Original article

OPEN ACCESS

A Close Correlation between Sleep Apnea Syndrome and Gastroesophageal Reflux Disease: An Interdisciplinary Outpatient Retrospective Study in Southern Italy GERDOSA

Marco Umberto Scaramozzino [*1], Luciano Catalfamo [2], Simone Porcino [3], Angelo Coppola [4], Maurizia Festa [5], Giovanni Sapone [6]

[1]Director Ambulatory of Pulmonology "La Madonnina" Reggio Calabria (RC), Head of Thoracic Endoscopy Villa Aurora Hospital Reggio Calabria (RC).
[2]University Professor of Maxillofacial Surgery University of Messina, Specialist in Plastic Reconstructive Surgery, Maxillofacial Surgery Division of Maxillofacial Surgery, BIOMORF Department, University of Messina, Messina, Italy, AOU Policlinico "G. Martino", Via Consolare Valeria 1, 98125 Messina, ME Italy.
[3]Surgeon Specialist in Otolaryngology at the Porcino Medical Office Via Cairoli 24 Reggio Calabria (RC) 89129.
[4]Pulmonologist, P.O. San Filippo Neri- ASL Roma 1, Rome.
[5]Biologist, Human Nutrition Sciences at Outpatient Clinic of Pulmonology "La Madonnina", Reggio Calabria.
[6]Cardiology Department Head of Nursing Polyclinic M.D.C. Reggio Calabria Italy.

*Corresponding author: Dr. Marco Umberto Scaramozzino; *scaramozzinomarco91@gmail.com*

Received: 27 August 2023; **Revised:** 13 September 2023; **Accepted:** 16 September 2023; **Published:** 18 September 2023

Abstract

The following clinical study analyzes the multiparametric data of a Caucasian, obese population affected by sleep apnea syndrome and gastroesophageal reflux disease (total of 200 patients) enrolled between November 2020 and July 2023 within two private outpatient facilities located in Reggio Calabria; and diagnosed by nocturnal cardiorespiratory monitoring and laryngoscopy. The study shows that the association between the two pathologies and their prevalence in the obese population is increasingly frequent in recent decades. The statistical analysis of the multiparameter data was carried out through simple linear regression with obtaining the p values for single parameters, obtaining statistically significant data with reference to AHI, NBI score and ESS score. The study shows how the progressive reduction of the AHI over 24 months is contextual to the improvement of the ESS score which correlates with the day and night symptoms of the sleep pathology; furthermore, during these months a reduction in the endoscopic score of gastroesophageal reflux disease was found. The limitations of the study are related to the small sample examined and also related to the uncollected follow-up data in terms of adherence to OSA therapy.

Keywords: ***OSA, overlap, GERD, reflux, NBI score, cough, daytime sleepiness.***

Introduction

Sleep apnea syndrome (OSA) is a respiratory disease characterized by episodes of partial or complete collapse of the upper airways (VAS) determined by various causes. OSA is a frequent and often underestimated pathology affecting between 2 and 5% of the middle-aged population. The pathophysiological mechanisms underlying the genesis of the events are to be found during the Non-REM sleep phase during which there is hypotonia of the dilator and constrictor muscles of the pharynx, which determines partial (hypopnea) or total (apnea) collapse events load of the upper airways, generating snoring and sudden falls in oxygen saturation (SpO2) at a systemic level, determining an increased risk of incidence of cardiovascular and major ischemic events in an age ranging from 55 to 65 years of age. The pathology is very frequent in the obese population with a BMI >30m2/Kg and causes progressive increases Carbon dioxide (CO2) partial pressure in the peripheral arterial blood (PaCO2) in some subjects, especially in patients suffering from obesity/hypoventilation syndrome (OSA/OHS). Symptoms of the pathology include daytime sleepiness, frontal headache on awakening, daytime asthenia, nocturia, neuro-cognitive deficits [1]. Gastroesophageal Reflux Disease (GERD) it is a pathology that is increasingly emerging, very widespread in the world population and which sometimes manifests itself with symptoms, other times without obvious symptoms or with very few symptoms (silent form). At the basis of the pathophysiological mechanisms of GERD there are two theories: one of the reflex and one of the reflux (reflux and reflex theory), determined in part by vagus-mediated

microaspiration mechanisms (reflex theory) and in part by an altered motility of the lower esophageal sphincter (LES) (reflux theory), which apparently would fuel inflammation at the pulmonary level through mechanisms of diaphragmatic irritation and pulmonary hyper-inflation also at the basis of the genesis of reflux asthma; as well has been described by a pilot retrospective study called GERDAS [2]. A study in the literature carried out on a population of about 136 subjects, by now outdated, revealed how the association between OSA and GERD is very controversial as they have shown that GERD only affects the perceived quality of sleep but would not allow a causally link to be made between the two pathologies [3]. However, there are several recent studies in the literature that document the negative effects of GERD on patients with moderate and severe OSA either in systematic reviews or in meta-analyses or in case series or in prospective/retrospective studies. A recent study (2016) published in Sleep Medicine, on a group of patients suffering from OSA and GERD, would correlate the severity and frequency of apnoeic, hypopnoeic and arousal events with the development of acid reflux [4]. Other studies are very much aimed at closely correlating the sleep quality of patients with OSA and GERD without Barrett's eosphagus, measured through specific questionnaire (Pittsburgh Sleep Quality Index score - PSQI questionnaire). The limitation of the study cited was that it was aimed at a limited sample of the population with a prevalence of males and military veterans. The results of the study revealed a strong non-OSA-independent relationship between GERD and sleep apnea syndrome that negatively affects sleep quality [5]. A study carried out on a very large American scale (about 22,000,000 people) of patients with GERD, showed that in about 12% there was OSA and GERD compared with patients with only OSA without GERD (4.72%) [6]. According to other clinical studies, however, the therapy for OSA, would determine in patients with GERD and OSA, an improvement in nocturnal symptoms from GERD, and sleep quality. A prevalence of GERD in OSA is estimated at approximately 39% compared to 32% in the groups of patients not affected by OSA and GERD. It seems that the correlation between the two diseases exists, as there are similar risk factors for both diseases (asthma, arterial hypertension, obesity, depression) and this still calls into question the presence or absence of the causal link that for many is a simple similarity between risk factors [7]. In several recent scientific works, polysomnographic data the reduction of sleep quality indices and distal esophageal pH-metry have been analyzed, which have confirmed a simultaneous presence of both pathologies in an obese population, this allows to correlate the two pathologies closely [8-9]. A recent (2018) study published in the journal CHEST, highlighted how this correlation between gastroesophageal reflux and OSA is really present, and it was possible to analyze these events, having a duration that can range from a minimum of a few seconds to a maximum of minutes, through an actigraph, a pressure gauge with impedance pH probe, which recorded the presence of acid reflux during nocturnal events [10]. The aims of the study are multiple: 1) to demonstrate how weight loss affects both pathologies (OSA and GERD) studied. 2) The role of the NBI score in the detection of signs of gastroesophageal reflux disease 3) the nutritional pathway leads to an objective reduction of the AHI and NBI score as well as nocturnal symptoms; 4) The reduction in AHI is closely related to the ESS score.

Materials and method

The study GERDOSA, is a retrospective cohort study, which examined a cohort of Italian Caucasian population of about 200 people, aged between 20 and 60 years, with a male predominance (70% men and 30% women), with body mass index (BMI) > 30m2/kg, who visited two outpatient clinics: 'La Madonnina' and 'Porcino's study' from November 2020 to July 2023, for reported symptoms associated with typical and non-typical gastro-oesophageal reflux and OSA (Moderate to severe OSA) (**Figure 1**). The reported symptoms are chronic cough, odynophagia, dysphonia, retrosternal heartburn, chest pain, nocturnal dyspnea, nocturnal awakenings, snoring, daytime sleepiness, daytime asthenia, nocturia, neurocognitive deficits with memory loss.

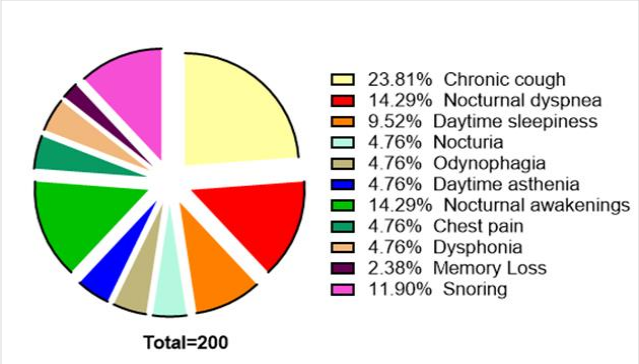

Figure 1: The exploded pie chart shows the presence and prevalence of symptoms such as: chronic cough (23,81%), nocturnal awakenings (14,29%), nocturnal snoring (11,90%), nocturnal dyspnea (14,29%) and daytime sleepiness (9,52%).

Inclusion and Exclusion criteria of the Study

Study inclusion criteria included: 1) Diagnosis of sleep apnea syndrome by nocturnal polysomnography and Epworth scale (ESS) questionnaire at first visit, 2) Diagnosis of GERD by laryngoscopy (indirect signs of GERD and/or mucosal changes) and/ or oesophageal pH-metry, 3) BMI > 30 m2/kg. The exclusion criteria are represented by: 1) pregnant women, 2) patients with already confirmed diagnosis of both pathologies, 3) pediatric patients (**See the Table 1**).

Table 1: Table of population, inclusion, and exclusion criteria.

Population (total: 200 caucasian patients)	**70% men, 30% women**
Inclusion Criteria: • Diagnosis of sleep apnea syndrome by nocturnal polysomnography and Epworth scale (ESS) questionnaire at first visit, • Diagnosis of GERD by laryngoscopy (indirect signs of GERD and/or mucosal changes) and/ or oesophageal pH-metry. • BMI > 30m2/Kg	Exclusion Criteria: • Pregnant women, • Patients with already confirmed diagnosis of both pathologies, • Pediatric patients.

Statistical analysis and follow-up

The statistical results obtained by parameters that were monitored at time 0, at time 6, at time 12 and time 24months, following the start of therapy and the nutritional course: AHI, ODI, ESS score, NBI score of GERD and BMI. The result shows that the data on AHI, daytime sleepiness (ESS score) and NBI score (endoscopic score);

markedly reduced after 24 months (**Figure 2 below**). The results were obtained from simple linear regression of multiparametric statistical analysis and showed statistically significant values (AHI, NBI score p values <0.0001, ESS score p value: 0,0030) of values of AHI, ESS score, NBI score. There are no statistically significant values of ODI, BMI (p value: 0,4128 and 0,1133). After the first diagnosis of both pathologies, a therapy based on proton pump inhibitors (at dosage of 20 or 40mg/day) and new generation alginates twice a day was set up; indication for nutritional evaluation with loss of at least 10% body weight and CPAP therapy. The limitations of the study are related to the fact that the statistical analysis of the monitoring data during CPAP therapy are so scarce that they are not statistically significant; therefore, they did not want to be reported below, we report only into the graph data from nocturnal SpO2 monitoring with Contec Respiration Monitor Nose Flow device (AHI and ODI). All patients were informed about the use of the data in terms of research and each patient regularly signed informed consents.

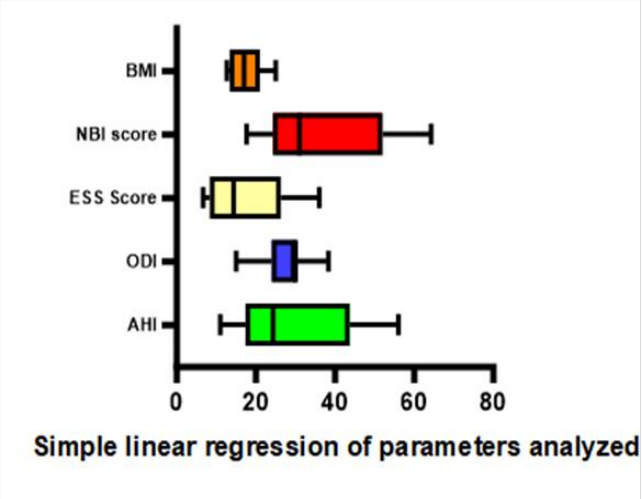

Figure 2: As we can see in the graph the simple linear regression of multiparametric analysis, it is possible to see that the reduction in AHI, NBI score (p values: <0,0001) and ESS score (p value: 0,0030) that corresponds to a marked reduction in daytime symptoms detectable through the ESS score. This makes us understand how important it is to apply a nutritional visit in parallel to the specialist visit and to follow the patient during a long follow-up.

Discussion

As can be seen from the population group under study, there is a high percentage of obesity associated with OSA and GERD. This is because, in numerous clinical studies it has been observed that, there are high serum values of Obestatin, Leptin, Ghrelin, the latter correlates with the degree of severity of esophagitis, GERD and OSA [11]. It is important to correlate the OSA to the GERD, to assess its severity. Recent publications in the literature, analyze algorithms to predict the severity of the Apnea/hypopnea index (AHI) through artificial intelligence in OSA, with satisfactory and promising results in terms of specificity and sensitivity. However, this does not yet allow to exclude demographic data, clinical and endoscopic scores to assess the overall severity of the disease [12]. The importance of artificial intelligence in diagnosing and predicting the extent and severity of respiratory diseases is now widely thought and can be applied to different fields of telemedicine, in clinical medicine and in the outpatient setting, as described on a work that through a pilot case report of a patient suffering from fibrotic pulmonary pathology has made it possible to launch the use of wireless technology and AI to also diagnose restrictive lung diseases in the outpatient setting [13]. In addition, endoscopic studies performed on patients with OSA and GERD, endoscopically proven that GERD was associated with more severe OSA. GERD symptoms were also associated and with deteriorated sleep quality and severity index (AHI) of OSA [14-15]. Recently, new endoscopic techniques such as endoscopic narrowband imaging (NBI) and detection of serum pepsin in tears have also been evaluated, but they are still under study and have been conducted in small population samples with promising results. [16]. What emerges from the researched bibliographic sources and from this retrospective study, is that OSA and GERD pathologies have pathophysiological mechanisms that determine the stimulation of common inflammatory pathways triggered by damage caused by oxidative stress and intermittent hypoxemia generated respectively by both events that occur during sleep. At the base of inflammation in both pathologies there are pro and anti-inflammatory cytokines such as: Tumour necrosis factors, inflammatory cytokines (IL2, IL4, IL6), lipid peroxidation, and cell-free DNA, that have been found in a study to increase in OSAS patients The intermittent hypoxia would lead to increased obstruction of airflow in the lungs, increased air remodelling and pro-fibrosing markers, increased Th1-type inflammation and neutrophil levels; as well as IL-8 (interleukin-8) and MMP-9 (metalloproteinase-9). [2,17]. Soon, it would be important to understand well the inflammatory link that underlies the two diseases; and develop drugs that have applications on both diseases, also determining a reduction in obesity and extraesophageal reflux symptoms, the latter caused by autonomic fluctuations of the autonomic nervous system, as well described widely in the literature [18]. Finally, we can say that in these patients, despite a little adherence to CPAP therapy also due to a poor cultural background present in southern Italy, in patients who regularly carried out therapy with continuous positive pressure devices, there was an improvement in both OSA and GERD symptoms, and the incidence of reflux events in patients with OSA as evidenced by meta-analysis on this topic [19].

Conclusion

OSA is a systemic syndrome, that has implications at various levels and that can coexist with other respiratory and non-respiratory diseases (such as: asthma, COPD, GERD etc.) for numerous common risk factors and pro-inflammatory activation pathways as well described by the extensive literature treated. The retrospective study showed that there is a strong prevalence and incidence of OSA and GERD, with an increased M:F ratio of 2,5:1 and that the symptoms of OSA and GERD overlap going to affect the Epworth scale negatively. Additional randomized, controlled clinical trials are needed to support the hypothesis supported by this article. It would seem from the endoscopic experience of our otolaryngologist, that indirect signs of laryngo-pharyngeal reflux are found much more frequently endoscopically; with in some cases development of nodules and polyps affecting the vocal cords that cause worsening of the dysphonia symptom, which is common to both pathologies under examination. The limitations of study GERDOSA and like this in outpatient setting, are related to the fact that patients do not regularly carry out the prescribed checks, therefore there are no data of patients undergoing treatment with CPAP, only AHI and ODI calculate from SpO2 monitoring with Contec Respiration Monitor Nose Flow device, SpO2 which indirectly calculates the AHI.

Declarations

Ethical Considerations, informed consent, and Consent for publication

Informed consent was signed by all study participants. All mentioned ethical aspects and related consents were taken into consideration during the conduct of this study.

Contributions

MUS helped in conception and design of the study, MUS did data collection, MUS and SP did analysis and interpretation of data; LC and SP contributed to drafting the work and revising it critically for important intellectual content. All authors approved the final version for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare they have no competing interests, and all authors confirm accuracy.

Grant support & financial disclosures

None

Article category

Retrospective study

References

[1] Iannella G, Magliulo G, Greco A, et al. Obstructive Sleep Apnea Syndrome: From Symptoms to Treatment. Int J Environ Res Public Health. 2022 Feb 21;19(4):2459. doi: 10.3390/ijerph19042459.

[2] Scaramozzino MU, Festa M, Levi G, et al. Correlation between gastro-oesophageal reflux disease (GERD) lung volumes and exacerbation of bronchial asthma: Italian pilot observational retrospective study GERDAS. Monaldi Arch Chest Dis. 2023 Jun 15. doi: 10.4081/monaldi.2023.2640.

[3] Morse CA, Quan SF, Mays MZ, et al. Is there a relationship between obstructive sleep apnea and gastroesophageal reflux disease? Clin Gastroenterol Hepatol. 2004 Sep;2(9):761-8. doi: 10.1016/s1542-3565(04)00347-7.

[4] Jaimchariyatam N, Tantipornsinchai W, Desudchit T, et al. Association between respiratory events and nocturnal gastroesophageal reflux events in patients with coexisting obstructive sleep apnea and gastroesophageal reflux disease. Sleep Med. 2016 Jun; 22:33-38. doi: 10.1016/j.sleep.2016.04.013.

[5] Vela MF, Kramer JR, Richardson PA, et al. Poor sleep quality and obstructive sleep apnea in patients with GERD and Barrett's esophagus. Neurogastroenterol Motil. 2014 Mar;26(3):346-52. doi: 10.1111/nmo.12265.

[6] Mahfouz R, Barchuk A, Obeidat AE, et al. The Relationship Between Obstructive Sleep Apnea (OSA) and Gastroesophageal Reflux Disease (GERD) in Inpatient Settings: A Nationwide Study. Cureus. 2022 Mar 3;14(3): e22810. doi: 10.7759/cureus.22810.

[7] Oh JH. Gastroesophageal reflux disease: recent advances and its association with sleep. Ann N Y Acad Sci. 2016 Sep;1380(1):195-203. doi: 10.1111/nyas.13143.

[8] Dickman R, Green C, Fass SS, et al. Relationships between sleep quality and pH monitoring findings in persons with gastroesophageal reflux disease. J Clin Sleep Med. 2007 Aug 15;3(5):505-13.

[9] Ing AJ, Ngu MC, Breslin AB. Obstructive sleep apnea and gastroesophageal reflux. Am J Med. 2000 Mar 6;108 Suppl 4a:120S-125S. doi: 10.1016/s0002-9343(99)00350-2.

[10] Lim KG, Morgenthaler TI, Katzka DA. Sleep and Nocturnal Gastroesophageal Reflux: An Update. Chest. 2018 Oct;154(4):963-971. doi: 10.1016/j.chest.2018.05.030.

[11] Pardak P, Filip R, Woliński J, et al. Associations of Obstructive Sleep Apnea, Obestatin, Leptin, and Ghrelin with Gastroesophageal Reflux. J Clin Med. 2021 Nov 7;10(21):5195. doi: 10.3390/jcm10215195.

[12] Maniaci A, Riela PM, Iannella G, et al. Machine Learning Identification of Obstructive Sleep Apnea Severity through the Patient Clinical Features: A Retrospective Study. Life. 2023; 13(3):702. https://doi.org/10.3390/life13030702

[13] Scaramozzino, M. U., Sapone, G., Plastina, U. R., et al. (2023). The use of wireless technology for thoracic physical examination: a pilot case based on a literature review. infermieristica journal, 2(2), 81-87.

[14] Kim Y, Lee YJ, Park JS, et al. Associations between obstructive sleep apnea severity and endoscopically proven gastroesophageal reflux disease. Sleep Breath. 2018 Mar;22(1):85-90. doi: 10.1007/s11325-017-1533-2.

[15] Demeter P, Visy KV, Magyar P. Correlation between severity of endoscopic findings and apnea-hypopnea index in patients with gastroesophageal reflux disease and obstructive sleep apnea. World J Gastroenterol. 2005 Feb 14;11(6):839-41. doi: 10.3748/wjg.v11.i6.839.

[16] Pace A, Rossetti V, Milani A, et al. Obstructive sleep apnoea patients vs laryngopharyngeal reflux disease: Non-invasive evaluation with NBI and pepsin detection in tears. Bosn J Basic Med Sci. 2022 Jul 29;22(4):629-634. doi: 10.17305/bjbms.2021.6712.

[17] Maniaci A, Iannella G, Cocuzza S, et al. Oxidative Stress and Inflammation Biomarker Expression in Obstructive Sleep Apnea Patients. J Clin Med. 2021 Jan 13;10(2):277. doi: 10.3390/jcm10020277.

[18] Zanation AM, Senior BA. The relationship between extraesophageal reflux (EER) and obstructive sleep apnea (OSA). Sleep Med Rev. 2005 Dec;9(6):453-8. doi: 10.1016/j.smrv.2005.05.003.

[19] Li C, Wu ZH, Pan XL, et al. Effect of continuous positive airway pressure on gastroesophageal reflux in patients with obstructive sleep apnea: a meta-analysis. Sleep Breath. 2021 Sep;25(3):1203-1210. doi: 10.1007/s11325-020-02224-9.