What we know about gastroesophageal reflux disease and obstructive sleep apnea?

O que sabemos sobre a doença do refluxo gastro-esofágico e apneia obstrutiva do sono?

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ABSTRACT

Objectives: The primary objective of this systematic review is assessing whether treatment of gastroesophageal disease (GERD) may reduce the apnea and hypopnea index (HAI) and the secondary objective of assessing whether there is a correlation between the HAI and gastroesophageal acid reflux. Methods: Using a systematic review of clinical studies that investigated the relationship between obstructive sleep apnea and GERD. The search included all cited publications up to April 22, 2012, using the keywords “sleep apnea, obstructive” AND “gastroesophageal reflux/diagnosis” OR “gastroesophageal reflux/drug therapy” OR “gastroesophageal reflux/therapy” AND “randomized controlled trial”. The following electronic databases were used: PubMed, EMBASE, LILACS, MedLine, SCISEARCH, WEB of Science, CINAHL, BIREMI, SCOPUS, and the database of controlled clinical trials of the COCHANE collaboration. The total sample size was 60 patients (55% males). All patients in the eligible studies were submitted to both polysomnography and esophageal pH measurements before and after treatment. Results: Initially, 24 articles were selected. Of these, only three met the criteria for this study. All the 3 studies found in this analysis were “before and after” clinical trials. Through the grouping of patients in our systematic review, we found a statistically significant decline in the average time of GERD after treatment, and a trend for reduction in the rate of HAI. Conclusion: The studies examined demonstrate that medical treatment of GERD may reduce apnea and hypopnea. Nevertheless, more controlled clinical trials are needed to confirm the benefits of drug therapy for GERD in the context of obstructive sleep apnea.

Keywords: adults, apnea, clinical trial, upper airway.

RESUMO

Objetivos: O principal objetivo desta revisão sistemática é avaliar se o tratamento das doenças gastro-esofágicas (DRGE) pode reduzir o índice de apneia e hipopneia (IAH) e o objetivo secundário avaliar se existe uma correlação com o refluxo ácido gastroesofágico. Métodos: Utilizando uma revisão sistemática de estudos clínicos que investigaram a relação entre apneia obstrutiva do sono e DRGE. A pesquisa incluiu todas as publicações citadas até 22 abril de 2012, utilizando as palavras-chave “apneia obstrutiva do sono,” AND “do refluxo gastroesofágico/diagnóstico” OR “refluxo/queimadura gastroesofágico” OR “refluxo gastroesofágico/terapia” AND “ensaios controlado randomizado”. Foram utilizadas as seguintes bases de dados eletrônicas: PubMed, EMBASE, LILACS, MedLine, SCISEARCH, WEB of Science, CINAHL, BIREMI, SCOPUS, e o banco de dados de ensaios clínicos controlados da colaboração COCHANE. O tamanho total da amostra foi de 60 pacientes (55% do sexo masculino). Todos os pacientes nos estudos elegíveis foram submetidos tanto a polissonografia e a pHmetria esofágica antes e após o tratamento. Resultados: Inicialmente, 24 artigos foram selecionados. Destes, apenas três preencheram os critérios para este estudo. Os três estudos encontrados nesta análise foram “antes e depois” de ensaios clínicos. Através do agrupamento de pacientes em nossa revisão sistemática, encontramos uma redução estatisticamente significativa no tempo médio de DRGE após o tratamento, e uma tendência para a redução da taxa de IAH. Conclusão: Os estudos analisados demonstram que o tratamento médico da DRGE pode reduzir a apneia e hipopneia. No entanto, mais ensaios clínicos controlados são necessários para confirmar os benefícios da terapia medicamentosa para a DRGE, no contexto da apneia obstrutiva do sono.

Descritores: adultos, apneia, apneia obstrutiva do sono, ensaios clínicos.

INTRODUCTION

Obstructive sleep apnea (OSA) syndrome affects 4% of men and 2% of women in the United States of America1, according to Young et al., 1993. OSA is associated with an increased risk of developing cardiovascular diseases, such as systemic and pulmonary hypertension, cardiac arrhythmias, ischemic heart disease and congestive heart failure2. Due to these co-morbidities, OSA is often associated with increased medical expenses, although costs can be reduced with appropriate treatments. Kapur et al.3 showed that the mean medical cost...
per case in the year prior to a diagnosis of sleep-disordered breathing was $2,720, which is roughly double the cost for patients who were diagnosed and received treatment ($1,387).

OSA results in intermittent episodes of hypoxemia, hypercapnia, arousals, and sleep fragmentation(5) and can sometimes be caused by gastroesophageal reflux (GER). GER is considered pathological when it generates dysfunction or injury to the respiratory and/or digestive tract, at which stage it is labelled gastroesophageal reflux disease (GERD)(6).

OSA and GERD are considered separate diseases, although they share similar signs and symptoms that can overlap and become indistinguishable from each other. The incidence of GERD symptoms in patients with OSA ranges from 62% to 74%(5,8). OSA and GERD have common risk factors including age, and obesity, and share similar aspects of pathogenesis(7).

The literature has addressed several important issues related to OSA and GERD, but many questions remain unanswered, including whether GERD has a causal relationship with OSA(9). This information has relevant therapeutic and economic consequences.

The increased prevalence of nocturnal reflux in patients with snoring and obstructive sleep apnea has been well described(9-15). Muscle tone, including the lower esophageal sphincter and pylorus, is physiologically decreased during sleep. Due to a reduction in salivary flow and decreased motility, clearance of the esophagus is appreciably reduced relative to an awakened state(11-15). These physiologic aspects appear to play a specific role in GERD, particularly in overcoming the upper esophageal sphincter, which is a considerably more effective reflux barrier than the lower esophageal sphincter(12,14). The horizontal posture assumed during sleep results in higher intra-abdominal pressure with a cranially directed effect, particularly in obese individuals(9-11,13). The pathophysiological mechanisms that have been proposed to link GERD and OSA are not mutually exclusive, and it is possible that the two conditions may interact and create a self-perpetuating positive feedback loop(16). This hypothesis is supported by evidence showing that treatment of GERD improves OSA and vice versa(16).

Although it has been firmly established that GERD and OSA can co-occur, the nature of the relationship between the two conditions is not yet fully understood(16). Limited data have suggested a relationship between symptomatic OSA and GERD. The prevalence of GERD has been shown to be approximately 58-62% in patients with OSA(17-19). Apnea may increase the trans-diaphragmatic pressure and decrease the intra-thoracic pressure, favouring the development of GERD(19,20).

This systematic literature review gathered scientific evidence on the possible impact of the clinical treatment of GERD on obstructive sleep apnea. The primary objective of the review was to assess whether treating GERD reduces the incidence of apnea and hypopnea. The secondary objective was to determine if there is a correlation between the incidence of apnea and hypopnea and gastroesophageal acid reflux.

MATERIAL AND METHODS

Literature search

A systematic review of clinical studies that investigated the relationship between obstructive sleep apnea and GERD was conducted. The search included all cited publications up through April 22, 2012, using the keywords “sleep apnea, obstructive” AND (“gastroesophageal reflux/diagnosis” OR “gastroesophageal reflux/drug therapy” OR “gastroesophageal reflux/therapy”) AND “randomised controlled trial.” One clinical trial entitled Proton Pump Inhibitor Therapy for Mild to Moderate Obstructive Sleep Apnea(21) was found on clinicaltrials.gov. However, this article was excluded because the authors did not conduct polysomnographic studies nor esophageal pH measurements.

Study selection

Three reviewers independently selected articles by examining the titles and abstracts of all of the clinical studies identified in the electronic search. These evaluations were not blinded with respect to authors or the results of the studies. The following electronic databases were used: PubMed, EMBASE, LILACS, MedLine, SCISEARCH, Web of Science, CINAHL, BIREMI, SCOPUS, and the database of controlled clinical trials in the COCHRANE collaboration. Additional electronic and manual searches were conducted for cited works from the articles included in this study, using websites and national and international journals related to the topic. Inclusion and exclusion criteria, shown in Table 1, were used to screen for acceptance into the database for this study. None of the study populations were investigated more than once. A subset of the studies that met the criteria for inclusion was obtained, re-evaluated and analysed by the reviewers. The extracted data were crosschecked for consistency. All of the studies in this analysis were “before and after” clinical trials.

Table 1. Criteria for inclusion or exclusion of selected articles.

<table>
<thead>
<tr>
<th>Inclusion criteria (General)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Articles should be in Portuguese, English, or Spanish.</td>
</tr>
<tr>
<td>2. Articles should be complete (no abstract or letter to the editor was accepted).</td>
</tr>
<tr>
<td>3. The involved individuals were over the age of 18 years.</td>
</tr>
<tr>
<td>4. Both sexes were included.</td>
</tr>
<tr>
<td>5. Any ethnicity was studied.</td>
</tr>
<tr>
<td>6. In the event that the same study resulted in multiple publications, the most comprehensive study would be accepted as the primary reference, so that no data duplication would occur.</td>
</tr>
<tr>
<td>7. Studies must involve obstructive sleep apnea; central apnea was not included.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion criteria for objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Both polysomnography and the total time of acid reflux before and after drug treatment for GER, except for treatment with cisapride and metoclopramide.</td>
</tr>
<tr>
<td>2. Apnea-hypopnea index (AHI) values, defined by the authors of the clinical trials as the number of respiratory pauses per hour of sleep, before and after drug treatment.</td>
</tr>
</tbody>
</table>
Exclusion criteria for the objectives

1. Diagnosis of Barrett’s esophagus
2. Having undergone abdominal surgery
3. Important respiratory disorder
4. Psychiatric or neurological disease
5. Renal disease
6. Chronic liver disease

Statistical analysis
All of the identified studies were assessed for inclusion in the systematic review. Effect measures are presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs) and a significance level of $p < 0.05$. A random-effects model was used to calculate a pooled effect estimate, and the heterogeneity of the effect sizes was evaluated using the $I^2$ statistic. A $p$ value $< 0.05$ and/or an $I^2$ of at least 50% was considered an indicator of substantial heterogeneity in the outcomes.

All analyses and calculations were performed using Comprehensive Meta-Analysis, version 2.2.

RESULTS

Data extraction
A total of 24 articles were initially selected. Of these, only three met the inclusion criteria defined for this study, as shown in Figure 1.

The process of article selection from the database.

The design characteristics of the study and outcomes are shown in Table 2. The following were major reasons for exclusion of the studies did not show any objective improvement in the sleep parameters before and after acid suppression: the authors did not adequately describe the values of the apnea-hypopnea index (AHI), which is defined as the number of respiratory pauses per hour of sleep, before and after drug treatment; the total duration of acid reflux, defined as the length of time that the esophageal pH is below 4.0, before and after drug treatment was not provided. Other studies were excluded for specific reasons. For example, Noronha et al., selected infants that ranged from 1 to 6 months old; Sabaté et al., selected morbidly obese patients (body mass index $> 40$ or $> 35$ kg/m$^2$) in association with comorbidities who were candidates for bariatric surgery; the polysomnographies performed in Watson et al., 2008, were single-night diagnostic studies, and all the subjects underwent diagnostic polysomnography and were treated with CPAP within 30 days of their initial clinic visit; Dickman et al., invited subjects to undergo ambulatory 24-hour esophageal pH monitoring to determine the extent of distal esophageal acid exposure, the number of acid reflux events, the number of reflux events longer than 5 minutes, and indexed their symptoms. Fifteen of the participants were randomly selected to undergo polysomnography during esophageal pH monitoring, only after treatment; Hawylkiewicz et al., studied 21 consecutive patients with severe OSA (mean AHI 44.943; 8) before CPAP treatment, but none of them had any clinical symptoms of GERD; Ozturk et al., 2004, investigated the respiratory and sleep parameters in patients with OSA with or without nocturnal GER episodes. Nineteen of the patients who were referred to the sleep laboratory for suspected sleep apnea were included in the study. All of the subjects underwent polysomnographic evaluation simultaneously with distal and proximal esophageal pH monitoring, but polysomnography and acid reflux before and after drug treatment for GER were not evaluated.

In Orr et al., 2009, 139 participants consented to participate; but, 90 did not meet the screening criteria, and 24 dropped out of the study. As a result, only 25 patients completed both the sleep and esophageal evaluations. All participants had symptoms consistent with a diagnosis of OSA (snoring and daytime sleepiness or fatigue) and subjective complaints of GER. Participants were excluded if they had a history of Barrett esophagus, history of abdominal surgery, significant respiratory distress, neurologic or psychiatric disorder, or significant chronic renal or liver disease. Patients were subjected to powerful acid suppression (rabeprazole 20 mg, twice a day) for 2 months. Patients were assessed with full polysomnography and 24-hour esophageal pH monitoring, before and after treatment with powerful acid suppression.

Friedman et al. (2007) which reported the phase 2 results of a two-part study designed as a prospective clinical trial, studied 52 patients with GERD and OSA. During follow-up, 14 of the patients dropped out and 9 were excluded because GERD did not improve after drug treatment. These cases were considered treatment failures and were analysed accordingly. Patients with comorbid conditions of GERD and OSA proven by 24-hour pH-monitoring studies and overnight
polysomnograms were treated with a proton pump inhibitor (esomeprazole magnesium, 40 mg once daily) for 2 to 6 months and then retested and reevaluated for assessment of both subjective and objective changes\(^{22}\).

Ing et al.\(^{28}\), 2003, selected 12 patients with OSA and GERD to participate in a placebo controlled randomised clinical trial. All patients having screening polysomnography for OSA in their laboratory (Compumedics S Series Sleep System V4.0) also underwent distal esophageal pH monitoring\(^{29}\). All polysomnographic studies were analyzed manually with AHI determined. Subjects were used as controls if the AHI was < 5. Subjects were defined as having OSA if the AHI was > 15. All apneas, hypopneas, and arousals were analyzed manually to determine their relationship to any reflux events\(^{20}\). Patients with OSA and proven esophageal reflux were randomized to a 1-month trial of either nizatidine 150 mg po twice daily or placebo. Repeat polysomnographic study and distal esophageal pH monitoring were then performed after the nizatidine or placebo treatment period\(^{20}\).

The studies selected for inclusion in this review were comparative clinical trials involving patients with GERD with obstructive sleep apnea. All of the patients in the eligible studies underwent both polysomnography and esophagus pH measurements before and after drug treatment. A total of 60 patients (55% male) were evaluated. The pH measurements were obtained with either 24-hour esophageal pH analysis or transnasal wireless 24-hour pH monitoring. The medications esomeprazole and rabeprazole were used for at least 2 months. In the Friedman et al.\(^{25}\) study, there was a significant tendency toward improvement in the apnea-hypopnea index (AHI) with drug treatment, while Orr et al.\(^{6}\) did not report a statistically significant trend.

The general characteristics of the selected studies are shown in Table 3. One of the limitations of the studies included in this systematic review was a lack of control groups, with the exception of Ing et al.\(^{28}\), which included 41 controls and 63 patients with OSA. A total of 12 patients diagnosed with GERD were selected and randomly assigned to two groups of 6 patients each that underwent treatment with nizatidine (150 mg, twice daily) or a placebo for 1 month. However, for the purpose of this review, only the nizatidine-treated group was included.

In this systematic review, we did not find a statistically significant difference between the average rate of apnea and hypopnea before and after drug treatment and the average length of time to GERD before and after drug treatment (as shown in Figure 2).

Table 2. Selection of articles that were identified through electronic searches.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Polysomnography before and after treatment</th>
<th>pH evaluations before and after treatment</th>
<th>Treatment with proton pump inhibitor (for at least 4 weeks)</th>
<th>Article selected or excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009, Orr et al.(^{16})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Selected</td>
</tr>
<tr>
<td>2009, Noronha et al.(^{23})</td>
<td>Polysomnography performed once</td>
<td>One pH measurement</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2008, Suurna et al.(^{26})</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Excluded</td>
</tr>
<tr>
<td>2008, Shaheen et al.(^{25})</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Excluded</td>
</tr>
<tr>
<td>2008, Schaefer et al.(^{26})</td>
<td>Polysomnography performed once</td>
<td>One pH measurement</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2008, Watson et al.(^{29})</td>
<td>Polysomnography performed once</td>
<td>No</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2007, Friedman et al.(^{22})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Selected</td>
</tr>
<tr>
<td>2007, Friedman et al.(^{28})</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Excluded</td>
</tr>
<tr>
<td>2007, Dickman et al.(^{29})</td>
<td>Polysomnography performed once</td>
<td>One pH measurement</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2006, Bottolotti et al.(^{30})</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Excluded</td>
</tr>
<tr>
<td>2006, Hawrylkieiwicz et al.(^{31})</td>
<td>Polysomnography performed once</td>
<td>One pH measurement</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2006, Tawk et al.(^{32})</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Excluded</td>
</tr>
<tr>
<td>2005, Orr et al.(^{25})</td>
<td>Yes</td>
<td>Yes</td>
<td>Medication was used for only one week</td>
<td>Excluded</td>
</tr>
<tr>
<td>2005, Kim et al.(^{24})</td>
<td>Polysomnography performed once</td>
<td>No</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2004, Wasilewska et al.(^{29})</td>
<td>Polysomnography performed once</td>
<td>One pH measurement</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2004, Steward(^{34})</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Excluded</td>
</tr>
<tr>
<td>2004, Steward(^{37})</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2004, Morse et al.(^{38})</td>
<td>Polysomnography performed once</td>
<td>No</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2003, Ozurk et al.(^{29})</td>
<td>Polysomnography performed once</td>
<td>One pH measurement</td>
<td>No</td>
<td>Excluded</td>
</tr>
<tr>
<td>2002, Konermann et al.(^{36})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes CPAP was also used</td>
<td>Excluded</td>
</tr>
<tr>
<td>2001, Senior et al.(^{40})</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Excluded</td>
</tr>
<tr>
<td>2000, Ing et al.(^{26})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Selected</td>
</tr>
<tr>
<td>1999, Konermann et al.(^{41})</td>
<td>Done prior to treatment</td>
<td>Done prior to treatment</td>
<td>Yes</td>
<td>Excluded</td>
</tr>
<tr>
<td>1999, Xiao et al.(^{22})</td>
<td>Yes</td>
<td>Yes</td>
<td>No, cisapride was used</td>
<td>Excluded Chinese article</td>
</tr>
</tbody>
</table>
events during the night compared to healthy individuals. The increase in reflux episodes is related to an increased frequency in transient relaxation of the lower esophageal sphincter. In patients with GERD, nocturnal reflux episodes, that occur when the patient is asleep are clinically important because they are more prolonged than the episodes that occur during the day. This finding may be related to the reduced motility of the esophagus during the night and because esophageal clearance in the supine position is less efficient. Ing et al., 2000, showed that nizatidine had no significant effect on AHI or minimum oxygen saturation when compared with baseline (pretreatment) parameters, but that the arousal index was significantly reduced. There were no changes in any of the OSA parameters in the placebo group. Patients receiving nizatidine had a lower AHI after therapy compared to the placebo group, but this parameter was not matched at the baseline. In another therapeutic study, patients with OSA and confirmed esophageal reflux selected from the initial study were randomised in a 1-month trial with nizatidine 150 mg twice daily or a placebo. The authors reported that nizatidine reduced arousals, but that the AHI, compared with the baseline, in patients who received active therapy, was not matched at the baseline. In another therapeutic study, patients who were treated with nizatidine had a significantly lower RDI and number of arousals arousals after the treatment period. Ing et al., 2000, implied that acid esophageal reflux may contribute to the pathogenesis of arousals and excessive daytime somnolence in patients with OSA. The effect of nizatidine on AHI and apneas is equivocal, and larger studies are necessary. The authors concluded that the use of proton pump inhibitors may assist in determining the true effects of antireflux therapy on the AHI in patients with OSA, and that studies with more participants would allow improved matching of the placebo group to the active treatment group, particularly for measuring the AHI.

The present study shows that the total acid GER time was reduced after medical treatment, which was consistent in all of the studies. Each of the studies used an objective evaluation of acid GER and showed improvement after treatment. The pathophysiology that links OSA to increased esophageal acid reflux contact and increased upper airway obstruction in patients with OSA remains unknown. It has been postulated that a significant increase in intrathoracic negative pressure due to obstruction of the upper airways may predispose patients to the retrograde movement of the gastric contents due to an increase in transdiaphragmatic pressure and increased phrenoesophageal ligament (connects the diaphragm to the lower esophageal sphincter) tension during an obstructive episode. When the force exerted on the lower esophageal sphincter exceeds the closure limit, the sphincter can open and allow the passage of gastric contents through the esophagus. Penzel et al. evaluated 15 patients and showed a mean AHI of 30.1 (events per hour of sleep) using polysomnography, and pH monitoring revealed that all of the patients had episodes of reflux. Another study showed that 71.4% of patients with OSA had GER as measured using pH monitoring, while 10.4% of the cases were asymptomatic.

### DISCUSSION

An ideal study evaluating the effects of the clinical treatment of GERD on obstructive sleep apnea should gather information on the potential benefits and risks of various interventions to fully assess the net comparative benefits. Interventions should be relatively inexpensive and enable the treatment of patients early in the disease process. All of the patients in these studies were seeking treatment for snoring and other symptoms of sleep apnea, and the minimum duration of treatment was as short as 2 months. It is possible that more improvement to the OSA symptoms in patients might have occurred as a result of a longer term study.

In reviewing the effects of clinically treating GERD on obstructive sleep apnea, we found a paucity of evidence on which to base standards of practice recommendations. Most of the data were drawn from small case series of selected patients. Although significant improvements in the AHI were reported in several of the small series, the efficacy was attributed in part to the limitations of the study, such as not including a placebo-controlled arm.

We observed that clinically treating GERD reduced the apnea-hypopnea index, but that the trend was not statistically significant. One possible explanation for the lack of statistically significant differences may be related to the relatively small sample sizes in each study. The population in this systematic review was restricted to only 66 patients. One of the mechanisms that has been postulated to explain the trend toward improvement of OSA symptoms using medication to control GERD is that esophageal acid reflux stimulates the vagus nerve and causes bronchoconstriction, which can lead to OSA. Using magnetic resonance imaging, Schwab et al. observed that patients with OSA have a smaller pharynx, with laterolaterally narrowing and an altered shape that is circular instead of laterolaterally elliptical. This anatomical variation may be related to the manifestations of GERD. The direct effect of gastric contents on the laryngeal mucosa may induce symptoms suggestive of obstructive sleep apnea due to inflammation and consequent swelling of the laryngeal structures. However, healthy adults have very few episodes of nocturnal GER. Friedin et al. observed that patients who were diagnosed with reflux disease have more nocturnal reflux episodes than controls, and it has been observed that patients with symptoms during the day tend to have more reflux.

### Table 3. Study design and outcome.

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Study Design</th>
<th>N</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orr et al.</td>
<td>2009</td>
<td>Prospective clinical trial</td>
<td>25 patients</td>
<td>GERD treatment can improve obstructive sleep apnea syndrome</td>
</tr>
<tr>
<td>Friedman et al.</td>
<td>2007</td>
<td>Prospective clinical trial</td>
<td>29 patients</td>
<td>GERD treatment can improve obstructive sleep apnea syndrome</td>
</tr>
<tr>
<td>Ing et al.</td>
<td>2000</td>
<td>Placebo controlled randomized clinical trial</td>
<td>12 patients</td>
<td>GERD treatment can improve obstructive sleep apnea syndrome</td>
</tr>
</tbody>
</table>

*Gastroesophageal reflux and obstructive sleep apnea*
In 94 patients with high Epworth Scale score who complained of excessive sleepiness, Guda et al.\(^6\) (2004) observed that the AHI was significantly higher in patients with GER using polysomnography and pH monitoring (34.1 vs. 59.0; \(p = 0.04\)). The authors suggested that patients with GER have more apnea episodes than those without reflux symptoms. In another study, Ing et al.\(^20\) selected 14 patients with OSA (diagnosed by polysomnography) and GER (diagnosed by pH monitoring) and treated them with nasal continuous positive airway pressure (nCPAP). The authors repeated the tests and observed that nCPAP reduced the AHI and GER parameters (i.e., the number of reflux events, percentage of time with pH < 4, and esophageal clearance). In the same study, 12 additional patients with OSA and GER were treated with nizatidine and a placebo. Nizatidine reduced both the OSA and acid GER parameters, while the placebo had no effect on the parameters when compared with the initial values. In 2002, Valipour et al.\(^51\) selected 271 individuals with suspected sleep-disordered breathing to complete questionnaires related to GERD and polysomnography studies. A total of 228 individuals were included in the final statistical analysis. The authors found that the odds ratio for GERD in individuals without OSA who snored compared with those with OSA was 1.21\% (95\% CI, 0.7-21; \(p = 0.74\)) and observed that patients who snored used medication more frequently to control GERD than the patients with OSA (OR: 0.98; 95\% CI; 0.8-1.1; \(p = 0.70\)). No differences were observed in the number of GER episodes experienced by the individuals included in the study, with apnea or snoring (62.8\% vs. 41.4\%; \(p = 0.013\)).

The findings in this systematic review point to the limitations of the studies that have been published and emphasise that little is known about the impact of GERD treatment on OSA. For example, in the literature studied, only one randomised clinical trial study evaluated the relationship between obstructive sleep apnea and GERD and the effect of GERD treatment on OSA. It was not possible to compare the group that received treatment with a placebo group in the meta-analysis, and measures were not used to assess the quality of the studies because all of the studies in this analysis were “before and after” clinical trials. This systematic review suggests that more randomised clinical trials are necessary and draws attention to the need to further investigate the hypothesis that GERD can worsen OSA and that GERD treatment can improve OSA. A better understanding of these crucial issues may have a significant impact on the effectiveness and costs of managing OSA. Jung et al.19, 2010, concluded that data on non-acidic reflux and the potential relationship with sleep are also needed (e.g., using impedance and high resolution manometry). A better understanding of the relationship between sleep and GERD may allow clinicians to manage these patients more effectively in the future.

We identified a trend in the reduction of AHI in subjects with OSA and GERD when using medication for to treat GERD. The available evidence in the literature is insufficient to form any specific recommendations, but indicates that additional studies are needed to assess the possible role of GERD treatment with medication to control OSA.

This systematic review of the available data regarding the possible impact of the clinical treatment of GERD on obstructive sleep apneasuggests that the published evidence is insufficient as a basis for establishing recommendations or guidelines.

**CONCLUSIONS**

In this systematic review evaluating the clinical treatment of GERD on obstructive sleep apnea, we have found a paucity of evidence on which to base standards of practice recommendations. Most of the data were drawn from small case series of selected patients. Although significant improvements in AHI were reported in several of the small series, the efficacy was attributed in part to careful patient selection. In light of these outcomes and the increasing interest in the treatment of obstructive sleep apnea, we suggest implementing additional trials focusing on standardising pre and post-treatment targets.
REFERENCES

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