanalyzer.
Results-Significant positive relationships were found in the association study between the LPR and the following characteristics related to sleep and reflux: total number of arousals, RSA, reflux time at pH<6.5, and Ryan score. The amount of pepsin in the morning was negatively correlated with the length of the paradoxical sleep period. The length of sleep with a saturation level less than 90% was correlated with the amount of pepsin taken before bed. The results of the GI endoscopy and OSA did not significantly correlate.
Conclusion-The study revealed a significant occurrence of reflux events during oropharyngeal pH monitoring and elevated levels of pepsin in saliva among patients with obstructive sleep apnea (OSA).
Keywords- Obstructive sleep apnea, Laryngopharyngeal reflux, Pepsin
(SCC), Intensity Modulated Radiotherapy (IMRT).

Introduction

Obstructive sleep apnea (OSA) is a common health problem affecting about 5% of the adult population[1]. It is a sleep disorder characterized by multiple episodes of airflow obstruction due to the collapse of different upper airway structures [2]. Abnormalities in upper airway

anatomy (tonsils, soft palate, base of the tongue, and/or hypopharynx) as well as neuromuscular control are the primary factors that contribute to upper airway collapsibility in OSA patients[3,4]. The severity of the OSA syndrome is mainly measured using the AHI (apnea–hypopnea index) which is based on the number of apnea/hypopnea events per hour of sleep. Laryngopharyngeal reflux (LPR) is an inflammatory condition affecting the tissues of the upper aerodigestive tract, resulting from the direct and indirect impact of refluxed gastro duodenal contents. This reflux leads to morphological changes in the upper aerodigestive tract . The presence of pepsin deposits triggers inflammatory reactions in the mucosa, implicating reflux in various common inflammatory otolaryngological conditions. These include Eustachian tube dysfunction and associated otitis media, chronic rhino sinusitis, subglottic stenosis, tobacco-induced laryngopharyngitis, and non-functional laryngeal disorders[5,6].Numerous studies have highlighted the coexistence of LPR and obstructive sleep apnea (OSA). However, the precise prevalence of pharyngeal reflux events, the reflux profile in OSA patients, and their potential association with sleep parameters remain unclear[7]. Some investigations have explored the occurrence of LPR in OSA patients using objective diagnostic tools such as hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing or oropharyngeal pH monitoring [8]. Nevertheless, identifying the coexistence of LPR and OSA is crucial for enhancing patient management. While some studies suggest that OSA patients may experience worsened symptoms of LPR, others have demonstrated the benefits of antireflux therapy in OSA patients, leading to improvements in daytime sleepiness and reductions in nocturnal reflux-related arousals.[9]This study aimed to explore the relationship between obstructive sleep apnea syndrome (OSA) and laryngopharyngeal reflux (LPR) in patients with OSA, utilizing oropharyngeal pH-monitoring and detecting pepsin in saliva samples.

Materials and methods

A total of 55 adult patients experiencing primary patient-reported sleep disturbances alongside symptoms indicative of laryngopharyngeal reflux (LPR), were recruited in this study. The prevalence of both LPR and obstructive sleep apnea (OSA) was evaluated using objective diagnostic methods. LPR diagnosis was based on the identification of more than two instances of pharyngeal reflux events during oropharyngeal pH-testing. OSA diagnosis was determined through polysomnography. The confirmation of LPR diagnosis involved 48-hour oropharyngeal pH monitoring, which was conducted simultaneously with polysomnography for all enrolled patients. In addition to diagnostic testing, saliva samples were collected from patients on the day of pH-testing, both in the morning (fasting), afternoon and at bedtime. Gastrointestinal endoscopy was offered to patients exhibiting symptoms associated with gastroesophageal reflux disease, as well as to elderly patients aged over 50 years who might be less sensitive to gastroesophageal reflux disease symptoms. The assessment of reflux symptoms utilized the Reflux Symptom Score-12 (RSS-12). RSS-12 score > 11 is suggestive of LPR. Reflux signs were examined using the Reflux Sign Assessment, a validated clinical tool consisting of 61 points.Patients with a Reflux Symptom Score-12 exceeding 11 underwent 48-hour oropharyngeal pH-monitoring. Diagnosis of laryngopharyngeal reflux (LPR) was established based on the detection of more than 2 pharyngeal reflux events. In addition to oropharyngeal pH-monitoring, saliva samples were collected from patients three times a day: in the morning (while fasting), afternoon, and at bedtime. Pepsin concentration in saliva was measured usingautoanalyzer. All the results were used for evaluation of level of significance.

Results

55 adult patients with mean age of 52.1 were enrolled. Among them OSA was detected in 30 of these patients. Additionally, Laryngopharyngeal Reflux (LPR) was diagnosed through oropharyngeal pH among 20 patients with OSA. Out of 30 patients with OSA, 18patients reported positive for pepsin test results either in the morning, afternoon, or at bedtime. Significant positive relationships were found in the association study between the LPR and the following characteristics related to sleep and reflux: total number of arousals, RSA, reflux time at pH<6.5, and Ryan score. The amount of pepsin in the morning was negatively correlated with the length of the paradoxical sleep period. The length of sleep with a saturation level less than 90% was correlated with the amount of pepsin taken before bed. The results of the GI endoscopy and OSA did not significantly correlate.

Table 1: Clinical variables

Variable		Number	Percentage
Mean age (years)		52.1	
Gender	Males	31	56.36
	Females	24	43.64
Patients with OSA		30	54.55
Mean pepsin saliva concentration (ng/mL)- morning		62.3	
Mean pepsin saliva concentration (ng/mL)- evening		83.9	
Abnormal pepsin levels among patients with OSA	Morning	12	40
	Evening	10	33.33
	Atleast one abnormal measure	18	60

Table 2: Association variables

Association variables		Versus	p-value
Sleep and reflux parameters	Total number of arousals	LPR	0.02*
	Reflux sign assessment (RSA)		0.00*
	Reflux time at pH<6.5		0.01*
	Ryan Score		0.00*

*: Significant

Discussion

Patients with OSA suffer from LPR far more frequently than those of the general population[10,11]. The causative relationship between obstructive events and LPR disease could depend on a vicious circle. The vicious cycle is initially triggered by respiratory efforts. As airflow obstruction develops in OSA, the progressive increase in respiratory effort produces greater negative intrathoracic pressure[12]. As this negative intrathoracic pressure exceeds the ability of the containment function of the lower esophageal sphincter, reflux of gastric contents (acid, pepsin, etc.) into the oesophagus, larynx, and pharynx occurs. Contrarily, LPR creates inflammation and sensory deficits in the laryngeal and pharyngeal tissues that contribute to progression of OSA via both inflammatory and neuromuscular pathways.[13-16] 55 adult patients with mean age of 52.1 were enrolled. Among them OSA was detected in 30 of these patients. Additionally, Laryngopharyngeal Reflux (LPR) was diagnosed through oropharyngeal pH among 20 patients with OSA. Out of 30 patients with OSA, 18 patients reported positive for pepsin test results either in the morning, afternoon, or at bedtime. Significant positive relationships were found in the association study between the LPR and the following characteristics related to sleep and reflux: total number of arousals, RSA, reflux

time at pH<6.5, and Ryan score. Iannella G et al investigated the presence of laryngopharyngeal reflux in patients with obstructive sleep apnea (OSA) employing the salivary pepsin concentration method. Seventy-five OSA patients (44 males, 31 females) were enrolled in the study. For each patient, the AHI (apnea–hypopnea index) and the BMI (body mass index) were initially evaluated. All the patients enrolled were assessed using the reflux symptom index (RSI) and the reflux finding score (RFS) in order to perform a clinical diagnosis of laryngopharyngeal reflux. In all patients a salivary sample was taken to estimate the presence of pepsin and its concentration. The incidence of LPR (laryngopharyngeal reflux) in OSA patients, evaluated using the salivary pepsin concentration test (PEP-test), was found to be 32% of cases. Linear regression testing did not show any correlation between AHI and pepsin concentration in salivary samples ($p = 0.1$). A high number of patients with OSA seem to show positivity for salivary pepsin, correlated to an LPR. There does not appear to be a correlation between the severity of apnea and the grade of salivary pepsin reflux. On the other hand, direct correlation between BMI and the value of pepsin in salivary specimens was observed.[16] In the present study, the amount of pepsin in the morning was negatively correlated with the length of the paradoxical sleep period. The length of sleep with a saturation level less than 90% was correlated with the amount of pepsin taken before bed. The results of the GI endoscopy and OSA did not significantly correlate. He J et al evaluated the LPR prevalence in individuals with OSAHS and to analyze the correlation of LPR positivity with the clinical features of patients with OSAHS. A detailed review of the English and Chinese literature on the occurrence of LPR in patients with OSAHS was performed by employing online search tools such as PubMed, EMBASE, Web of Science, VIP, CNKI, WanFang, etc. Two researchers analyzed the studies for quality according to the STROBE standard checklist. The acquired data were analyzed using Stata 11.0 and R 3.6.1 software. The effect size was estimated and calculated using weighted mean difference (WMD) and correlation coefficients. Moreover, a combined analysis was performed by employing either a random- or fixed-effects model. Ultimately, 27 studies met our inclusion criteria. Our study revealed that the LPR prevalence in OSAHS patients was 49%. We carried out subgroup analyses as per OSAHS severity, ethnicity, and body mass index (BMI). The results suggested that the probability of LPR in European and American patients with OSAHS was higher, and the prevalence of LPR was higher in obese individuals and patients with severe OSAHS. Moreover, apnea-hypopnea index (AHI) and BMI were higher in LPR-positive OSAHS patients than in LPR-negative OSAHS patients, but no significant variation in age was observed in the two groups. Moreover, the reflux symptom index (RSI) scores and the reflux finding score (RFS) exhibited a positive correlation with AHI. The current literature shows a higher incidence of LPR in individuals with OSAHS (49%).[17]

Conclusion

The study revealed a significant occurrence of reflux events during oropharyngeal pH monitoring and elevated levels of pepsin in saliva among patients with obstructive sleep apnea (OSA).

References

1. Heinzer R., Vat S., Marques-Vidal P., Marti-Soler H., Andries D., Tobback N., Mooser V., Preisig M., Malhotra A., Waeber G., et al. Prevalence of sleep-disordered breathing in the general population: The HypnoLaus study. Lancet Respir. Med. 2015;3:310–318. doi: 10.1016/S2213-2600(15)00043-0.
2. Senaratna C.V., Perret J.L., Lodge C.J., Lowe A.J., Campbell B.E., Matheson M.C., Hamilton G.S., Dharmage S.C. Prevalence of obstructive sleep apnea in the general

population: A systematic review. Sleep Med. Rev. 2017;34:70–81. doi: 10.1016/j.smrv.2016.07.002.
3. .Magliulo G., de Vincentiis M., Iannella G., Ciofalo A., Manno A., Pasquariello B. Eustachian tube evaluation in patients with obstructive sleep apnea syndrome. Acta Otolaryngol. 2018;138:159–164. doi: 10.1080/00016489.2017.1385846.
4. White D.P. Pathogenesis of obstructive and central sleep apnea. Am. J. Respir. Crit. Care Med. 2005;172:1363–1370. doi: 10.1164/rccm.200412-1631SO.
5. Kayalı Dinc AS, Cayonu M, Sengezer T, Sahin MM. Smoking cessation improves the symptoms and the findings of laryngeal irritation. Ear Nose Throat J. 2020;99(2):124–7.
6. Halstead LA. Gastroesophageal reflux: a critical factor in pediatric subglottic stenosis. Otolaryngol Head Neck Surg. 1999;120(5):683–8.
7. Suurna MV, Welge J, Surdulescu V, Kushner J, Steward DL. Randomized placebo-controlled trial of pantoprazole for daytime sleepiness in GERD and obstructive sleep disordered breathing. Otolaryngol Head Neck Surg. 2008;139(2):286–90.
8. O'Connor-Reina C, Garcia JMI, Baptista P, Garcia-Iriarte MT, Alba CC, Perona M, Borrmann PF, Alcala LR, Plaza G. Non-acid reflux and sleep apnea: the importance of drug induced sleep endoscopy. J Otolaryngol Head Neck Surg. 2021;50(1):42.
9. Teklu M, Gouveia CJ, Yalamanchili A, Ghadersohi S, Price CPE, Bove M, Attarian HP, Tan BK. Predicting obstructive sleep apnea status with the reflux symptom index in a sleep study population. Laryngoscope. 2020.
10. Elhennawi D.M., Ahmed M.R., Abou-Halawa A.S. Correlation of obstructive sleep apnoea and laryngopharyngeal reflux: Phmetry study. Clin. Otolaryngol. 2016;41:758–761. doi: 10.1111/coa.12640
11. Rodrigues M.M., Dibbern R.S., Santos V.J.B., Passeri L.A. Influence of obesity on the correlation between laryngopharyngeal reflux and obstructive sleep apnea. Braz. J. Otorhinolaryngol. 2014;80:5–10. doi: 10.5935/1808-8694.20140004.
12. Eskiizmir G., Kezirian E. Is there a vicious cycle between obstructive sleep apnea and laryngopharyngeal reflux disease? Med. Hypotheses. 2009;**73**:706–708. doi: 10.1016/j.mehy.2009.04.042.
13. Bobin F, Auregan G, Muls V, Cammaroto G, Hans S, Saussez S, Lechien JR. Impedance-pH monitoring profile of patients with reflux and obstructive sleep apnea syndrome: a controlled study. Clin Otolaryngol. 2021;46(4):816–22.
14. Müller DT, Schulte E, Babic B, Knepper L, Fuchs C, Schröder W, Bruns CJ, Leers JM, Fuchs HF. Software improvement for evaluation of laryngopharyngeal pH testing (Restech) - a comparison between DataView 3 and 4. World J Gastrointest Surg. 2020;12(5):236–46.
15. Sung MW, Lee WH, Wee JH, Lee CH, Kim E, Kim JW. Factors associated with hypertrophy of the lingual tonsils in adults with sleep-disordered breathing. JAMA Otolaryngol Head Neck Surg. 2013;139(6):598–603.
16. Iannella G, Vicini C, Polimeni A, et al. Laryngopharyngeal Reflux Diagnosis in Obstructive Sleep Apnea Patients Using the Pepsin Salivary Test. Int J Environ Res Public Health. 2019;16(11):2056. Published 2019 Jun 10. doi:10.3390/ijerph16112056
17. He J, Wang C, Li W. Laryngopharyngeal Reflux in Obstructive Sleep Apnea-Hypopnea Syndrome: An Updated Meta-Analysis. Nat Sci Sleep. 2022;14:2189-2201. Published 2022 Dec 15. doi:10.2147/NSS.S390272