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

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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 uvulopalatoplasty 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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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 PICOS 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 international 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 nonapneic snorers [11]. Contraction 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 nonapneic 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/IIB 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 afferent 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, sprouting 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-snoring 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

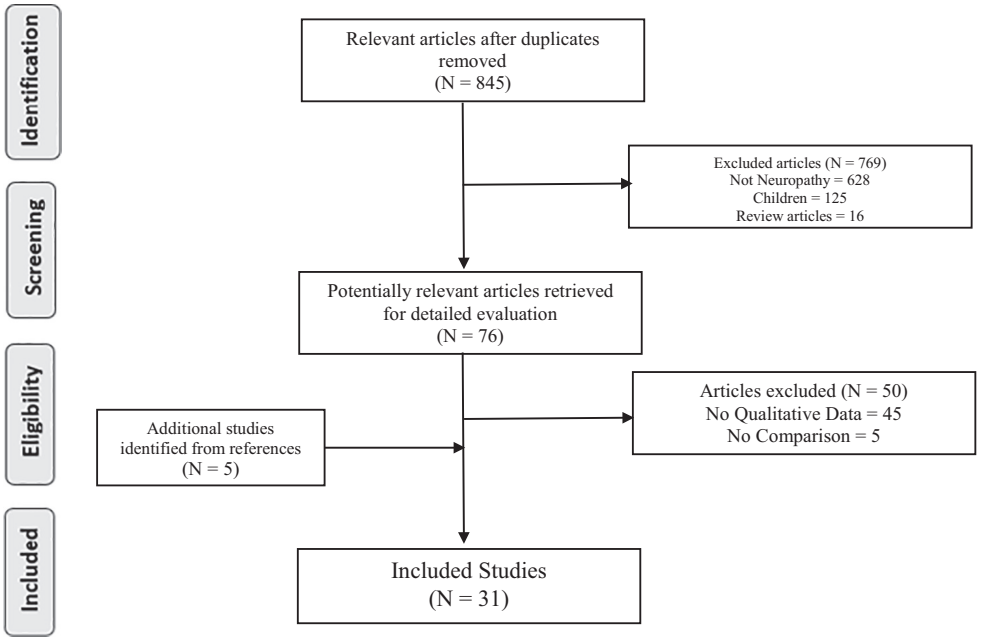

Fig. 1. Flow chart for study selection. (N: number of studies).

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 and 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 corpuscles in muscle samples of SAHS patients, which is a sign of early aging [17].

In a prospective observational study, Bassiouny 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 1
Histologic analysis.
LM: Light Microscopy, TEM: Transmission Electron Microscopy, GG: Genioglossus, MU: Musculus uvulae, CGRP: Calcitonin Gene-Related Peptide, SP: Substance P, PGP: Protein-Gene Product 9.5, AHI: Apnea-Hypopnea Index, ODI: Oxygen desaturation index, UPPP: Uvulo-Palato-Pharyngoplasty, RDI: Respiration disturbance index, SAHS: Sleep Apnea Hypopnea Index, OSA: Obstructive Sleep Apnea.

	Study's general characteristics and number of included patients				
Year, study, design	N =	Study site	Outcomes analyzed	OSA diagnosis by:	Main findings
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
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 I/IB in SAHS patients
1997, Friberg et al., cross sectional	10 OSA, 11 snorers, 11 non snorers	Sweden	Content of neuropeptidases; CGRP, SP, PGP	ODI	• ↑ number of PGP 9.5, CGRP, 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 • Lowest # of nerve endings seen in OSA patient with highest ODI
1998, Friberg et al., cross sectional	10 OSA, 11 snorers, 10 non snorers	Sweden	Morphological differences in palatopharyngeus muscles	ODI	• Signs of neurogenic lesions in palatopharyngeus muscle (grouped atrophy, type grouping and fascicular atrophy) of OSA patients and snorers • Significant correlation between % periodic obstructive breathing and morphological abnormalities in snorers and OSA patients
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	• ↑ amount of connective tissue, morphological variability in muscle fiber type and appearance, and presence of developmental myosin heavy chain composition seen in patients with SDB
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
2010, Molina et al., cross sectional	10 mild, 10 moderate, 10 severe SAHS, 10 controls	Brazil	LM and TEM of palatopharyngeal muscles	RDI	• 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
2009, Bassiouny et al., cross sectional	10 OSA, 10 snorers, 5 controls	Egypt	Morphology of nerve fibers with TEM	RDI	• Moderate-severe degenerative changes of myelinated and unmyelinated nerve fibers seen in 10/10 OSA patients • Mild-moderate degenerative changes seen in 6/10 simple snorers • Normal architecture and shape of nerve fibers in all controls

Table 2
Morphometric analysis.
PGP: Protein-Gene Product 9.5, NCAM: Neural Cell Adhesion Molecule, UA: Upper Airway AHI: Apnea-Hypopnea index, RDI: Respiratory disturbance index.

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

Table 3
Sensation testing.
UA: Upper Airway TPD: Two Point Discrimination, VDT: Vibration Detection Threshold, VST: Vibration Sensation Threshold WDT: Warm Detection Threshold, CDT: Cold Detection Threshold, SPT: Sensory Perception Threshold, AHI: Apnea-Hypopnea Index, ODI: Oxygen desaturation index, RDI: Respiration disturbance index.

	Study's general characteristics and number of included patients				
Year, study, design	N=	Study site	Outcomes analyzed	OSA diagnosed by:	Main findings
1992, Larsson et al., cross-sectional	15 OSA, 15 control	Sweden	WDT, CDT at tongue and anterior tonsillar pillar	ODI	• 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
2011, Sunenergren et al., cross-sectional	33 OSA, 32 snorers, 25 control	Sweden	CDT at soft palate and lip	AHI	• 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 snoring years to CDT
2009, Hagander et al., cross-sectional	31 OSA, 13 snorers, 23 control	Sweden	VDT and CDT in oropharynx	AHI	• 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.
2002, Guilleminault et al., cross-sectional study	15 OSA, 15 UARS, 15 control	USA	TPD at soft palate	AHI	• 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
2016, Jeong et al., cross-sectional	27 OSA, 12 snorer, 10 control	Korea	TPD at soft palate and anterior tongue	AHI	• 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
2001, Kimoff et al., cross- sectional	38 OSA, 12 snorers, 15 control	Canada	TPD, VST in UA	AHI	• 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
2005, Nguyen et al., cross-sectional	39 OSA, 17 control	Canada	TPD, VDT, mucosal sensory dysfunction with air pulses	AHI, RDI	• 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
2013, Kim et al., cross-sectional	40 snorers, 19 controls	South Korea	Relationship between clinical parameters and standardized palatal sensory threshold	AHI	• 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 < 0.001)
2005, Dematteis et al., cross-sectional	50 SDB, 17 controls	France	SPT with intraoral device that applied airflow to soft palate	RDI	• 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

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 neural 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-snoring 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 ($r_s = 0.41$) and self-reported snoring years ($r_s = 0.47$) 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 (3 ± 2/h) and normal subjects (2 ± 1.5/h) [30]. TPD revealed significantly impaired ($p = 0.0001$) 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 impairment in the oropharynx of OSA patients [33].

3.3.3. 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 palatal 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^3; 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 of last pre-apneic effort in all three muscles and resolved after all three muscles reached maximal activity simultaneously [36]. This was the first study to advocate for simultaneous inspiratory recruitment of velopharyngeal and oropharyngeal muscles to maintain upper airway patency during sleep in OSA patients.

Mezzanotte et al. assessed EMG activity of genioglossus (GG) and tensor palatini (TP) muscles 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

Table 4
Response testing/EMG.
EMG: electromyographic, LVG: levator veli palitini, PG: palatoglossus, GG:genioglossus, TP: tensor palatine, AHI: Apnea-Hypopnea index, OSA: Obstructive sleep apnea, ODI: Oxygen desaturation index.

Study's general characteristics and number of included patients				OSA diagnosis by:	Main findings
Year, study, design	N =	Study site	Outcomes analyzed		
1995, Carlson et al., cross-sectional	8 OSA patients	USA	EMG activity of LVG, PG, two velopharyngeal muscles and GG	AHI	• Simultaneous inspiratory recruitment of velopharyngeal and oropharyngeal muscles may be needed to maintain upper airway patency during sleep in patients with OSA
1996, Mezzanotte et al., cross- sectional	10 OSA, 8 controls	USA	EMG activity of GG and TP	Episodes of obstructive or mixed apneas plus hypopneas per hour of sleep.	• In OSA patients, sleep onset is associated with significantly greater decrease in activity of tensor palatini muscles as compared to wakefulness This may suggest a loss in neuromuscular compensatory mechanism to maintain airway patency in patients with sleep apnea
1997, Mortimore et al., cross-sectional	16 SAHS, 16 controls	Scotland	EMG activity of LVP and PG muscles in response to negative upper airway pressure	AHI	• SAHS patients have impaired EMG responses to negative upper airway pressure in levator veli palatini and palatoglossus muscles that may alter the neuromuscular control of upper airway patency. This attenuated reflex response may be improved with chronic CPAP use.
2005, Svanburg et al., cross-sectional	12 OSA, 15 habitual snorers, 5 control	Sweden	Concentric needle EMG in palatopharyngeus muscle	AHI, history of snoring	• EMG evidence of neurogenic changes in palatopharyngeus muscle of some snorers and most patients with OSAS when compared to controls
2005, Fogel et al., cross sectional	12 OSA, 12 healthy young men, 13 healthy old men	USA	EMG activity of GG and TP	Previous history of OSA	• Genioglossus muscle, not tensor palatini, is more responsible for relief of UA obstruction The initial fall in upper airway muscle activity is likely due to loss of wakefulness stimulus that leads to obstruction in OSA patients

palatopharyngeus 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 soft palate and uvula in those along the primary snoring and OSA spectrum as compared to normal controls. Overall, this study supports the hypothesis of a generalized neurologic dysfunction in the soft palate of snoring and sleep apnea patients. The main findings of the review are highlighted below.

First, histological studies demonstrated diffuse inflammatory changes, muscular changes consistent with neuropathy, and neural aberrancies of the soft palate in OSA patients. Most of the histological studies were based on light microscopy, but two studies also showed evidence of focal neuronal degeneration under electron microscopy [10,18]. Soft palate and uvular specimens of snorers and OSA patients seem to have higher proportion of type IIA fibers, which hints at adaptive physiological transformation from fatigue-resistant (Type I) to fatigue-prone (Type IIA) muscles [10,14,18,22,36]. This muscular alteration may prove to be an adaptive compensation in snoring and milder forms of OSA, but as the severity of disease increases, this muscular tissue will fail to resist pharyngeal collapse despite the adaptive changes in the physiology of the muscle fibers. Morphometric analysis also supported myopathy and neuronal degeneration in soft palate and/or uvula of snorers and OSA patients. A possible explanation for these identified changes is years of vibratory trauma leads to inflammation of soft palate and uvula that may culminate with fibrosis and subsequent neuronal damage.

Second, sensory testing studies favor progressive neuronal dysfunction along the spectrum of snoring and OSA. Although Jeong et al. showed no significant difference with sensory testing between OSA patients and control, they did identify a subgroup within OSA patients that had significantly impaired sensation [31]. Different modalities of sensory testing consistently confirmed that patients with sleep disordered breathing have afferent dysfunction of the palate. One study even reported significant reversal in sensory dysfunction in a group of OSA patients treated with CPAP [32]. Hence, it is highly probable that chronic hypoxia and/or chronic palatal vibratory stimulation may lead to oropharyngeal neuropathy in habitual snorers and OSA. There have been studies that assessed differences in respiratory related evoked potentials (RREP) as a test for afferent function of oropharynx. The data is mixed with a few favoring afferent neuropathy [41,42] and some finding no evidence to support it [43–47]. Since RREP is not a reliable method for oropharyngeal afferent testing, we decided to not include the RREP studies in this review [48].

Lastly, there are very few studies that compared efferent changes of the soft palate in non-snorers and OSA patients with only one study that compared all three groups. These studies also assessed different soft palate muscles. The majority of these studies reported decreases in EMG activity of muscles of the soft palate during sleep, but one study reported no changes in EMG activity of tensor palatini muscle [40]. Hence, the effect of snoring and hypoxia on efferent function of the soft palate is not completely clear. More EMG studies specifically focusing on soft palate muscles during sleep are needed to assess the consequence of the above histological and afferent changes noted in snorers and OSA patients.

These findings have several implications to the understanding, as well as treatment, of OSA. First, the identified studies suggest a possible risk factor for the development of OSA, as those with neuronal dysfunction may have decreased response to increased respiratory effort during sleep. It is possible that sensory clinical testing of the soft palate in snorers and undiagnosed OSA patients may identify high-risk patients that could benefit from early intervention. Patients with greater neurogenic dysfunction may also be at higher risk of surgical treatment failure, as they could induce a similar palatal neuropathy and paradoxical worsening in sleep apnea [2].

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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References

[1] Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013;177(9):1006–14. http://dx.doi.org/10.1093/aje/kws342.

[2] Camacho M, Nesbitt NB, Lambert E, Song SA, Chang ET, Yung Liu S, et al. Laser Assisted Uvulopalatoplasty (LAUP) for obstructive sleep apnea: a systematic review and meta-analysis. Sleep 2017. http://dx.doi.org/10.1093/sleep/zsx004.

[3] McNicholas WT, Coffey M, McDonnell T, O'Regan R, Fitzgerald MX. Upper airway obstruction during sleep in normal subjects after selective topical oropharyngeal anesthesia. Am Rev Respir Dis 1987;135(6):1316–9.

[4] Chadwick GA, Crowley P, Fitzgerald MX, O'Regan RG, McNicholas WT. Obstructive sleep apnea following topical oropharyngeal anesthesia in loud snorers. Am Rev Respir Dis 1991;143(4 Pt 1):810–3. http://dx.doi.org/10.1164/ajrccm/143.4_Pt_1.810.

[5] Cala SJ, Sliwinski P, Cosio MG, Kimoff RJ. Effect of topical upper airway anesthesia on apnea duration through the night in obstructive sleep apnea. J Appl Physiol (1985) 1996;81(6):2618–26.

[6] Takeuchi T, Futatsuka M, Imanishi H, Yamada S. Pathological changes observed in the finger biopsy of patients with vibration-induced white finger. Scand J Work Environ Health 1986;12:280–3. (4 Spec No).

[7] Svanborg E, Larsson H. Development of nocturnal respiratory disturbance in untreated patients with obstructive sleep apnea syndrome. Chest 1993;104(2):340–3.

[8] Kales A, Cadieux RJ, Bixler EO, Soldatos CR, Vela-Bueno A, Misoul CA, et al. Severe obstructive sleep apnea–I: onset, clinical course, and characteristics. J Chronic Dis 1985;38(5):419–25.

[9] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097http://dx.doi.org/10.1371/journal.pmed.1000097.

[10] Woodson BT, Garancis JC, Toohill RJ. Histopathologic changes in snoring and obstructive sleep apnea syndrome. Laryngoscope 1991;101(12 Pt 1):1318–22.

[11] Series F, Cote C, Simoneau JA, Gelinas Y, St Pierre S, Leclerc J, et al. Physiologic, metabolic, and muscle fiber type characteristics of musculus uvulae in sleep apnea hypopnea syndrome and in snorers. J Clin Invest 1995;95(1):20–5. http://dx.doi.org/10.1172/jci117640.

[12] Series FJ, Simoneau SA, St Pierre S, Marc I. Characteristics of the genioglossus and musculus uvulae in sleep apnea hypopnea syndrome and in snorers. Am J Respir Crit Care Med 1996;153(6 Pt 1):1870–4. http://dx.doi.org/10.1164/ajrccm.153.6.8665048.

[13] Friberg D, Gazelius B, Hokfelt T, Nordlander B. Abnormal afferent nerve endings in the soft palatal mucosa of sleep apnoics and habitual snorers. Regul Pept 1997;71(1):29–36.

[14] Friberg D, Ansved T, Borg K, Carlsson-Nordlander B, Larsson H, Svanborg E. Histological indications of a progressive snorers disease in an upper airway muscle. Am J Respir Crit Care Med 1998;157(2):586–93. http://dx.doi.org/10.1164/ajrccm.157.2.96-06049.

[15] Lindman R, Stal PS. Abnormal palatopharyngeal muscle morphology in sleep-disordered breathing. J Neurol Sci 2002;195(1):11–23.

[16] Paulsen FP, Steven P, Tsokos M, Jungmann K, Muller A, Verse T, et al. Upper airway epithelial structural changes in obstructive sleep-disordered breathing. Am J Respir Crit Care Med 2002;166(4):501–9. http://dx.doi.org/10.1164/rccm.2109099.

[17] Molina FD, Santos FC, Falleiros Jr. LR, Goloni-Bertollo EM, Felisbino SL, Justulin Jr. LA, et al. Microscopical evaluation of extracellular matrix and its relation to the palatopharyngeal muscle in obstructive sleep apnea. Microsc Res Tech 2011;74(5):430–9. http://dx.doi.org/10.1002/jemt.20927.

[18] Bassiouny A, Nasr S, Mashaly M, Ayad E, Qotb M, Atef A. Electron microscopy study of peripheral nerves in the uvulae of snorers and obstructive sleep apnoea patients. J Laryngol Otol 2009;123(2):203–7. http://dx.doi.org/10.1017/s0022215108002971.

[19] Edstrom L, Larsson H, Larsson L. Neurogenic effects on the palatopharyngeal muscle in patients with obstructive sleep apnoea: a muscle biopsy study. J Neurol Neurosurg Psychiatry 1992;55(10):916–20.

[20] Stauffer JL, Buick MK, Bixler EO, Sharkey FE, Abt AB, Manders EK, et al. Morphology of the uvula in obstructive sleep apnea. Am Rev Respir Dis 1989;140(3):724–8. http://dx.doi.org/10.1164/ajrccm/140.3.724.

[21] Swift AC, Goulding H, Elder J, Haqqani MT. A histopathological comparison of the uvula between snorers and non-snorers. Clin Otolaryngol Allied Sci 1995;20(6):517–21.

[22] Sekosan M, Zakkar M, Wenig BL, Olopade CO, Rubinstein I. Inflammation in the uvula mucosa of patients with obstructive sleep apnea. Laryngoscope 1996;106(8):1018–20.

[23] Series F, Simoneau JA, St Pierre S. Muscle fiber area distribution of musculus uvulae in obstructive sleep apnea and non-apneic snorers. Int J Obes Relat Metab Disord 2000;24(4):410–5.

[24] Berger G, Gilbey P, Hammel I, Ophir D. Histopathology of the uvula and the soft palate in patients with mild, moderate, and severe obstructive sleep apnea. Laryngoscope 2002;112(2):357–63. http://dx.doi.org/10.1097/00005537-200202000-00028.

[25] Boyd JH, Petrof BJ, Hamid Q, Fraser R, Kimoff RJ. Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. Am J Respir Crit Care Med 2004;170(5):541–6. http://dx.doi.org/10.1164/rccm.200308-1100OC.

[26] De Bellis M, Pagni F, Ronchi S, Limonta G, Gorla S, Nicoletti G, et al. Immunohistochemical and histomorphometric study of human uvula innervation: a comparative analysis of non-snorers versus apneic snorers. Sleep Breath 2012;16(4):1033–40. http://dx.doi.org/10.1007/s11325-011-0597-7.

[27] Larsson H, Carlsson-Nordlander B, Lindblad LE, Norbeck O, Svanborg E. Temperature thresholds in the oropharynx of patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 1992;146(5 Pt 1):1246–9. http://dx.doi.org/10.1164/ajrccm/146.5_Pt_1.1246.

[28] Sunnergren O, Brostrom A, Svanborg E. Soft palate sensory neuropathy in the pathogenesis of obstructive sleep apnea. Laryngoscope 2011;121(2):451–6. http://dx.doi.org/10.1002/lary.21371.

[29] Hagander L, Harlid R, Svanborg E. Quantitative sensory testing in the oropharynx: a means of showing nervous lesions in patients with obstructive sleep apnea and snoring. Chest 2009;136(2):481–9. http://dx.doi.org/10.1378/chest.08-2747.

[30] Guilleminault C, Li K, Chen NH, Poyares D. Two-point palatal discrimination in patients with upper airway resistance syndrome, obstructive sleep apnea syndrome, and normal control subjects. Chest 2002;122(3):866–70.

[31] Jeong KH, Yang Y, Choi HR, Cho JH, Kim GT, Kim JK. Assessment of change in palatal sensation in obstructive sleep apnea patients by using two-point palatal discrimination. Clin Exp Otorhinolaryngol 2016;9(3):226–32. http://dx.doi.org/10.21053/ceo.2015.01375.

[32] Kimoff RJ, Sforza E, Champagne V, Ofiara L, Gendron D. Upper airway sensation in snoring and obstructive sleep apnea. Am J Respir Crit Care Med 2001;164(2):250–5. http://dx.doi.org/10.1164/ajrccm.164.2.2010012.

[33] Nguyen AT, Jobin V, Payne R, Beauregard J, Naor N, Kimoff RJ. Laryngeal and velopharyngeal sensory impairment in obstructive sleep apnea. Sleep 2005;28(5):585–93.

[34] Kim SW, Park HW, Won SJ, Jeon SY, Jin HR, Lee SJ, et al. Palatal sensory threshold reflects nocturnal hypoxemia and airway occlusion in snorers and obstructive sleep apnea patients. J Clin Sleep Med 2013;9(11):1179–86. http://dx.doi.org/10.5664/jcsm.3164.

[35] Dematteis M, Levy P, Pepin JL. A simple procedure for measuring pharyngeal sensitivity: a contribution to the diagnosis of sleep apnoea. Thorax 2005;60(5):418–26. http://dx.doi.org/10.1136/thx.2003.015032.

[36] Carlson DM, Onal E, Carley DW, Lopata M, Basner RC. Palatal muscle electromyogram activity in obstructive sleep apnea. Am J Respir Crit Care Med 1995;152(3):1022–7. http://dx.doi.org/10.1164/ajrccm.152.3.7663778.

[37] Mezzanotte WS, Tangel DJ, White DP. Influence of sleep onset on upper-airway muscle activity in apnea patients versus normal controls. Am J Respir Crit Care Med 1996;153(6 Pt 1):1880–7. http://dx.doi.org/10.1164/ajrccm.153.6.8665050.

[38] Mortimore IL, Douglas NJ. Palatal muscle EMG response to negative pressure in awake sleep apneic and control subjects. Am J Respir Crit Care Med 1997;156(3 Pt 1):867–73. http://dx.doi.org/10.1164/ajrccm.156.3.9608008.

[39] Svanborg E. Impact of obstructive apnea syndrome on upper airway respiratory muscles. Respir Physiol Neurobiol 2005;147(2–3):263–72. http://dx.doi.org/10.1016/j.resp.2005.06.012.

[40] Fogel RB, Trinder J, White DP, Malhotra A, Raneri J, Schory K, et al. The effect of sleep onset on upper airway muscle activity in patients with sleep apnoea versus controls. J Physiol 2005;564(Pt 2):549–62. http://dx.doi.org/10.1113/jphysiol.2005.083659.

[41] Akay M, Leiter JC, Daubenspeck JA. Reduced respiratory-related evoked activity in subjects with obstructive sleep apnea syndrome. Can J Appl Physiol (1985) 2003;94(2):429–38. http://dx.doi.org/10.1152/japplphysiol.00018.2001.

[42] Grippo A, Carrai R, Romagnoli I, Pinto F, Fanfulla F, Sanna A. Blunted respiratory-related evoked potential in awake obstructive sleep apnoea subjects: a NEP technique study. Clin Neurophysiol 2011;122(8):1562–8. http://dx.doi.org/10.1016/j.

clinph.2011.01.005.

[43] Afifi L, Guilleminault C, Colrain IM. Sleep and respiratory stimulus specific dampening of cortical responsiveness in OSAS. Respir Physiol Neurobiol 2003;136(2–3):221–34.

[44] Donzel-Raynaud C, Redolfi S, Arnulf I, Similowski T, Straus C. Abnormal respiratory-related evoked potentials in untreated awake patients with severe obstructive sleep apnoea syndrome. Clin Physiol Funct Imaging 2009;29(1):10–7. http://dx.doi.org/10.1111/j.1475-097X.2008.00830.x.

[45] Eckert DJ, Lo YL, Saboisky JP, Jordan AS, White DP, Malhotra A. Sensorimotor function of the upper-airway muscles and respiratory sensory processing in untreated obstructive sleep apnea. J Appl Physiol (1985) 2011;111(6):1644–53. http://dx.doi.org/10.1152/japplphysiol.00653.2011.

[46] Gora J, Trinder J, Pierce R, Colrain IM. Evidence of a sleep-specific blunted cortical response to inspiratory occlusions in mild obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2002;166(9):1225–34. http://dx.doi.org/10.1164/rccm.2106005.

[47] Ruehland WR, Rochford PD, Pierce RJ, Webster KE, Trinder JA, Jordan AS, et al. Sensory detection of threshold intensity resistive loads in severe obstructive sleep apnoea. Respir Physiol Neurobiol 2017;236:29–41. http://dx.doi.org/10.1016/j.resp.2016.10.014.

[48] Redolfi S, Raux M, Donzel-Raynaud C, Morelot-Panzini C, Zelter M, Derenne JP, et al. Effects of upper airway anaesthesia on respiratory-related evoked potentials in humans. Eur Respir J 2005;26(6):1097–103. http://dx.doi.org/10.1183/09031936.05.00139804.