Influence of obesity on the correlation between laryngopharyngeal reflux and obstructive sleep apnea

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\textbf{Abstract}

Introduction: The obstructive sleep apnea (OSA) is caused by recurrent episodes of partial or total obstruction of the upper airway lasting more than 10 seconds during sleep. Laryngopharyngeal reflux (LPR) is a variant of the disease Gastroesophageal Reflux that affects the larynx and pharynx. Objectives: Evaluate the influence of obesity on the relationship between RFL and OSAS in patients with OSA. Materials and methods: An observational retrospective cross. We reviewed care protocol for patients with OSA that includes validated questionnaires for RFL as Symptom Reflux Index (RSI) and Reflux Finding Score (RSF), and polysomnography nasolaringofibroscopia. Results: 105 patients were divided into obese group (39 patients) and non-obese patients (66 patients). In the evaluation of the mean RSI group of non-obese was similar between patients with mild OSA (11.96) and moderate (11.43). In the obese group the mean RSI was 6.7 in patients with mild OSA and 11.53 in patients with moderate to severe OSA (p < 0.05). Discussion: The subgroup of patients with OSA and RFL have several factors that promote inflammation of the upper airway. Patients with OSA should be screened and treated as the RFL increasing the quality of life. Conclusion: The RFL are positively correlated and OSAS in obese patients.

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PALAVRAS-CHAVE
Aneia obstrutiva do sono; Obesidade; Laringite

Influência da obesidade na correlação entre refluxo faringolaríngeo e apneia obstrutiva do sono

Resumo

Introdução: A apneia obstrutiva do sono (AOS) é causada por episódios recorrentes de obstrução total ou parcial da via aérea superior com duração superior a 10 segundos durante o sono. Refluxo faringolaríngeo (RFL) é uma variante da doença do refluxo gastroesofágico que afeta a laringe e a faringe.

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Introduction

Obstructive sleep apnea (OSA) is caused by recurrent episodes of partial or complete obstruction of the upper airways (UAs) lasting more than 10 seconds during sleep, causing a decrease in oxyhemoglobin saturation and an increase in adrenergic discharge. A thorough upper airway assessment is very important to evaluate the obstruction points. In 1999, the American Academy of Sleep Medicine established the diagnostic criteria for OSA, which included presence of excessive daytime sleepiness not explained by other factors; presence of at least two of the following: nocturnal choking, recurrent arousals, unrefreshing sleep, daytime fatigue, and decrease in concentration; and presence of apnea-hypopnea index (AHI) score greater than five events per hour, a mandatory criterion.

The physiopathogeny of OSA has not yet been fully elucidated. During respiratory events, there is a decrease in oxygen saturation, which leads to baroreflex activation, triggering a generalized activation of the sympathetic autonomic nervous system. There is an adrenergic discharge leading to peaks of tachycardia and hypertension. This process is repeated several times during sleep in apneic patients and, in the long term, it leads to high sensitivity of the peripheral chemoreflex, with exaggerated response even in normoxia, baroreflex dysfunction, increased adrenergic discharge, cardiovascular dysfunction in the long term, systemic inflammation, and metabolic dysregulation with insulin resistance and type II diabetes mellitus. All these alterations result in chronic inflammation of the entire upper airway, leading to the appearance of the varied symptoms in these patients.

Studies have demonstrated the diversity of OSA prevalence, as it can affect children, young adults, and the elderly. It is associated with different risk factors such as anatomical abnormalities, diseases, and habits. An epidemiological study performed in São Paulo, Brazil showed that the prevalence of OSA was 32.8% of the adult population of the city. The risk factors associated with the development of the syndrome were male gender, body mass index (BMI) > 25 kg/m², low socioeconomic status, age, and menopausal status. Snoring has a prevalence of 19.1% among men and 7.9% among women in the population aged 30 to 60 years.

Approximately 20% of the adult population complains of snoring, a figure that increases to 60% when considering males older than 40 years of age. Laryngopharyngeal reflux (LPR) is a variant of the gastroesophageal reflux disease (GERD) that affects the larynx and pharynx. In most cases, it is secondary to retrograde flow of gastric contents into the laryngopharynx, resulting in a series of laryngeal signs and symptoms. It has become one of the most common conditions in otorhinolaryngology. It is diagnosed in approximately 10% of patients with otorhinolaryngological symptoms and in at least 50% of patients with voice-related complaints. Obesity has also been recognized as an important factor, which is increasingly more prevalent in the world’s population.

LPR tends to occur during the day and has no clear association with obesity, in contrast to GERD.

Belafsky et al. validated two questionnaires for the systematic evaluation of the LPR-related complaints. The first, called the Reflux Symptom Index (RSI), assesses LPR symptoms. The scale consists of nine items scored 0 to 5, with a minimum score of 0 (asymptomatic) and maximum of 45. An RSI index ≥ 13 is considered to be suggestive of LPR.

The other scale developed by Belafsky et al. is the Reflux Finding Score (RFS) of laryngoscopic findings suggestive of LPR. An LPR score > 7 is considered positive for LPR.

OSA and LPR are two conditions that cause chronic upper airway inflammation. Symptoms such as hoarseness, pharyngeal globus, dysphagia, and choking are observed in both diseases. The association between OSA and LPR has been discussed in the literature in recent years, but the correlation between the two diseases has not reached a consensus. Gastroesophageal motility is decreased during sleep. Intraesophageal pressure is decreased in patients with OSA, but Kuribayashi et al. demonstrated that the upper esophageal sphincter and the gastroesophageal junction increase their tonus, decreasing LPR events.

The presence of LPR or GERD is associated with an increased number of awakenings, regardless of the presence of OSA. Patients with mild to moderate OSA experience greater influence from LPR on the number of awakenings than patients with severe OSA. Few studies have evaluated the influence of obesity on the association between OSA and LPR. Thus, this assessment is relevant, since the incidence of obesity has...
been consistently increasing and has an important influence on the natural course of OSA.

Objectives

To evaluate the influence of obesity on the association between LPR and OSA in a population of patients with OSA.

Materials and methods

This study was approved by the Ethics and Research Committee under protocol 113/08, and registered at the Clinical Trials Registry under ID NCT00883025. This was a retrospective, cross-sectional, and observational study, which evaluated patients with OSA who attended the otorhinolaryngology service by reviewing treatment protocols from medical records.

The evaluation protocol included anamnesis; the application of Epworth Sleepiness Scale, snoring scale, Friedman classification, and validated questionnaires for LPR (RSI and RFS); and complete otorhinolaryngological examination with nasal endoscopy and polysomnography.

The Friedman classification evaluates palatine tonsils, modified Mallampati score, and BMI, and comprises four stages (I, II, III, and IV). Patients underwent nasal endoscopy with a 3.2-mm Machida ENT PIII nasal endoscope. The level of upper airway obstruction was evaluated using the Fujita classification. Patients were referred for type I polysomnography performed in a sleep laboratory by a trained technician. Monitoring included the following channels: eye movements, leg movements, nasal airflow, chest movement, electroencephalogram (EEG), electrocardiogram (ECG), heart rate, and oxygen saturation. Patients were divided regarding disease severity, according to the criteria of the task force of the American Academy of Sleep Medicine.

Statistical analysis

A study model for continuous variables with t-test was used for data analysis. Levene’s t-test was used for equality of variances and the Student’s t-test was used for equality of means.

The following statistical hypotheses were analyzed in the statistical model used:

- Null hypothesis - The severity of OSA by AHI does not correlate with LPR assessed by RSI.
- Alternative hypothesis - The severity of OSA by AHI is positively correlated with LPR assessed by RSI.

The significance level used in the analysis was 0.05 for type α error and 0.2 for type β error. The Statistical Package for Social Sciences (SPSS) software for Mac, release 20.0, was used for the statistical analysis.

Inclusion and exclusion criteria

Inclusion

1. Patients belonging to the OSA Outpatient Clinic cohort;
2. Patients with complete protocol;
3. Patients aged 18 to 80 years;
4. Patients of both genders.

Exclusion

1. Patients with upper airway tumors and/or polyps;
2. Patients with craniofacial deformities such as craniosynostosis and cranio-dysostosis;
3. Previous history of airway and/or abdominal surgery;
4. Incomplete protocol and/or no analysis of key study variables such as RSI, RFS, and polysomnography.

Results

The number of patients in the cohort described in “Materials and methods” totaled 343. One hundred and five patients who had LPR evaluation data assessed by the RSI, RFS scales, and polysomnography were included.

The sample was divided by BMI using a cutoff of 30 kg/m² for the obese group, with 39 patients (37.1%); the non-obese group had 66 patients (62.9%). Gender distribution showed 57 (53.3%) males and 50 (46.7%) females.

Table 1 shows the description of continuous variables evaluated in this study.

| Table 1 Description of continuous variables. | Minimum | Maximum | Mean  | Standard deviation |
|---------------------------------------------|---------|---------|-------|--------------------|
| BMI                                         | 20.00   | 44.11   | 29.0202| 4.58815            |
| Age                                         | 18.00   | 76.00   | 44.5701| 12.97757           |
| RSI                                         | 0       | 42      | 10.96 | 7.645              |
| RFS                                         | 0       | 14      | 5.22  | 3.356              |
| AHI                                         | 4       | 76      | 21.51 | 15.634             |

AHS, Apnea-hyponea Index; BMI, body mass index; RSI, Reflux Symptom Index; RFS, Reflux Finding Score.
For the purposes of paired analysis using the t-test, and in order to maximize the statistical power, the AHI was divided into two groups with a cutoff of 15 events per hour. Mild OSA patients totaled 51 (48.5%) patients, and 53 (51.5%) had moderate and severe OSA. Both categories were correlated with the continuous variables RSI and RFS using the t-test. Table 2 shows the results of pairing in the group of non-obese patients. This study was designed to assess obesity alone as a confounding factor, with balanced samples and obesity defined by BMI.

When analyzing non-obese patients, Table 2 evidences the association between apnea severity and the indices validated in LPR assessment (RSI and RFS). In this subgroup, there was no statistical significance. In relation to the same analysis in Table 3, in the group of obese patients, there was no statistical significance between RSI and the OSA severity, as shown by the test of equality of means, with p < 0.05. The association between RFS and OSA severity was not significant. This association is depicted in Fig. 1.

**Table 2 t-test for equality of means in non-obese patients.**

|        | Mean  | Standard deviation | p    |
|--------|-------|--------------------|------|
| RSI    | Mild OSA | 11.96             | 8.470| 0.333^a |
|        | Moderate-severe OSA | 11.43         | 8.891|       |
| RFS    | Mild OSA  | 6.00              | 3.651| 0.587^a |
|        | Moderate-severe OSA | 5.35           | 3.673|       |

OSA, obstructive sleep apnea; RSI, Reflux Symptom Index; RFS, Reflux Finding Score.

^a Non-significant.

**Table 3 t-test for equality of means in obese patients.**

|        | Mean  | Standard deviation | p    |
|--------|-------|--------------------|------|
| RSI    | Mild OSA | 6.70             | 5.498| 0.054^a |
|        | Moderate-severe OSA | 11.30         | 6.097|       |
| RFS    | Mild OSA  | 4.43              | 2.507| 0.648^b |
|        | Moderate-severe OSA | 4.69           | 3.199|       |

OSA, obstructive sleep apnea; RSI, Reflux Symptom Index; RFS, Reflux Finding Score.

^a Significant.

^b Non-significant.

**Figure 1** Box-plot between Reflux Symptom Index (RSI) and Apnea-hyponea Index (AHI) in obese patients. Mild obstructive sleep apnea (OSA), AHI < 15 events/hour; moderate/severe OSA, AHI ≥ 15 events/hour.
Discussion

The importance of OSA and LPR in otolaryngology has considerably increased in recent years; they are among the main complaints in the specialty clinics. These are chronic diseases that affect the airways, causing chronic mucosal inflammation and decreased quality of life. According to Wise et al., GERD is more commonly found in patients with OSA, but the direct correlation was not significant.12

In a recent systematic review, Karkos et al. concluded that the association between LPR and OSA has been previously described in the literature, but the studies had low levels of evidence with few controlled studies.13 Several factors may generate biases in this analysis, since these are multifactorial diseases that are influenced by anatomic upper airway abnormalities, weight, and comorbidities.

Obesity is closely related to OSA, and it is considered as an independent predictor.10 According to Halum et al., the correlation with GERD is also quite clear, but the association with LPR alone is not.14 Xiao et al. studied the correlation between LPR and OSA using multichannel pH monitoring and found no significant correlation, but listed BMI as a confounding variable that could affect the results of association and prediction of LPR in OSA.15

In the present study, when evaluating the correlation in patients with BMI < 30 kg/m², i.e. not obese, no increase in RSI and RFS in patients with moderate to severe OSA (AHI > 15) were observed. Mean values were similar; demonstrating that, in this subgroup of patients, LPR and OSA are independent factors.

When evaluating the group of obese patients, a change in trend was observed, as the RSI of obese patients was significantly higher in patients with moderate to severe OSA, with almost twice the mean RSI. The same correlation was not observed in the evaluation of RFS.

Obesity has a major influence on the natural course of OSA, and is directly associated with disease severity.16 In the present series, obese patients and patients with OSA had higher incidence of LPR. This subgroup of patients, therefore, has several factors (OSA, LPR, and obesity) that increase upper airway inflammation, increasing edema and causing greater laxity of the mucosa and musculature, with morbidity worsening in both diseases. The aforementioned factors act together to promote inflammatory changes that increase the symptoms of upper airway irritation, which justifies the increase of RSI in obese patients and patients with moderate to severe OSA.

Obesity leads to increased intra-abdominal pressure; this mechanism has important physiopathological implications in LPR and OSA. In the latter, it causes increased respiratory effort, resulting in decreased thoracic range of movement. Stomach clearance is decreased and the incidence of reflux episodes increases.

In the present study, no positive correlation was observed between the severity of OSA by AHI and LPR laryngeal alterations measured by RFS. Obesity did not influence this variable behavior in both groups, as RFS maintained similar means within the normal range in patients with mild OSA and in those with moderate to severe OSA.

Symptoms of LPR and OSA are mistaken for symptoms of chronic airway inflammation. In obese patients, these symptoms become more intense in patients with moderate and severe OSA. This correlation was not sustained in the laryngoscopic evaluation, and the possibility of a false positive result in this review cannot be ignored.

During the evaluation of patients with OSA, the coexistence of LPR should be considered, which must be treated, promoting increased quality of life and reducing airway inflammation, as well as attenuating the deleterious effects on the upper airways.

Conclusion

LPR, OSA, and obesity are positively correlated. Obese patients with moderate to severe OSA have more severe symptoms than non-obese patients. The study demonstrated the importance of diagnosis and treatment of LPR in patients with OSA and obesity.

Conflicts of interest

The authors declare no conflicts of interest.

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