JOURNAL OF CLINICAL AND HEALTH SCIENCES

REVIEW

Pathogenesis and Pathophysiological Mechanism of Obstructive Sleep Apnea: A Review of Anatomical, Cytoskeletal, Muscular, and Neurological Abnormalities

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Received
13th September 2023
Received in revised form
13th February 2024
Accepted
11th March 2024
Published
1st March 2025

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ABSTRACT

Introduction: Obstructive sleep apnea (OS) affects approximately 1 billion people globally. It leads to significant morbidity and mortality, causing a significant burden on the healthcare system. Collapse of the upper airway during sleep is the main pathology in OSA. The aim of this review is to update OSA's pathogenesis and pathophysiological mechanisms, focusing on microanatomical features, including neuronal and muscular morphological abnormalities. **Results:** OSA patients have smaller maxilla and mandible, longer, thicker soft palate, and larger tongue. Microscopically, the upper airway in these patients shows increased variability in muscle fiber size and form due to concurrent hypertrophy and atrophy. The muscular layer is also inflamed, reducing its contractility and functionality. Immunohistochemistry shows that OSA patients' upper airway muscles lack desmin expression, impairing mitochondria placement and, thus, decreasing muscular oxidative activity. Neurologically, OSA patients were reported to have abnormalities of the large, small, motor, sensory, myelinated, and myelinated nerves of the palate and pharynx. Axon density and diameter are reduced. An increased number of regenerating nerves is reflected in increased GAP43 protein, indicating nerve injury. **Conclusion:** OSA is associated with macro and microscopic abnormalities involving the muscles and nerves of the patient's upper airway.

KEYWORDS: Obstructive sleep apnea, cytoskeletal protein, neuronal injury, S100, GAP-43

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive partial (hypo-apnea) or complete (apnea) breathing difficulties during sleep. History of daytime sleepiness and impairments attributed to disturbed sleep, such as poor memory or concentration, irritability, and fatigue, are typical [1, 2]. Patients also gasp during sleeping, snore, or stop breathing [2, 3]. Many screening tests are available to detect OSA, such as the Berlin questionnaire and the Epworth Sleepiness Scale [4]. However, the gold standard for OSA diagnosis is polysomnography [1, 2, 5, 6]. OSA is categorized into mild, moderate, and severe based on the Apnea Hypopnea Index (AHI), defined as the combined average number of apneas and hypopneas per hour of sleep. The values of 5 to 14.9 are considered mild, 15 to 29.9 moderate, and greater than 30 severe [5].

The reported prevalence of OSA in the literature differs according to the detection methods used, whether using a questionnaire or polysomnography [1, 4, 7, 8]. A recent study collected prevalence data from 193 countries, applied an objective analysis method with a standardized algorithm, and reliably estimated OSA prevalence from 16 countries [5]. This study estimated that globally, 936 million people were suffering from OSA with AHI>5

[5]. China was estimated to have the highest prevalence of mild and moderate OSA, affecting 66 million people (8.8% of the population aged between 30 and 69 years) [5, 7].

OSA has been reported more in men compared to women, with a ratio of up to 5:1 [1]. Clinically, men present with snoring symptoms and witnessed apnea, while females have lower-intensity snoring with less witnessed apnea. Instead, women tend to present with daytime fatigue, lack of energy, insomnia, anxiety, and depression [1, 9]. Due to the late diagnosis, women lose more workdays due to sleep apnea-related sickness compared to men, which can occur up to 5 years before the diagnosis is made [10].

The characteristic pathogenetic or pathophysiological mechanism leading to OSA is repetitive pharyngeal airway collapse during sleep, leading to either a complete or considerable decrease in airflow [11]. This leads to hypercapnia and hypoxemia, which trigger activation of the sympathetic system, causing awakening from sleep. The cycle continues throughout the night resulting in fragmented sleep and daytime somnolence, reduced cognitive abilities, poor quality of life, and increased incidence of motor vehicle accidents [11].

This review aims to collate and update findings related to OSA's pathogenesis and pathophysiological mechanism, focusing on microanatomical abnormalities, including abnormalities in cytoskeletal protein, neuronal, and muscular morphology.

REVIEW

Anatomy of the Upper Airway and Pathophysiological Mechanism of OSA

The upper airway consists of muscles and soft tissue with minimal bony support [11], thus, it is vulnerable to collapse during sleep [12]. OSA patients have been reported to have smaller maxilla and mandibular bones compared to non-OSA patients, leading to narrowing of the oral cavity [12]. They have also been reported to have larger pharyngeal walls, which contributed to the narrowing of the lateral dimension of their airway and decreased tone of the pharyngeal dilator muscles [13, 14]. In addition, they have been reported to have longer and thicker soft palates with increased heights and angles, resulting in reduced vertical airway dimensions [12]. Due to the abnormalities above, the smaller oral cavity and pharynx areas contribute to obstruction of the patient's upper airways, increasing their predisposition towards OSA.

Nasal obstruction is frequently observed in OSA patients compelling them to switch from nasal to oral breathing [15]. Oral breathing during sleep results in increased upper airway resistance, a phenomenon that is absent in a wakeful state [15]. Oral breathing leads to narrowing of the pharyngeal lumen and reduced retroglossal diameter due to posterior displacement of the tongue, with elongation of the soft palate. In addition, nasal receptor activation is reduced, causing impaired nasal ventilatory reflex, which ultimately impairs the activation of pharyngeal dilator muscles, inhibiting its tone, thus worsening OSA [8, 9]. These findings have also been supported by the computational fluid dynamics method, where oral breathing is the main cause of pharyngeal airway collapse based on the Starling Resistor model [16].

In obese individuals, increased fat deposition is seen in the tongue, parapharyngeal, and submandibular space, resulting in concentric reduction in the upper airways [17, 18]. In addition, the increased intramuscular fat leads to increasing muscle length, resulting in abnormalities in muscle contraction and muscle prolapse into the airway [19]. This further contributes to the narrowing of the airway and the worsening of the disease [19]. Indeed, patients who had lost weight reported improvement in OSA symptoms [18], with the observed reduction in the amount of tongue fat and upper respiratory tract soft tissue [18].

Considering the relatively distinctive anatomic abnormalities described above, imaging studies can be a perfect tool to diagnose this condition [13, 20]. However, despite the differences in anatomical structures of OSA patients, a review of imaging studies of the upper airways of adults and children was unable to distinguish OSA sufferers from healthy individuals despite advancements in imaging techniques [21]. Nevertheless, work is being performed on improving the detection ability of upper airway abnormalities by imaging, especially with machine learning and artificial intelligence [22].

Vol 10(1) (2025) 6-13 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v10i1.5422

Upper Airway Muscular Abnormalities in OSA

The upper airway muscles that have been studied in OSA are the palatopharyngeus and other pharyngeal constrictor muscles, musculus uvulae (uvula muscle), genioglossus (muscle of the tongue), and levator and tensor palatini (soft palate muscles) [19, 23-31]. In OSA patients, these upper airway muscles exhibit higher variability in muscle fiber size and form, which was found to be due to a mixture of hypertrophied and atrophied myocytes in the patients [26, 32]. Interestingly, age and body mass index (BMI) are not correlated significantly to the increase in the range of muscle fiber size, indicating that the changes are due to OSA and not obesity or ageing [26].

The muscles are more loosely packed, accompanied by increased connective and adipose tissue content compared to the healthy control [29]. Other abnormal muscle shapes, such as irregular or lobulated outer contour, necrotic or angulated fibers, clustered nuclei within the center of small-sized muscle cells, and evidence of ring fibers, which are characterized by disorganization of myofilaments, have also been reported [33].

Most of the upper airway muscles (specifically the palatopharyngeus, genioglossus, and medium pharyngeal constrictor) in non-OSA patients are composed of an almost equal amount of slow-twitch (Type I) and fast-twitch (Type II) fibres [25, 30, 34-36]. OSA patients have been found to have increased type IIa muscle fibres [25, 30, 34-36], reflecting long-term resistance "training" of these muscles by chronic hypoxia [35]. The change in muscle phenotype helps the patients "generate" more force with the unfortunate effect of increased fatigability and a decrease in endurance [35]. We postulate that the vigor generated would allow OSA patients to breathe more forcefully against a collapsed airway. However, after a short duration, the muscle fatigues, and apnea manifests. The resulting hypoxia would force the patients into consciousness to initiate the voluntary breathing cycle once more, and the cycle would begin anew.

Upper Airway Mucosa Abnormalities in OSA

OSA has been linked to an increase in upper airway and systemic inflammation; the latter is postulated to be the connection between this condition and cardiovascular disease [37, 38]. Inflammatory infiltration in the mucosa and muscular layer of the upper airway of OSA patients is predominantly composed of T cells [39], with distinct differences in the T cell subsets between mucosal and muscular layers. CD8+ and CD4+ infiltrate the mucosa layer, whilst the muscular layer exhibits a predominance of CD4+ T cells. Both layers are infiltrated by CD25+ T cells, indicating activated T cells [39]. This report suggests that the inflammation is compartmentalized between the mucosa and the muscular layers. Muscular inflammation may damage this layer, thus contributing to the changes in the upper airway by making it less contractile and more dysfunctional [39].

The uvula mucosa in OSA has also been reported to have a higher prevalence of edema, thickened basement membrane, and increased plasma cell infiltration [40]. There has been no significant evidence of mucosal mucus gland enlargement in OSA compared to non-OSA patients [24]. Other than that, allergic rhinitis with mucosa inflammation is also found to be more prevalent in OSA patients [38].

Changes in Cytoskeletal Protein in OSA

Cytoskeletal protein is a complex network of contractile apparatus with three major components: actin, microtubules, and intermediate filaments [41]. Desmin is a muscle-specific intermediate filament that is most abundant in mature striated and smooth muscle cells. It is located at the rim of the Z-disc, extending from the nuclear envelope to the sarcolemma and tethered to membranous organelles such as mitochondria and the sarcoplasmic reticulum [29, 36].

Dystrophin is also an intermediate filament; it is a rod-shaped protein located in the inner aspect of the sarcolemma, muscle cell plasma membrane, and within sarcomeres. It provides stabilization of sarcolemma via dystrophin-associated glycoprotein complex (DAPC) which consists of dystroglycan, sarcoglycans, and dystrophin [41]. The absence of dystrophin leads to costamere disorganization, sarcolemmal fragility, muscle weakness, and necrosis [42].

Interestingly, the immunohistochemical pattern of desmin and dystrophin in human palatal muscle is distinct from limb muscles. The palatal muscles (i.e., the palatopharyngeus and uvula) show reduced desmin

Vol 10(1) (2025) 6-13 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v10i1.5422

and dystrophin expressions, whereas the limb muscles show strong immunopositivity against these proteins [28, 29]. Additionally, desmin expression, measured by immunoblotting, has been reported to change after 6 weeks of peripheral muscle resistance training [31], while dystrophin was not significantly affected [31]. The findings suggest that increased desmin is related to increased muscle strength. We postulate that the normal upper airway muscles already have little strength, as evidenced by a lack of desmin fibers in normal subjects.

The upper airway muscle in OSA patients express even less desmin compared to normal, with some showing complete absence [29]. Similarly, OSA patients display a lack of immunoreaction to dystrophin C-terminus, with normal rod and N-terminus immunoreactivity [43]. Furthermore, most dystrophin-C-terminus-negative fibers are also negative for desmin (desmin-negative fibers) [29].

Further, the desmin filaments are found to form small to large aggregates [29] with disrupted striations at the Z-band sarcomeric region [29, 43]. As the juxtaposition of mitochondria and sarcomeres is tied to desmin [29], the disruption causes impaired oxidative activity in the muscles. This is evidenced by the discovery of abnormal intramyofibrillar mitochondria staining pattern (indicated by reduced NADH-TR and SDH enzyme activities) and disorganization of the internal organization of mitochondria in OSA patients [44].

The above findings provide a subcellular explanation for the upper airway muscle weakness in OSA patients. The muscle changes are theorized to be due to denervation injury, which resulted from traumatic vibration associated with snoring [27, 29, 43].

Neuronal Injury in Obstructive Sleep Apnea and associated Neuronal Markers

In OSA patients, the reported neuronal injuries affect both motor and sensory nerves [35], myelinated and unmyelinated nerves [32], and large and small nerves [26, 32]. The histological changes include varicosity of sensory nerve endings of the epithelium and papillae of the tongue [26], decreased density of axons, reduction in axon diameter, increased number of regenerating axons [43], and even total degeneration of the whole nerve [32]. These changes are observed in the uvula, palatopharyngeus muscle, soft palate, and tongue [32, 35, 43, 45]. The decrease in axonal diameter is found to be contributed by a decrease in the Schwan area as well as thinning or absence of the axon itself, where the nerves involved showed the presence of a large number of circular Schwan cells without any central axon [43]. The reduction in axon density is found to be associated with increasing severity of swallowing dysfunction and higher AHI, indicating a relationship between axonal loss and pharyngeal dysfunction [43].

The cause of the observed neuropathy is cyclical chronic hypoxia that occurs in OSA patients, leading to infarction of the nerves. The second cause is chronic vibratory trauma due to the abnormal airflow within narrowed and prolapsed air passages [32]. The vibration directly injures the nerve components such as the axons, Schwann cells, and even the nerve cell bodies. The denervation will cause upper airway and pharyngeal muscle atrophy, which ultimately further obstructs the airways [43].

Other than histomorphological evidence, immunohistochemical detection of subcellular protein showed abnormal accumulation of neuronal markers (PGP 9.5, substance P, and calcitonin-gene-related protein) in sensory nerve endings of the tongue of OSA patients, indicating damaged nerve receptor terminals (sensory nerve) [32, 45].

S100B and GAP-43 proteins are the other 2 markers that have been used to detect neuronal injury. S100 protein is a family of calcium-binding proteins that regulate the intracellular levels of calcium. It consists of two dimeric proteins, namely: S100A which is mainly found in the kidney, neurons, muscles, and other organs, and S100B which is principally found in neuroglial and Schwann cells [46]. Serum S100B has been investigated as a marker to diagnose OSA. Unfortunately, the level of S100B in OSA is not significantly different from normal individuals [43, 46, 47]. This may indicate that the nervous system injury in OSA may not be severe enough to cause an increase in this protein [47].

Growth Associated Protein (GAP-43) is an intracellular protein located at branching points, growth cones, and axon terminals which reflects axon growth during neural development and regrowth following injury [43, 48, 49]. This protein is present in low levels

Vol 10(1) (2025) 6-13 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
https://doi.org/10.24191/jchs.v10i1.5422

in developed nerves of adulthood [43]. Not surprisingly, GAP-43 positive nerve fibers were reported to be significantly higher in OSA compared to non-OSA patients, indicating attempts at axon regeneration and thus, confirming nerve injury [43]. A similar observation is reported in an OSA animal model study, [49], the hypoxic rats demonstrate high GAP-43 expression in their hippocampal tissue [49]. This study provides evidence of central nervous system injury in OSA. All the changes described are summarized in Figure 1.

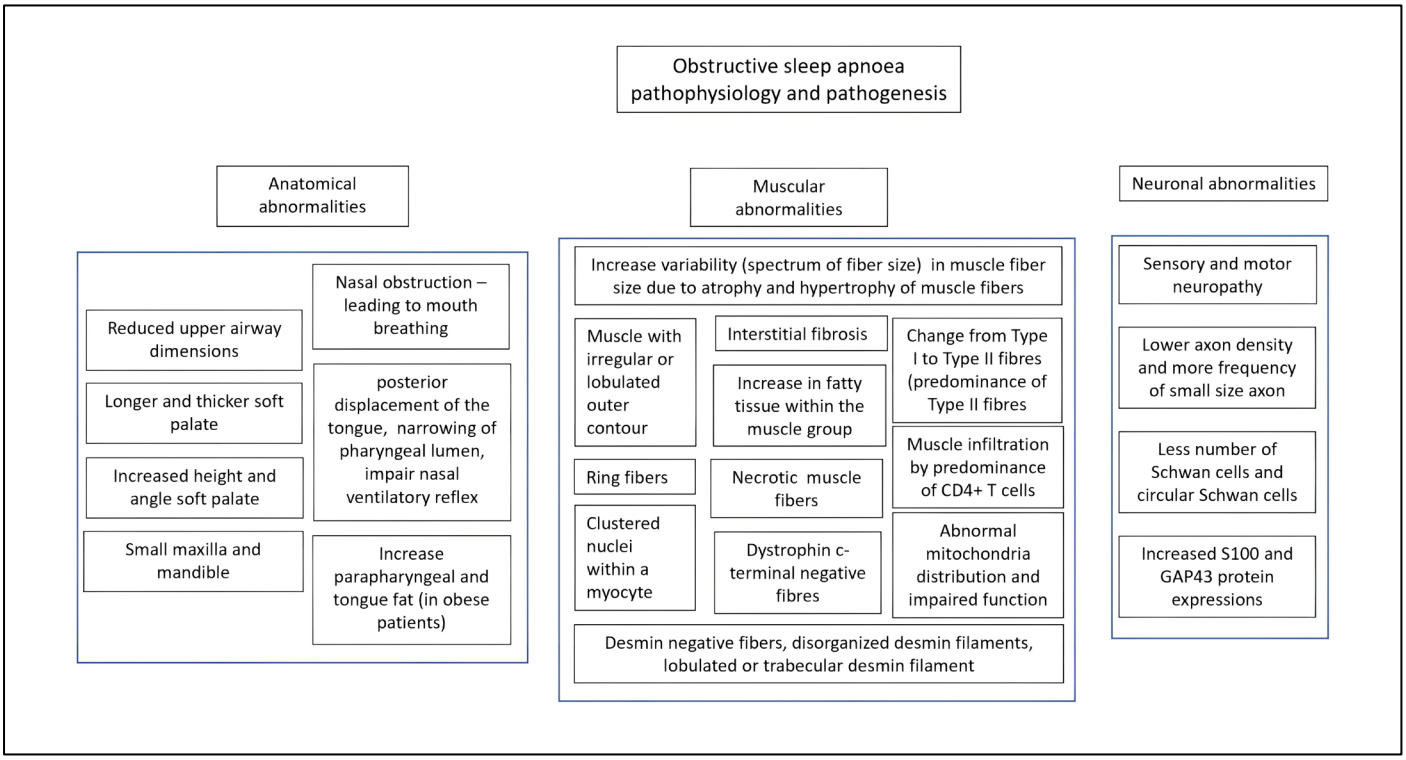

Figure 1 A concept map diagram summarizing the anatomical, muscular, and neuronal abnormalities seen in the upper airways of patients with obstructive sleep apnea

CONCLUSION

OSA is associated with anatomical, muscular, and neuronal abnormalities in the upper airway of the patients, including alterations in the morphology of muscle fibers, disruption of cytoskeletal protein (desmin and dystrophin), and neuronal injury, as evidenced by increased expression of GAP-43 protein. Understanding these changes would be helpful in further understanding the pathogenesis and pathophysiological mechanisms of OSA, which would aid in the identification of new research areas on the disease.

Conflict of interest

Authors declare none.

Acknowledgements

The authors are grateful to the Ministry of Higher Education, Malaysia for the Fundamental Research Grant (Ref: FRGS/1/2021/SKK06/UITM/01/1) which supports this research.

Authors' Contribution

All authors contributed to the manuscript's writing, revising, and editing.

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Vol 10(1) (2025) 6-13 | jchs-medicine.uitm.edu.my | eISSN 0127-984X
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https://doi.org/10.24191/jchs.v10i1.5422