

## Reflux and sleeping disorders: a systematic review

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### Abstract

**Introduction:** Laryngopharyngeal reflux is perhaps the most extensively researched laryngology topic of the last decade. It has been suggested that some supraoesophageal symptoms, most notably asthma and laryngospasm, may be associated with night-time, or supine, reflux. The aim of this review was to assess the levels of evidence regarding a correlation between night-time reflux, snoring and apnoea.

**Methods:** A Medline search was performed using the terms ‘reflux’, ‘night-time’, ‘larynx’, ‘gastroesophageal’, ‘laryngopharyngeal’, ‘sleep’, ‘apnoea’, ‘snoring’ and ‘ear nose throat’. The retrieved literature was reviewed, focusing on randomised and non-randomised, controlled, prospective trials. Papers on both paediatric and adult populations were included. Non-English language papers were excluded.

**Results:** We found no randomised, controlled trials or meta-analyses addressing the possible correlation between reflux and snoring and/or apnoea.

**Conclusions:** The role of night-time reflux in paediatric and adult snoring and apnoea is well described in the literature, but is based on poor levels of evidence from uncontrolled studies and case reports.

**Key words:** Gastroesophageal Reflux; Sleep

### Introduction

We live in the golden era of laryngology, with laryngopharyngeal reflux (LPR) being perhaps the most extensively researched ENT topic of the last decade. The H<sup>+</sup>/K<sup>+</sup>-adenosine triphosphatase (proton) pump has been found in serous cells and ducts of submucosal glands in the human larynx, representing a potential site for proton pump inhibitor action, with possible relevance for the treatment of patients with chronic laryngitis with or without LPR disease.<sup>1</sup> However, the relevance of this observation remains unclear, given the negative therapeutic response in the randomised, controlled trials identified.<sup>2</sup> The difficulties surrounding the diagnosis and management of LPR contradict the emerging and undoubtedly promising role of pepsin and carbonic anhydrase in the treatment of tissue damage caused by reflux. The search is underway for a non-invasive, reproducible test – operating at the cellular biology level – for the diagnosis of LPR.<sup>3,4</sup>

Gastroesophageal reflux during sleep is thought to be an important mechanism for the development of certain supraoesophageal complications of gastroesophageal reflux, such as asthma and idiopathic pulmonary fibrosis.<sup>5</sup> While some patients with LPR have been described as experiencing daytime or upright reflux,<sup>6</sup> other patients have reported supraoesophageal symptoms, most notably asthma and laryngospasm, shown to have an association with night-time, or supine, reflux. There are several proposed mechanisms believed to support the

significance of night-time reflux in the pathogenesis of certain reflux-related laryngeal disorders.<sup>5</sup> During waking hours, several protective responses defend the oesophageal and supraoesophageal structures against injury due to exposure to gastric contents. These protective responses are absent or less effective during sleep. In addition, during sleep several mechanisms act to slow oesophageal acid clearance and to prolong the contact time of gastric acid in the oesophagus. These mechanisms include: slower gastric emptying; decreased saliva production; decreased swallowing frequency; and a reduction in voluntary clearance behaviours, due to a lower awareness of heartburn. During deep sleep, upper oesophageal sphincter pressure diminishes significantly. This drop in sphincter pressure weakens the barrier which prevents movement of gastric refluxate from the oesophagus to the larynx or pharynx during sleep.<sup>5</sup> Furthermore, basal acid output increases in the late evening, allowing for the possibility of a more injurious gastric refluxate.<sup>5</sup>

The aim of this review was to assess the levels of evidence regarding a correlation between night-time reflux, snoring and apnoea.

### Methods

A Medline search was performed using the terms ‘reflux’, ‘night-time’, ‘larynx’, ‘gastroesophageal’, ‘laryngopharyngeal’, ‘sleep’, ‘apnoea’, ‘snoring’ and

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'ear nose throat'. The retrieved literature was reviewed, focusing on randomised and non-randomised, controlled, prospective trials. Papers on both paediatric and adult populations were included. Non-English language papers were excluded.

## Results

We found no controlled trials or meta-analyses addressing the possible correlation between reflux and snoring and/or apnoea. The role of night-time reflux in paediatric and adult snoring and apnoea is well described in the literature, but is based on poor levels of evidence from uncontrolled studies and case reports.

## Discussion

The coexistence of gastroesophageal reflux and pulmonary disease in children has been known for many years. In fact, gastroesophageal reflux has been postulated as a possible cause of many childhood respiratory diseases, such as asthma, snoring and obstructive sleep apnoea syndrome (OSAS).<sup>7,8</sup> Children with reflux have normal sleep stage distribution when OSAS is predominantly a phenomenon occurring during rapid eye movement (REM) sleep.<sup>9</sup> Obstructive apnoea worsens over the course of the night, independent of the changing amounts of REM sleep. The increase in apnoea severity may be secondary to upper airway muscle fatigue, changes in upper airway neuromotor control or changes in REM density. Obstructive sleep apnoea syndrome in children is characterised by restless sleep, electroencephalographic arousals and movement arousals.<sup>10</sup>

Studies have shown that children presenting with respiratory symptoms have reflux episodes of prolonged duration during sleep.<sup>11</sup> However, the issue of whether gastroesophageal reflux causes pulmonary disease remains unresolved. The presentation of reflux in children is frequently atypical and hence either misdiagnosed or undiagnosed.<sup>12</sup> In addition, paediatric gastroesophageal reflux is a physiological occurrence which tends to resolve after the age of one year. Halpern *et al.* reported that children with reflux-related respiratory problems had reflux episodes of longer duration during sleep.<sup>11</sup> However, this study did not evaluate the role of gastroesophageal reflux in OSAS. Simultaneous polysomnographic and intra-oesophageal pH recordings performed in infants showed that apnoea was equally likely to occur during reflux episodes and non-reflux episodes.<sup>13</sup> Brief obstructive apnoeic episodes were more common during the onset of gastroesophageal reflux episodes. These findings were supported by Arad-Cohen *et al.*, who also found no relationship between gastroesophageal reflux and apnoea.<sup>14</sup> In this study cohort of 21 infants, apnoea preceded reflux in 93.6 per cent of episodes, and only 6.4 per cent of apnoeic episodes followed reflux.

Kerr *et al.* noted that patients with severe OSAS had significant oesophageal reflux during overnight sleep, as detected by oesophageal pH monitoring.<sup>15</sup> Furthermore, when these patients were treated with nasal continuous positive airway pressure (CPAP), the frequency and duration of nocturnal gastroesophageal

reflux episodes reduced. The mechanism of action of this change has been hypothesised by Shepherd *et al.*<sup>16</sup> They measured the upper and lower oesophageal sphincter pressures, the gastric pressure and also the barrier pressure to reflux in 10 healthy volunteers at four levels of CPAP (0, 5, 10 and 15 cmH<sub>2</sub>O). The barrier pressure increased with CPAP by virtue of a disproportionate increase in the lower sphincter pressure compared with the gastric pressure. This may be due either to reflex activation of smooth muscle around the lower oesophageal sphincter, or to nonspecific transmission of pressure to the sphincter by CPAP. These findings suggest that CPAP may make the lower sphincter less susceptible to reflux. Tawk *et al.* showed that oesophageal pH measurements fell with treatment of OSAS with CPAP.<sup>17</sup> Interestingly, it would appear that long-term use of CPAP has no adverse effect on nasal mucosa function and mucociliary clearance.<sup>17</sup>

Several adult, questionnaire-based studies have suggested that a significant proportion of snorers with or without OSAS suffer from 'typical' reflux, with heartburn and regurgitation being the most commonly reported symptoms.<sup>18</sup> It has also been noted that patients who suffer with gastroesophageal reflux and who snore are more likely to be obese, hypertensive and asthmatic.<sup>5,19</sup> Although no similar study has been performed in children, it would be reasonable to presume that paediatric gastroesophageal reflux and OSAS are similarly linked. It must be remembered, however, that the presentation of symptomatic reflux in children is usually atypical. Symptoms such as excessive crying, irritability, failure to thrive and feeding problems do not always point to a diagnosis of reflux.<sup>12</sup> Ulualp and Brodsky described a case of a four-year-old boy in whom nasal pain disrupting sleep was a presenting symptom of extraesophageal reflux.<sup>20</sup> In this patient, a gastric scintiscan showed numerous episodes of refluxate reaching the upper oesophageal sphincter and pharynx, and there was concomitant slow gastric emptying. Treatment with proton pump inhibitor resulted in symptom resolution. Wasilewska and Kaczmarek compared 13 children suffering from nocturnal gastroesophageal reflux with 11 children free of gastroesophageal reflux, and found a significantly higher apnoea-hypopnoea index during REM sleep in the cohort with nocturnal reflux.<sup>21</sup>

As in adults, not all children who present with snoring or apnoea have pathological reflux. In fact, childhood breathing problems are usually attributed to adenotonsillar enlargement, rather than reflux alone. Xu *et al.* studied two groups of children – 31 with clinically significant OSAS and 19 with primary snoring – in order to evaluate the predominant symptomatology of each group.<sup>22</sup> The prevalence of risk factors was similar between the two groups, including allergic rhinitis, obesity and craniofacial anomaly. Observable sleep apnoea, nocturnal enuresis, intrusive naps, mouth-breathing, enlarged tonsils and radiological features of upper airway narrowing due to adenoid hypertrophy were found to be predictors for clinically significant OSA. Interestingly enough, reflux symptoms were not reported.

## Conclusions

The role of night-time reflux in paediatric and adult snoring and apnoea is well described in the literature, but is based on poor levels of evidence from uncontrolled studies and case reports.

The conclusions drawn from these studies must be evaluated with care. Epidemiologically, it is almost impossible to prove a link between two very common diseases, such as between reflux and sleeping disorders. It must be remembered that the investigative tests used have yet to establish the fundamental distinction between physiological and pathological reflux, especially in children. The normal pH parameters and manometry of physiological reflux have not been elucidated. It is well known that reflux is observed in neonates more frequently compared with older children, but usually has no long-term sequelae. Reflux is associated with periods of lower oesophageal sphincter relaxation (which typically occurs during swallowing). Increasingly, researchers also believe that reflux and OSA are linked and share similar contributing factors such as age and obesity. It has been postulated that the high number of reflux events in patients with apnoea is due to the negative intrathoracic pressure occurring during periods of apnoea. Thus, treating apnoea may have a positive impact on reflux.

It seems natural that reflux and sleep disorders might be related, as – at least in adults – the majority of sufferers share common predisposing factors. Nevertheless, LPR diagnosis is currently based on empiric antacid treatment, rather than on accurate diagnostic tests with a high sensitivity and specificity. Problems with ethics approval will always hinder well designed, randomised, controlled trials involving children, at least until non-invasive diagnostic tests are widely and readily available. The available evidence seems to support the hypothesis that reflux is associated with upper airway symptoms in children. However, the strength of this correlation and the risk of upper airway symptoms attributable to reflux are difficult to determine, given the limitations of the current literature.

At the moment, it is uncertain whether there is a causal relationship or simply an epidemiological association between sleep disorders and reflux. There is a need for better randomised trials, and it seems that this will be achieved when better diagnostic tools for LPR diagnosis become readily available.

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