Neuromuscular function of the soft palate and uvula in snoring and obstructive sleep apnea: A systematic review

Jagatkumar A. Patel a, *, Bryan J. Ray a, Camilo Fernandez-Salvador a, Christopher Gouveia a, Soroush Zaghid b, Macario Camacho b

a F. Edward Hebert School of Medicine, Uniformed Services University (USU), Bethesda, MD, 20814, USA
b Tripler Army Medical Center, Division of Otolaryngology-Head and Neck Surgery, 1 Jarrett White Rd, Tripler AMC, HI 96859, USA

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ABSTRACT

Objective: A collapsible upper airway is a common cause of obstructive sleep apnea. The exact pathophysiology leading to a more collapsible airway is not well understood. A progressive neuropathy of the soft palate and pharyngeal dilators may be associated with the progression of snoring to OSA. The purpose of this study is to systematically review the international literature investigating the neurophysiologic changes in the soft palate and uvula that contribute to progression from snoring to OSA.

Methods: PubMed/MEDLINE and 4 other databases were systematically searched through July 4, 2017. Eligibility: (1) Patients: controls, snoring or OSA patients (2) Intervention: neuromuscular evaluation of the palate and/or uvula (3) Comparison: differences between controls, snoring and OSA patients (4) Outcomes: neuromuscular outcomes (5) Study design: Peer reviewed publications of any design.

Results: 845 studies were screened, 76 were downloaded in full text form and thirty-one studies met criteria. Histological studies of the soft palate demonstrated diffuse inflammatory changes, muscular changes consistent with neuropathy, and neural aberrancies. Sensory testing studies provided heterogeneous outcomes though the majority favored neuronal dysfunction. Studies have consistently demonstrated that increasing severity of snoring and sleep apnea is associated with worsening sensory nerve function of the palate in association with atrophic histological changes to the nerves and muscle fibers of the soft palate and uvula.

Conclusions: Recent evidence highlighted in this systematic review implicates the role of neurogenic pathology underlying the loss of soft palate and/or uvular tone in the progression of snoring to sleep apnea.

1. Introduction

Obstructive sleep apnea (OSA) is a chronic and progressive breathing disorder characterized by repetitive episodes of partial or complete cessation of airflow as a result of recurrent upper airway obstruction during sleep. Effects of OSA on patients include excessive daytime somnolence, reduced neurocognitive outcomes, and adverse medical outcomes [1]. The estimated prevalence of OSA in North America is around 20% [1].

The pathophysiology of OSA is multifactorial. An easily collapsible upper airway is worsened by relaxation of pharyngeal dilator muscles during sleep, which can lead to recurrent obstructions and fragmented sleep. These obstructive events can occur at the nasopharynx/oropharynx interface; however, the exact physiopathology is incompletely understood. The classical teaching has stressed upper airway anatomical obstruction, usually as a result from obesity, an enlarged tongue, and/or craniofacial abnormalities, to be the culprit for the collapse. Because retropalatal collapse is the most common area of obstruction, the majority of surgical treatments for OSA are aimed at partial excision of the soft palate. However, a recent meta-analysis looking at laser-assisted uvuloplatoplasty for OSA treatment found poor response rates and a worsening apnea-hypopnea index among 44% of patients [2].

Although volumetric soft tissue component has been widely

Abbreviations: OSA, Obstructive Sleep Apnea
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* Corresponding author at: F. Edward Hebert School of Medicine, Uniformed Services University (USU), Bethesda, MD 20814, USA.
E-mail address: jagatkumar.a.patel.mil@mail.mil (J.A. Patel).

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accepted as the cause of upper airway narrowing and collapsibility, evidence has implicated a neurogenic component for the pathophysiology. For example, neuronal degeneration due to age, snoring trauma, or disuse atrophy can lead to a decrement in pharyngeal dilator function during sleep. McNicholas et al. showed that there is an increased incidence of apneas and hypopneas during sleep in normal subjects with application of topical oropharyngeal anesthesia [3]. Studies have shown increased obstructive respiratory events during sleep following topical upper airway anesthesia in loud snorers and patients with OSA [4,5]. These studies suggest that the loss of afferent neuronal activity in the upper airway makes it vulnerable during sleep, supporting the neurogenic component of OSA. Long-term vibration has been shown to induce changes in peripheral neuronal activity of fingers [6]. Because snoring results from turbulent flow of air vibrating the soft palate, it is possible that long-term vibratory trauma from snoring might result in alteration of neuronal activity of the soft palate, resulting in OSA. Supporting this, habitual snoring often leads to increasing obstructive events and obstructive sleep apnea if left untreated [7,8]. Numerous studies have begun to examine the relationship between neurologic dysfunction of the upper airway and obstructive sleep apnea. These seem to advocate a significant role of neurogenic activity in the multifactorial pathophysiology of OSA.

In order to more thoroughly evaluate this theory, we conducted a systematic review of literature to collate and objectively assess the evidence regarding the idea that there are local neurogenic determinants in the upper airway that may precipitate the onset and progression of OSA. Specifically, we sought to identify any publications that would provide data regarding tests and/or biopsies of the soft palate and/or uvula in control patients versus patients with a history of snoring and/or obstructive sleep apnea.

2. Methods

2.1. Study eligibility criteria

Studies were included without any limitations placed on year of publication, country, or language. We selected the following study inclusion criteria using the PICO5 acronym: (1) Patients: any adult patient (≥ 18 years old) with data for controls, snorers or OSA patients; (2) Intervention: testing and/or biopsy of the soft palate and/or uvula; (3) Comparison: results from controls versus snorers versus obstructive sleep apnea patients; (4) Outcomes: any quantitative or qualitative information for tests and/or biopsies; (5) Study design: any study design from case reports through randomized controlled-trials. Exclusion criteria: studies in children and studies that did not report outcomes for the soft palate or uvula.

Three authors (J.A.P, B.J.R, and M.C) independently searched the literature from inception of each database through July 4, 2017. Databases searched included PubMed/MEDLINE, Embase, Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane and SCOPUS. A search strategy for PubMed/MEDLINE is: (((apnea OR apnoea OR snor*) AND (neuropath* OR histology OR histologic OR histological)) AND (uvul* OR palat*)). During this study, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [9].

3. Results

The systematic review of literature yielded a total of 845 studies. Seventy-six were downloaded in full text form and 31 studies met full criteria and were included in this systematic review. A flow-chart diagrams these results (see Fig. 1).

3.1. Histological analysis (Table 1)

Woodson et al. analyzed tissue samples of soft palate and uvula for four severe OSA patients, four snorers, and four controls under light microscope and transmission electron microscope (TEM) [10]. In OSA patients and snorers, they found diffuse hypertrophy of the mucous glands, focal atrophy, interstitial fibrosis of the muscle fibers, reduction of serous glands, and acanthosis of the overlying epidermis. In the control group, all uvula samples had uniform muscle fibers with a distinct separation of adjacent serous and mucous glands. Interestingly, on electron microscopy, two out of four samples of severe OSA patients showed focal degeneration of myelin sheath and axons, which was not observed in snorers and control groups [10].

Sériès et al. compared contractile, histochemical, and biochemical characteristics of musculus uvulae (MU) in 11 untreated patients with sleep apnea hypopnea syndrome (SAHS) and seven nonapnic snorers [11]. Contractile time, fatigability index, and half-relaxation time were identical in the two groups; however, both maximum twitch and tetanic absolute tensions were significantly greater in sleep apnea hypopnea patients when compared to snorers [11]. MU samples of SAHS patients and control subjects revealed significant differences in anaerobic enzyme activity [11]. The protein content of MU, total number of muscle fibers, the number and size of type IIA fibers, and total muscle fiber cross-sectional area were significantly greater in OSA patients than in snorers [11]. The authors theorize that chronic hyperstimulation through long-standing vibration and/or nocturnal hypoxemia of the upper airway muscles in SAHS patients can lead to significant adaptive processes that are congruent with findings in resistive exercise-trained muscles.

The lead author performed a separate study comparing metabolic and fiber type characteristics of genioglossus (GG) and musculus uvulae (MU) in 17 SAHS patients and 11 nonapnic snorers [12]. The glycolytic, glycogenolytic, and anaerobic enzyme activity in MU were significantly higher in SAHS patients than snorers (p < 0.05), and these differences were not seen in GG samples [12]. MU samples also had greater proportion of type IIA fibers vs type I/II in SAHS patients than snorers, which is a sign of modified muscle fiber distribution due to constant stress of UA collapse [12].

Friberg et al. investigated for signs of different neuropathy in the soft palate mucosa of eleven non-snorers, eleven habitual snorers, and ten OSA patients by semi-quantifying the immunofluorescence content of neuropeptidases: calcitonin gene-related peptide (CGRP), substance P (SP), and protein-gene product 9.5 (PGP) [13]. In comparison to controls, semi-quantitative analysis of immunofluorescent samples revealed an increased number of PGP 9.5, CGRP, and SP in the soft palate mucosa of OSA patients (9/10) and heavy snorers (4/11) [13]. The study also showed increased numbers of varicose nerve endings, most likely sensory nerves, in the epithelium of the mucosa of soft palate of OSA patients and snorers. Interestingly, the lowest number of varicose nerve endings was visualized in OSA patient with the highest oxygen desaturation index (ODI) as opposed to the peak varicose nerve endings seen in OSA patients with mild to moderate ODI. Hence, prolonged snoring could result in a halt in compensatory sprouting process and progress to degenerative neurogenic lesions of small nerve fibers in the soft palate of snorers and OSA patients.

Friberg et al. also analyzed differences in the palatopharyngeus muscles of 21 habitual snorers (ten with OSA) and ten non-snorers controls [14]. When compared to non-snorers, the snoring group showed signs of neurogenic lesions in palatopharyngeal muscles, including type grouping, fascicular atrophy, and/or grouped atrophy. Additionally, there was a significantly increased number of atrophied and/or hypertrophied fibers in snoring patients versus controls [14]. They also found a significant correlation between the percentage of periodic obstructive breathing and the degree of morphological abnormalities in snorers, thus suggesting that snorers with higher amounts of periodic obstructive breathing have an increased risk of achieving local muscular abnormalities [14].

Lindman et al. investigated morphological differences in two soft palate muscles (palatopharyngeus and uvula) of eleven patients with a
long duration of sleep-disordered breathing (SDB) and five healthy reference subjects [15]. When compared to references, both soft palate muscles showed higher amount of connective tissue, intra-muscular differences in fiber diameter, and rounded appearance as opposed to polygonal contour in patients with SDB [15]. In patients with SDB, histochemical stains for fiber type showed a predominance of type II fibers in both muscles and increased ratio of type IIA/IIAB in the palatopharyngeus muscle [15]. Biochemical and immunohistochemical analysis of these muscles showed an increased frequency of fibers expressing embryonic and fetal MyHC (slow or fast A type) and decreased amount of fibers with fast X MyHC expression in patients with SDB [15]. These morphological changes and presence of developmental myosin heavy chain composition suggest a progressive change in palatopharyngeal muscles of SDB patients.

Paulsen et al. evaluated uvular specimens of three snorers, nine OSA patients, and 43 non-snoring body donors using LM and TEM [16]. In snorers and OSA patients, they found significant reduction in cytokeratin 13 expression, connective tissue papillae, epithelial hyperplasia, and diffuse increase in leukocytes inside the lamina propria as compared to controls, which were not age-related [16]. Thus, epithelial and subepithelial structural changes in mucosa of UA are seen in snorers or OSA patients, which may be secondary to snoring trauma and not aging per se.

Molina et al. studied morphological, histochemical, and stereological evaluations of palatopharyngeal muscle using LM and TEM in 10 mild, 10 moderate, 10 severe SAHS patients and 10 controls [17]. Significant reductions in muscle fiber diameter and increases in metalloproteinases were observed with increasing severity of SAHS vs controls under LM. TEM showed increased cytoplasmic residual corpuses in muscle samples of SAHS patients, which is a sign of early aging [17].

In a prospective observational study, Bassioumy et al. studied nerve fibers of the uvula from ten OSA patients, ten simple snorers, and five autopsy controls using TEM [18]. The specimens from controls showed nerve fibers with normal architecture and shape with no degenerative changes [18]. Degenerative changes of myelinated and unmyelinated nerve fibers were seen in all ten OSA patients, with four cases of severe total degeneration of whole nerve fibers. Similar degenerative changes, albeit to a lesser degree, were also noted in six out of ten specimens from the simple snorers group [18].

3.2. Morphometric analysis (Table 2)

Edström et al. compared palatopharyngeal muscle biopsies of eight untreated OSA patients and seven control subjects [19]. In OSA patients, there was an increased size dispersion with alternating atrophic fibers and normal sized or hypertrophied ones; therefore, maintaining the mean muscle fiber size when compared to controls [19]. They found similar findings in uvular muscle of the five out of eight apneics, with two subjects exhibiting complete atrophy [19]. In the control group, the specimens showed a normal checkerboard pattern of type I and II fibers with no type II C fibers [19]. With regards to morphometrical observations, the control group's muscle fiber size had a normal Gaussian distribution, but the OSA group had a non-Gaussian distribution, with multiple peaks, secondary to an increased proportion of atrophic and hypertrophic fibers [19]. Thus, the patients with OSA have typical histopathologic findings of chronic motor neuron lesions (grouped atrophy, type grouping, and variability), which are consistent with a simultaneous denervation and re-innervation processes.

Stauffer et al. evaluated uvular specimens from 33 patients with OSA, 6 non-apneic snorers, and 22 cadavers with no evidence of snoring or OSA [20]. After controlling for differences caused by age and body mass index, OSA patients had significantly higher percentage of muscle in uvula compared to controls (18.1 ± 1.9% vs 9.3 ± 2.1%, p = 0.02) [20]. OSA patients also had significantly greater fat content in uvula as opposed to controls (9.5 ± 1.4% vs 4.0 ± 1.0%, p < 0.02), which positively correlated to AHI in OSA patients (r = 0.43, p < 0.01) [20]. Uvula of six non-apneic snorers had similar histological findings as OSA patients [20].

Similarly, Swift et al. conducted histopathological comparison of the uvula and soft palate in 17 heavy snorers and 14 cadaveric specimens [21]. The mean percentage of muscle in uvular specimen of snorers was 12.1% compared to control specimens 7.2% (p < 0.05). The mean percentage of fibrous tissue was greater in cadavers versus snorers (52.8% vs 45.5%, p < 0.05). The percentage of muscle in snoring group was inversely related percentage of fibrous tissue (r = −0.56 [−0.82 to-0.13]). They concluded that the inverse relationship of percentage of muscle to fibrous tissue in uvular specimen of snorers is likely due to repetitive vibratory forces of snoring and stretching due to intermittent arousal on the soft palate.

Sekosan et al. compared uvular mucosa from 21 OSA patients and...
<table>
<thead>
<tr>
<th>Year, study, design</th>
<th>N =</th>
<th>Study site</th>
<th>Outcomes analyzed</th>
<th>OSA diagnosis by:</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| 1991, Woodson et al., cross sectional | 4 severe OSA patients, 4 snorers, 4 control | USA | LM and TEM of soft palate and uvula tissue samples | AHI | • OSA patients and snorers showed significant histologic changes  
• 2/4 OSA patients showed focal degeneration of myelin sheath and axons under TEM  
• Maximum twitch tension, contraction time, half-relaxation time, fiber typing, area measurements |
| 1995, Sériès et al., cross sectional | 11 SAHS patients, 7 non-apneic snorers | Canada | Maximum twitch tension, contraction time, half-relaxation time, fiber typing, area measurements | AHI | • Protein content, total # of muscle fibers, total number & size of type IIA fibers and total muscle fiber cross-sectional area ↑ in SAHS patients  
• Maximum twitch and tetanic absolute tensions ↑ in SAHS patients  
• No difference in contraction time, fatigability index, and half relaxation time between two groups  
• Findings congruent with changes seen in resistive exercise-trained muscles |
| 1996, Sériès et al., cross sectional | 17 SAHS patients, 11 nonapneic snorers | Canada | Metabolic and fiber type characteristics of GG and MU | AHI | • Glycolytic, glycogenolytic, and anaerobic enzyme activity in MU samples significantly ↑ in SAHS patients vs snorers  
• Greater proportion of type IIA fibers vs type 1/1B in SAHS patients  
• ↑ number of PGP 9.5, GGRP, SP in soft palate mucosa of OSA patients and heavy snorers  
• ↑ number of varicose nerve endings in mucosa of soft palate of OSA patients and snorers |
| 1997, Friberg et al., cross sectional | 10 OSA, 11 snorers, 11 non snorers | Sweden | Content of neuropeptidases; GGRP, SP, PGP | ODI | • Significant correlation between % periodic obstructive breathing and morphologic abnormalities in snorers and OSA patients |
| 1998, Friberg et al., cross sectional | 10 OSA, 11 snorers, 10 non snorers | Sweden | Morphological differences in palatopharyngeal muscles | ODI | • Signs of neurogenic lesions in palatopharyngeal muscle (grouped atrophy, type grouping and fascicular atrophy) of OSA patients and snorers |
| 2002, Lindman et al., cross sectional | 11 SDB, 5 control | Sweden | Muscle morphology, fiber type, myosin heavy chain composition | Undergoing UPPP for socially handicapping snoring | • Significant correlation between % periodic obstructive breathing and morphologic abnormalities in snorers and OSA patients |
| 2002, Paulsen et al., cross sectional | 3 snorers, 9 OSA, 43 controls | Germany | LM and TEM of uvula samples | ODI | • Epithelial and subepithelial structural changes in mucosa of UA (↑ cytokeratin 13 expression and ↑ in leukocytes) were observed in snorers and OSA patients  
• Significant ↑ in muscle fiber diameter and ↑ in metalloproteinases with increasing severity of SAHS under LM  
• ↑ cytoplasmic residual corpuscles (sign of early aging) in muscle samples of SAHS patient  
• Moderate-severe degenerative changes of myelinated and unmyelinated nerve fibers seen in 10/30 OSA patients  
• Mild-moderate degenerative changes seen in 6/30 simple snorers  
• Normal architecture and shape of nerve fibers in all controls |
| 2010, Molina et al., cross sectional | 10 mild, 10 moderate, 10 severe SAHS, 10 controls | Brazil | LM and TEM of palatopharyngeal muscles | RDI | • Signs of neurogenic lesions in palatopharyngeal muscle (grouped atrophy, type grouping and fascicular atrophy) of OSA patients and snorers |
| 2002, Bassiouny et al., cross sectional | 10 OSA, 10 snorers, 5 controls | Egypt | Morphology of nerve fibers with TEM | RDI | • Signs of neurogenic lesions in palatopharyngeal muscle (grouped atrophy, type grouping and fascicular atrophy) of OSA patients and snorers |

**Table 1**

Histologic analysis.

<table>
<thead>
<tr>
<th>Year, study, design</th>
<th>N</th>
<th>Study site</th>
<th>Outcomes analyzed</th>
<th>OSA diagnosis by:</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992, Edström et al., cross sectional</td>
<td>8 OSA patients, 7 control</td>
<td>Sweden</td>
<td>Palatopharyngeal muscle fiber type, dispersion, and variability</td>
<td>History, Physical Exam, and a whole-night recording of arterial oxygen saturation and of respiration and body movements by means of a static charge sensitive bed.</td>
<td>Normal checkerboard pattern of type I and II fibers in control group</td>
</tr>
<tr>
<td>1989, Staufer et al., cross sectional</td>
<td>33 OSA, 6 non-apneic snorers, 22 control</td>
<td>USA</td>
<td>Tissue characteristics of uvula samples</td>
<td>AHI</td>
<td>Increased size dispersion with alternating atrophic and hypertrophic/fat fibers in OSA patients</td>
</tr>
<tr>
<td>1995, Swift et al., cross-sectional</td>
<td>17 OSA, 14 control</td>
<td>England</td>
<td>Relative tissue type in the uvula or soft palate</td>
<td>UPPP for excessive loud snoring</td>
<td>FINDINGS consistent with chronic motor neuron lesion with simultaneous denervation and re-innervation process</td>
</tr>
<tr>
<td>1996, Sekosan et al., cross-sectional</td>
<td>21 moderate OSA patients, 5 control</td>
<td>USA</td>
<td>Uvular mucosa differences</td>
<td>AHI</td>
<td>Uvula of OSA patients and snorers had higher percentage of muscle and fat content compared to controls</td>
</tr>
<tr>
<td>1999, Sériès et al., cross-sectional</td>
<td>10 non apneic snorers, 10 SAHS</td>
<td>Canada</td>
<td>Muscle fiber distribution in musculus uvulae</td>
<td>AHI</td>
<td>Fat content in OSA patients positively correlated to their AHI</td>
</tr>
<tr>
<td>2002, Berger et al., cross sectional</td>
<td>12 mild, 12 moderate, 10 severe OSA, 7 control</td>
<td>Israel</td>
<td>Histopathologic changes in soft palate and uvula</td>
<td>RDI</td>
<td>Increased mean % of muscle that was inversely related to mean % of fibrous tissues of uvular specimen of snorers</td>
</tr>
<tr>
<td>2004, Boyd et al., cross sectional</td>
<td>11 OSA, 7 controls</td>
<td>Canada</td>
<td>Signs of inflammation, neuronal markers (PGP, NCAM)</td>
<td>AHI</td>
<td>↑ # of leukocytes and plasma cells in lamina propria of uvular specimen of OSA patients</td>
</tr>
<tr>
<td>2012, Bellis et al., case control</td>
<td>51 apneic snorers, 47 control</td>
<td>Italy</td>
<td>Immunohistochemical and morphometric analysis of nerve fibers of uvula</td>
<td>AHI</td>
<td>Significant increase in thickness of lamina propria of OSA patients</td>
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<td></td>
<td>Higher proportion of type II muscle fibers are observed in SAHS patients with no significant differences in frequency of type I and II between apneic and non-apneic snorers</td>
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<td></td>
<td></td>
<td>No significant differences in regards to glands, muscle, fat, blood vessels, and epithelium across all subjects</td>
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<td></td>
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<td></td>
<td></td>
<td>Histopathologic changes in the soft palate and uvula of OSA patients are possibly a sequela of airway obstruction and not the cause of OSA.</td>
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<td>UA mucosa and musculature showed ↑ signs of inflammation (CD4 + &amp; CD8 + cells) in OSA patients</td>
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<td>Statistically significant ↑ PGP and NCAM markers in UA tissue samples of OSA patients</td>
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<td></td>
<td></td>
<td>All subjects had BMI &lt; 30</td>
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<td>Mean # of nerve fibers lower in snorers vs controls</td>
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<td>S100 stain confirmed lower # of nerve fibers in snorers</td>
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</table>
Table 3

Sensation testing.


<table>
<thead>
<tr>
<th>Year, study, design</th>
<th>N=</th>
<th>Study site</th>
<th>Outcomes analyzed</th>
<th>OSA diagnosed by:</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992, Larsson et al., cross-sectional</td>
<td>15 OSA, 15 control</td>
<td>Sweden</td>
<td>WDT, CDT at tongue and anterior tonsillar pillar</td>
<td>ODI</td>
<td>• Impaired WDT on anterior tonsillar pillar and tip of tongue in OSA patients CDT between 2 groups insignificant, but significant differences in neutral zone (WDT-CDT for each subject) on anterior tonsillar pillar in OSA patients</td>
</tr>
<tr>
<td>2011, Sunnergren et al., cross-sectional</td>
<td>33 OSA, 32 snorers, 25 control</td>
<td>Sweden</td>
<td>CDT at soft palate and lip</td>
<td>AHI</td>
<td>• CDT at lip insignificant between 2 groups CDT at soft palate significantly impaired between snorers and OSA patients vs controls Significant positive correlation between AHI and self-reported smoking years to CDT</td>
</tr>
<tr>
<td>2009, Hagander et al., cross-sectional</td>
<td>31 OSA, 13 snorers, 23 control</td>
<td>Sweden</td>
<td>VDT and CDT in oropharynx</td>
<td>AHI</td>
<td>• Cold detection testing was more discriminative and a better assessment tool for sensory impairment compared to vibration detection testing. CDT testing in the clinical setting could identify patients with early sensory lesion that might potentially benefit from early treatment.</td>
</tr>
<tr>
<td>2002, Guilleminault et al., cross-sectional study</td>
<td>15 OSA, 15 UARS, 15 control</td>
<td>USA</td>
<td>TPD at soft palate</td>
<td>AHI</td>
<td>• TPD at soft palate is significantly decreased in patients with OSA as opposed to patients with UARS or normal subjects Mean respiratory effort related arousals were higher in UARS patients as compared to OSA patients</td>
</tr>
<tr>
<td>2016, Jeong et al., cross-sectional</td>
<td>27 OSA, 12 snorer, 10 control</td>
<td>Korea</td>
<td>TPD at soft palate and anterior tongue</td>
<td>AHI</td>
<td>• Compared to OSA patients with normal sensation to cold TPD test, OSA patients with impaired sensation have longer (1) average duration of snoring episodes (p = 0.043), (2) relative snoring time (p = 0.032), and (3) longest snoring episode duration (p = 0.010) The authors proposed a cut off value of 2.5 mm (Sensitivity 91.7%, Specificity 85.7%) for sensory testing with cold TPD as an important clinical tool for early detection of peripheral palatal neuropathy in OSA patients</td>
</tr>
<tr>
<td>2001, Kimoff et al., cross-sectional</td>
<td>38 OSA, 12 snorers, 15 control</td>
<td>Canada</td>
<td>TPD, VST in UA</td>
<td>AHI</td>
<td>• TPD and VDT significantly higher in UA of OSA and snoring groups Repeat testing after 6 months of CPAP showed mild, but significant improvement in VST in OSA patients</td>
</tr>
<tr>
<td>2005, Nguyen et al., cross-sectional</td>
<td>39 OSA, 17 control</td>
<td>Canada</td>
<td>TPD, VDT, mucosal sensory dysfunction with air pulses</td>
<td>AHI, RDI</td>
<td>• Sensory testing with endoscopic air pressure pulses revealed mucosal sensory impairment within multiple upper airway sites (oropharynx, velopharynx, and aryepiglottic eminence) in patients with OSA TPD and VDT showed sensory impairments in oropharynx of OSA patients</td>
</tr>
<tr>
<td>2013, Kim et al., cross-sectional</td>
<td>40 snorers, 19 controls</td>
<td>South Korea</td>
<td>Relationship between clinical parameters and standardized palatal sensory threshold</td>
<td>AHI</td>
<td>• The level of standardized palatal sensory threshold, measured with Semmes Weinstein monofilaments, significantly different between controls and snorers/mild/moderate-severe apneic patients (all p-values &lt; 0.001)</td>
</tr>
<tr>
<td>2005, Dematteis et al., cross-sectional</td>
<td>50 SDB, 17 controls</td>
<td>France</td>
<td>SPT with intraoral device that applied airflow to soft palate</td>
<td>RDI</td>
<td>• The pharyngeal sensitivity was differentially impaired in patients with SDB with varying degrees based on type of respiratory events Sensory thresholds were correlated with the severity of SDB</td>
</tr>
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</table>
five autopsy controls under LM [22]. The number of leukocytes (179 ± 12 in OSA vs 71 ± 4 cells in controls) and plasma cells (89 ± 15 in OSA vs 21 ± 5 in controls) in the lamina propria of the uvula mucosa were significantly increased in OSA patients [22]. They also found a significant increase in the thickness of the lamina propria of the uvula of OSA patients when compared with controls (0.99 ± 0.12 mm vs 0.27 ± 0.02 mm) [22]. This indicates inflammation is present in the UA mucosa of OSA patients.

Sériès et al. compared differences in muscle fiber distribution of MU in 10 snoring SAHS patients and 10 non-apneic snorers, confirmed by polysomnography [23]. A significantly higher proportion of type IIA fibers were present in SAHS patients compared to non-apneic snorers (89.4 ± 5.8% vs 76.1 ± 15.1%, p = 0.01) [23]. The frequency distribution of type I and IIA fibers in samples of snorers and SAHS patients were not significantly different [23]. They concluded that these changes in UA muscles are likely secondary to snoring trauma rather than obstructive events.

Berger et al. analyzed qualitative and morphometric histopathologic changes in soft palate and uvula in seven cadavers, 12 mild OSA, 12 moderate OSA and 10 severe OSA patients [24]. The authors found insignificant differences in regards to glands, muscle, fat, blood vessels, and epithelium across all subjects [24]. They found differences in regards to edema and connective tissues in samples of OSA patients as opposed to controls [24]. Their working hypothesis is that histopathologic changes in the soft palate and uvula of OSA patients are a sequela of airway obstruction and not the cause of OSA.

Boyd et al. conducted morphometric analyses on tissue samples from soft palate and/or tonsillar pillars in 18 retrospectively identified patients, 11 with OSA and 7 controls [25]. In patients with OSA, both UA mucosa and musculature showed increased markers for inflammation, specifically CD8+ and CD4+ cells in mucosa and predominantly CD4+ cells in musculature [25]. They noted a statistically significant increase in pan neuronal marker staining for both afferent and efferent nerves, PGP 9.5 (almost six-fold increase), and muscle fiber specific neuronal marker staining for denervation changes. They also found increased neuronal cell adhesion markers (16% in OSA vs 1% in controls) in OSA patients [25]. These findings support an ongoing pathologic process of denervation and re-innervation changes in the upper airway of OSA patients due to inflammation, which may be contributing to the pathogenesis of OSA.

In a comparative, retrospective, case-control, double-blind study, Bellis et al. conducted immunohistochemical and histomorphometric analysis of uvular specimens from 51 apneic snorers and 47 normal subjects, with BMI > 30 as one of the exclusion criteria [26]. The mean number of nerve fibers were significantly lower in snorers (65.5 ± 29.08) when compared to controls (108.9 ± 28.14, p < 0.0001) [26]. S100 staining confirmed lower number of nerve fibers in OSA patients’ uvulas compared to control patients’ uvulas [26]. Thus, non-obese OSA patients may have a neurogenic predisposition to uvulopalatal collapse due to lower set of motor nerve fibers.

3.3. Sensation testing (Table 3)

3.3.1. Temperature-based sensory testing

Larsson et al. investigated sensory neuropathy by comparing temperature threshold for warmth and cold in 15 OSA patients and 15 age-matched non-snorers controls [27]. Impaired sensation in warmth threshold on the anterior tonsillar pillar (46.8 °C vs 42.5 °C, p = 0.0006) and the tip of the tongue (40.1 °C vs 38.6 °C, p = 0.036) was observed in OSA patients vs controls [27]. Although cold threshold temperature sensation differences between the two groups were insignificant, a significant difference in the neutral zone (defined as difference between the warm and cold threshold for each subject) between the OSA patients and controls on the anterior tonsillar pillar testing (13.3 °C vs 7.6 °C, p = 0.0015) was observed [27].

Sunnergren et al. investigated sensory neuropathy with quantitative cold sensory testing of soft palate and lip in three groups: 25 non-snorers, 32 snorers, and 33 OSA patients [28]. Cold sensation at the lip was insignificantly impaired between all groups; however, snorers and OSA patients had significantly impaired cold sensation at the soft palate when compared to non-snorers (both p < 0.01) [28]. Snorers also had better sensitivity to cold than OSA patients (p < 0.05). They found a weak, but significant, positive correlation between both AHI (r = 0.41) and self-reported snoring years (r = 0.47) to soft palatal neuropathy as tested with cold detection threshold (CDT) [28].

Hagander et al. compared sensory testing of with vibration detection threshold (VDT) and CDT in the oropharynx of 23 non-snorers, 13 habitual snorers, and 31 patients with OSA [29]. VDT showed a significant difference in sensation between non-snorers and patients with OSA (p = 0.003), but not between snorers and OSA groups or non-snorers and snorer groups [29]. CDT showed a significant difference in sensation between non-snorers and snorers (p = 0.001) and also between OSA patients and non-snorers (p < 0.001); however, no significant difference was found between snorers and OSA patients [29]. Thus, cold detection testing may be more discriminative and a better assessment tool for early detection of UA sensory impairment observed in OSA patients and snorers.

3.3.2. Two-point discrimination/vibratory sensory testing

Guilleminault et al. investigated differences in palatal sensation with Two-Point Discrimination (TPD) test among 15 OSA patients, 15 patients with upper airway resistance syndrome (UARS), and 15 normal subjects [30]. The mean frequency of arousals with abnormal breathing efforts was higher in UARS patients (17.9 ± 4/h), compared to OSA patients (5 ± 2/h) and normal subjects (2 ± 1.5/h) [30]. TPD revealed statistically significant differences in palatal sensation in OSA patients (3.86 ± 0.58 mm), compared to UARS patients (1.66 ± 1.0 mm) and normal subjects (1.63 ± 0.29 mm) [30]. They concluded that palatal sensation is impaired in OSA patients and preserved in UARS patients, which might explain increased number of respiratory effort related arousals in UARS and delayed responses to abnormal respiratory effort during sleep in OSA.

Jeong et al. compared sensory deficits in the anterior tongue and soft palate with TPD at 43 °C and 0 °C among 27 untreated OSA patients, 10 controls, and 12 primary snorers [31]. The mean TPD at 43 °C and 0 °C was longer in OSA group, when compared to controls, but was not statistically significant [31]. Further analysis revealed two groups of OSA patients, one with impaired sensation (12 patients) and other with normal sensation (15 patients) vs controls upon testing with cold TPD, and these differences were statistically significant (p < 0.001) [31]. The authors also proposed a cut off value of 2.5 mm (Sensitivity 91.7%, Specificity 85.7%) for sensory testing with cold TPD as an important clinical tool for early detection of peripheral palatal neuropathy in OSA patients [31].

Kimoff et al. tested upper airway sensation via TPD and vibratory sensation threshold (VST) in 38 OSA patients, 12 non-apneic snorers, and 15 controls [32]. They also tested for any changes in sensation among 23 OSA patients treated with six months of CPAP vs 18 untreated OSA patients. The sensory detection threshold for both TPD and VST were significantly higher in the upper airway of OSA and snoring groups compared with the control subjects (p < 0.05 vs controls) [32]. Repeat testing after six months of CPAP treatment vs non-treatment group of OSA patients showed mild improvement with statistically significant difference in VST sensory testing (p < 0.05 vs baseline), but not in the TPD test [32]. Thus, localized impairment exists in the upper airway mucosal sensory function of OSA and snoring patients; and differences in VST after six months of CPAP advocates for partial reversibility but mostly permanent neuronal damage in OSA patients.

Nguyen et al. assessed mucosal sensory function at multiple upper-airway sites (oropharynx, velopharynx, hypopharynx, and aryepiglottic eminence) using endoscopic air-pressure pulses, TPD, and VDT in 39 OSA patients and 17 controls [33]. In OSA patients, compared to
controls, the endoscopic sensory threshold was significantly impaired in the oropharynx ($p = 0.004$), the velopharynx ($p = 0.003$), and the aryepiglottic eminence ($p < 0.001$), but not in the hypopharynx [33]. TPD and VDT also showed significant sensory impairments in the oropharynx of OSA patients [33].

### 3.3. Other sensory testing

Kim et al. assessed palatal sensory threshold (PST), using standardized Semmes Weinstein monofilaments, among 19 non-snorers, 10 simple snorers, 15 mild apneic, and 15 moderate to severe apneic patients [34]. Standardized PST (SPST) values, obtained by subtracting the sensory threshold value at the hard palate reference point from uvular sensory threshold, were significantly different between control subjects and snorers/mild/moderate-severe apneic patients (all $p$-values $< 0.001$) [34]. The authors also proposed a reliable method (cutoff 0.45 g/mm$^2$; Sensitivity $= 81.3$%) to detect sensory impairment among apneic patients and snorers in clinical setting [34].

Dematteis et al. assessed pharyngeal sensitivity with intraoral device that applied air flow to the soft palate of 17 controls and 50 patients (five mild, 19 moderate, 26 severe) with SDB [35]. The baseline appearance sensory threshold (increasing airflow increments) and disappearance sensory threshold (decreasing airflow increments), were subjectively determined by patients, with raising or lowering their hand, respectively [35]. The patients with SDB had a significantly higher baseline disappearance and appearance sensory threshold to airflow compared to controls (0.62 ± 0.44 vs 0.26 ± 0.06 l/min and 0.85 ± 0.40 vs 0.40 ± 0.19 l/min, $p < 0.001$, respectively) [35].

### 3.4. Electromyogram testing (Table 4)

Carlson et al. evaluated electromyogram (EMG) data of two velopharyngeal muscles, palatoglossus (PG) and levator veli palatini (LVP), and genioglossus (GG) during non-REM sleep in eight OSA patients [36]. In all subjects, apneic event coincided with inspiratory EMG nadir and genioglossus (GG) during non-REM sleep in eight OSA patients pharyngeal muscles, palatoglossus (PG) and levator veli palatini (LVP), tensor palatini (TP) muscles during periods of wakefulness and patency during sleep in OSA patients.

Mezzanotte et al. assessed EMG activity of genioglossus (GG) and tensor palatini (TP) muscle during periods of wakefulness and first two breaths of sleep in ten OSA patients and eight controls [37]. Compared to controls, OSA patients demonstrated greater EMG activity of GG and TP muscles during wakefulness [37]. During sleep, controls showed small, but consistent detriment in EMG activity of both TP and GG muscle [37]. TP EMG activity showed significantly greater decrement in all OSA patients compared to controls ($p < 0.05$) during sleep, whereas the effect of sleep on GG EMG activity was not significantly different between the two groups [37]. Thus, in OSA patients, sleep onset is associated with significantly greater decrease in activity of tensor palatini muscles than genioglossus muscle as compared to wakefulness.

Mortimore et al. compared reflex EMG activity of LVP and PG muscles to negative upper airway pressure in 16 non-snoring controls and 16 SAHS male patients during wakefulness [38]. The same experiment was repeated in eight SAHS patients before and after CPAP use for at least two months [38]. The reflex EMG responses of LVP and PG muscles to negative upper airway pressure were significantly greater in controls than patients with SAHS, even with age-matched and BMI-matched groups (all $p < 0.001$) [38]. The reflex EMG responses of LVP and PG muscles in patients with SAHS significantly increased with CPAP use (LVP $p < 0.001$, PG $p = 0.003$) [38]. In short, SAHS patients have impaired EMG responses to negative upper airway pressure in levator veli palatini and palatoglossus muscles that may be improved with chronic CPAP use.

Svanborg et al. performed concentric needle EMG in the
pala
topharyngeus muscle of 12 OSAS patients, 15 habitual snorers, and five normal subjects during wakefulness [39]. 10/12 OSAS patients showed signs of motor neuron lesions with increased duration in polyphasic potentials, reduced interference pattern during maximal contraction of palate, and spontaneous activity during relaxation of palate [39]. 3/15 snorers showed signs of moderate nervous lesions with evidence of some polyphasic potentials and slightly reduced interference pattern during maximal contraction of palate [39]. Five normal subjects and 12 snorers had normal EMG [39].

Fogel et al. investigated EMG activity of GG and TP during wakefulness and sleep onset in 12 healthy young men, 13 healthy older men, and 12 men with OSA on CPAP [40]. During wakefulness, GG EMG activity was significantly greater in OSA patients compared to other group, which was reduced but still remained greater with nasal CPAP application [40]. During sleep onset, GG EMG activity had a greater initial fall in OSA patients compared to other groups, which resolved after few breaths with subsequent muscle recruitment [40]. TP EMG activity did fall after the sleep onset but was not significantly different among the groups [40]. They hypothesized the initial fall in upper airway muscle activity is likely due to loss of wakefulness stimulus that leads to obstruction in OSA patients. Genioglossus muscle, not tensor palatini, is more responsible for relief of UA obstruction.

4. Discussion

Although the entire pathophysiology of OSA remains incompletely understood, it is becoming increasingly clear that there is more to this problem than simple structural obstruction of the airway due to excessive soft tissues or limited skeletal framework. Our systematic review identified thirty-one studies focused on investigating the contribution of neurogenic component to the pathophysiology of OSA. This study sought to consolidate and review the evidence related to the contribution of neurogenic component to the pathophysiolo

5. Limitations

Our study has several limitations. While consistent histological findings and decreased sensory responses support a neurogenic basis to OSA, prospective studies are needed to elicit its impact on patient outcomes. Heterogeneity between outcome measures and limited sample sizes among the included studies also temper results and conclusions. It is worth mentioning that these are geographically diverse and well controlled studies. As with any literature review, this study is at risk of bias via search algorithm and reviewer selection; we feel we have limited this with a comprehensive, validated review strategy. Publication bias favors research with significant differences in groups, but given the concordance in our overall findings, it is unlikely to have changed this study.

6. Conclusion

Multiple independent studies corroborate the finding that increasing severity of snoring and obstructive sleep apnea is associated with worsening sensory nerve functioning of the palate. Evidence to support this exists in both functional and histological changes to the nerve fibers themselves, as well as the muscles they support. Although a causal relationship cannot be definitively supported at this time, one hypothesis may be that neuronal degeneration (due to age, snoring trauma, disuse atrophy, comorbid neurological conditions, or diet and environmental factors) could lead to a decrement in pharyngeal dilator function during sleep leading to narrowing and increased collapsibility of the upper airway. Patients with OSA have typical histopathologic findings of a chronic motor neuron lesion, including grouped atrophy, type grouping, and variability, which are consistent with a simultaneous denervation and re-innervation processes. The uvula of OSA patients and snorers has a higher percentage of muscle and fat content, which may contribute to increased pharyngeal resistance during sleep. An ongoing pathologic process of denervation and re-innervation changes in the upper airway of OSA patients due to inflammation is observed, which may be contributing to the pathogenesis of OSA.


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