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Effects of gender on upper airway collapsibility and severity of obstructive sleep apnea

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Abstract

Objective: Obstructive sleep apnea (OSA) is far more common in males than females. The discrepancy between the lower prevalence of OSA, the greater frequency of obesity and the smaller airway size in women compared to men suggests that a gender difference underlies this condition. We hypothesized that due to differences in tissue linkage women have more stable and less mobile upper airway structures than men, providing protection against severe forms of OSA.

Methods: Seventy-one consecutive patients with OSA, defined as having apnea-hypopnea index ≥5 events per hour, were enrolled into the study. The median (range) apnea-hypopnea index was 20 (5–132) events/h. In addition, measurements of upper airway dimensions were made, using an acoustic reflectance method, while the lower jaw was in the resting position and during retrusive posture. Measurements of upper airway dimensions were used during wakefulness to examine whether changes in pharyngeal dimensions, resulting from retrusive movement of the mandible commonly occurring during sleep, would explain the gender differences in the characteristics of OSA.

Results: OSA was much more positional and severe in men than women as indicated by the higher apnea-hypopnea index in supine position compared with sleeping on the side (difference between supine and side apnea-hypopnea index: 43.7 ± 5.2 (SEM) events/h in men versus 10.7 ± 7.6 events/h in women, $P = 0.0015$). The position dependency of OSA was most pronounced in those patients who demonstrated the largest decrease in pharyngeal cross-sectional area with retrusive movement of the mandible. There was no significant change in pharyngeal cross-sectional area as a result of retrusive movement of the mandible in women.

Conclusions: Men tend to have a larger but more collapsible airway during mandibular movement than women and this, in part, may play a role in the positional dependency and severity of OSA in men.

Keywords: Sleep apnea; Upper airways; Acoustic reflectance; Gender

1. Introduction

Obstructive sleep apnea (OSA) is more common in men than women despite the fact that women with OSA tend to be more obese and have smaller upper airway size than men [1–4]. This gender difference in the prevalence of OSA has not been adequately explained on the basis of obesity, upper airway size and neural control of upper airway muscles [5–7]. In a recent study by Pillar et al., men demonstrated more collapsibility of the upper airway during sleep than women when exposed to an external inspiratory load [8]. However, they found no gender difference in genioglossal or tensor palatini muscle activation in response to inspiratory resistive loading during sleep, suggesting differences in upper airway anatomy and mechanics rather than neural control of upper airway muscles. The current concept of the mechanism of upper airway maintenance during sleep suggests a complex interplay between intrinsic mechanical properties of the pharynx and neural regulation of pharyngeal dilator muscle activities. During sleep the neural inputs to pharyngeal dilator muscles are diminished, allowing the anatomical forces to increase pharyngeal collapsibility. Body position plays a significant role in the severity of OSA. Studies found that the number of obstructive events during sleep was much higher for the supine position than the lateral position in patients with OSA [9,10]. The pharyngeal airway is structurally surrounded by soft tissues such as the tongue and lateral soft tissue. Watanabe and colleagues recently suggested that

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the balance between the size of soft tissue and the bony enclosure, such as the mandible, determines the closing pressure of the airway [11]. Gravitational force is considered to be one significant determinant of the closing pressure [11]. The larger mass of the soft tissues, such as the tongue, located anterior to the pharynx, can exert greater gravitational force on the anterior pharyngeal airway wall while the patient is in the supine position, whereas the relatively smaller amount of the soft tissues located laterally may exert less pressure onto the lateral pharyngeal airway wall while the patient in the lateral position [11]. The mandible tends to move inferiorly and posteriorly during sleep in the supine position [12], a movement associated with decreased pharyngeal diameter and an increase in upper airway resistance [13,14]. We hypothesized that women might be protected from developing severe OSA because of the intrinsic stability of the pharynx and limited changes in upper airway caliber during inferior-posterior mandibular movement. The present study examines the relationship between changes in upper airway size and the severity and position-dependency of OSA in men and women.

2. Methods

2.1. Subjects

Among the consecutive patients referred to the sleep center for assessment, 71 patients were enrolled in the study after being diagnosed with OSA, as defined by a respiratory disturbance index (RDI, sum of apneas and hypopneas) ≥5 events per hour sleep. The current cohort is a subsample of a previously reported population that met the inclusion criteria for the present study [15]. Patients with a prior uvulopalatopharyngoplasty or clinically evident maxillofacial abnormalities such as retrognathia (the upper jaw and teeth overlapping the bottom jaw and teeth), micrognathia (receding and underdeveloped lower jaw), and history of temporomandibular joint abnormality were excluded from the study. An informed oral consent was obtained from the patients before upper airway measurements were made.

2.2. Sleep study

Polysomnography was performed between 21:00 and 07:00 h as previously described [16]. All variables were recorded simultaneously and continuously on either a 16-channel Grass polygraph model 8-20E (Astro-Med, Inc., West Warwick, MA) or a computerized sleep data acquisition system. Briefly, sleep was monitored using one chin electromyogram, four electroencephalogram and two electooculogram channels. Breathing was assessed using thermisters for oral and nasal airflows and strain-gauge pneumographs for chest and abdominal movements. Arterial oxygen saturation was measured using a pulse oximeter. Sleep recordings were scored in 30-s epochs and staged according to standard criteria [17]. Apnea was defined as at least an 80% reduction in airflow for more than 10 s, obstructive apnea when respiratory efforts were present and central apnea when respiratory efforts were absent; mixed apnea was defined as an event beginning with a central component, followed by an obstructive component. Hypopnea was scored when there was a 50–80% decrease in the airflow signal with ≥4% decrease in arterial oxygen saturation. Subjects were encouraged to sleep on their backs (supine) as well as on their sides (non-supine) during the sleep study. Those who only slept in one position were not included in the study. RDI was calculated for both positions. The sleep studies were reviewed in the morning and those patients with the diagnosis of OSA (Vide Supra) were enrolled into the study and underwent upper airway measurement.

2.3. Measurement of upper airway size

The pharyngeal cross-sectional area was measured using an acoustic reflection technique, as previously reported from this institution [15], which yields an accurate estimate of cross-sectional area of the upper airways [18–20]. Comparison between acoustically measured pharyngeal dimensions and those obtained through magnetic resonance imaging shows remarkable concordance [21]. This technique, compared with other methods such as computed tomography, fluoroscopy and magnetic resonance imaging, offers several advantages in that it is non-invasive, repeatable and permits dynamic imaging with no radiation exposure. The equipment, signal processing and filtering techniques for acoustic reflectance measurements have been described by Brooks et al. [18]. Briefly, the apparatus consists of a tube 24.1 cm long with a wave tube diameter of 1.94 cm, a 12 W loud speaker with a bandwidth of 250 Hz to 3.5 kHz and a peak energy of 1.25–1.5 kHz, and a pair of piezo-resistive microphones to measure the incidental and reflected acoustic waves. We measured ten to 20 cross-sectional areas at a rate of three times per second for each position as a function of distance down the airway of the mandible; the subjects breathed ambient air via a rubber mouthpiece without a nose clip (to have a uniform 8 mm mouth opening across the subjects). The coefficient of measurement variation was 3.4%. The measurements were made in a seated position with the mandible in a resting position or during a passive, maximally retrusive posture, commonly found during sleep in patients with sleep apnea [12], with a vertical opening of 8 mm. The subjects were trained to relax the jaw allowing manual retrusive displacement of the mandible during measurements. The resting jaw alignment and degree of mandibular movement were measured using a George gauge (Great Lakes

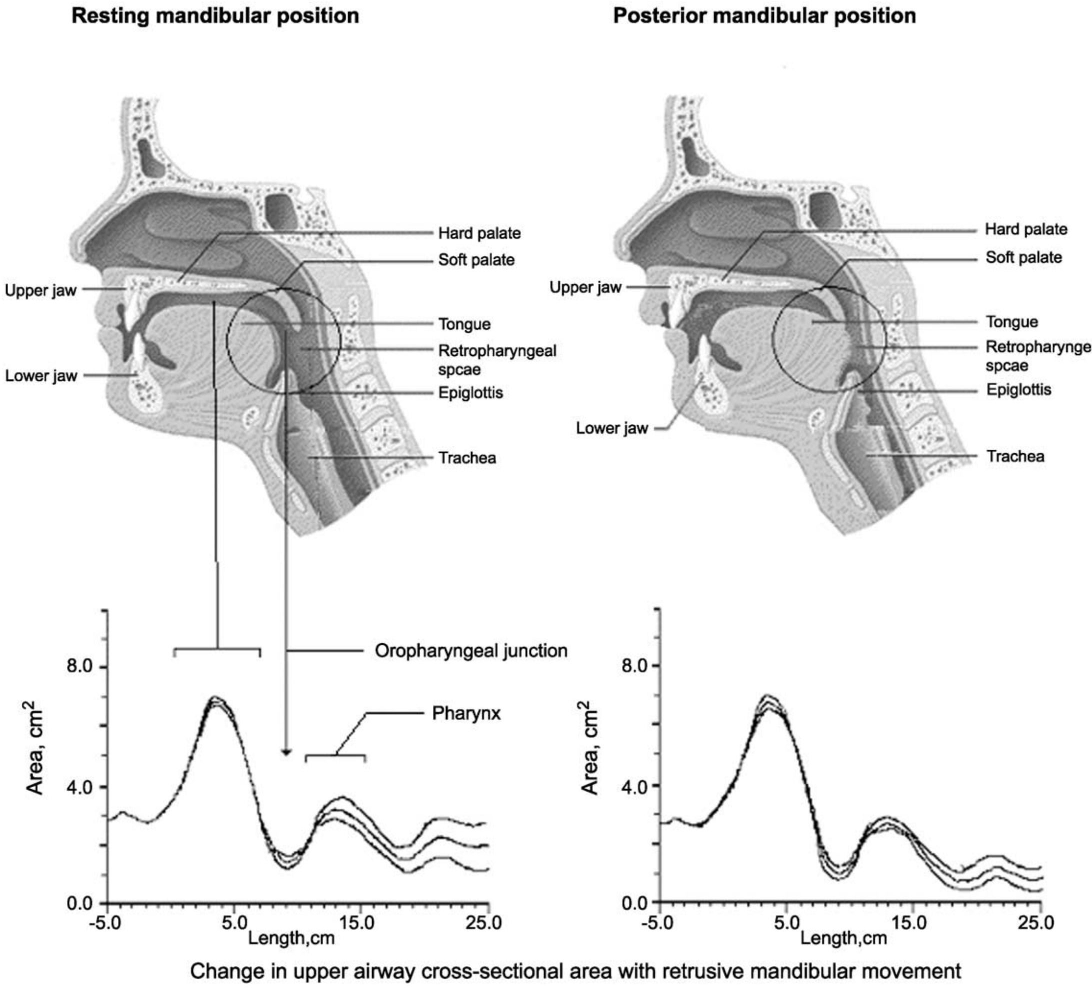

Fig. 1. Typical acoustic reflectance distance-area functions of the upper airway in relationship to anatomic region. The curves show the mean and 95% CI. The retrusive movement of the mandible results in decreased cross-sectional areas of the oropharyngeal junction and the pharynx.

Orthodontics, Tonawanda, NY) – an orthodontic device allowing an accurate measurement of the mandibular position relative to the maxilla. We examined the upper airway cross sectional area compared to distance traces for the presence of a standard curve of mouth peak, oropharyngeal valley, pharyngeal peak and laryngeal valley. The oropharyngeal junction is the cross-sectional area between the soft palate and the oropharynx. Pharyngeal area is the mean cross-sectional area from oropharyngeal junction to the glottis (Fig. 1).

2.4. Statistical analysis

Data are presented as means ± SE. The data were analyzed for gender differences in anthropometric measurements, upper airway dimensions and respiratory events during sleep using unpaired Mann–Whitney *U*-test [22]. The latter test was used because of unequal sample size. The minimum sample size was based on assumptions of 80% power to detect a difference of at least 40% in measured outcomes at a level $P < 0.05$.

3. Results

The study population consisted of 53 men and 18 women, with mean ages of 52.0 ± 1.5 and 48.6 ± 3.2 years, respectively. The anthropometric data and respiratory indices are shown in Table 1. The men and women were obese with body mass indexes (BMI) of 33.5 ± 0.7 and

Table 1
Anthropometric measures, respiratory disturbance index, and upper airway dimensions in males and females with obstructive sleep apnea

	Males ($N = 53$)	Females ($N = 18$)
Age, year	52.0 ± 1.5	48.6 ± 3.2
BMI, kg m^{-2}	33.5 ± 0.7	39.5 ± 3.0
Epworth sleepiness scale	14 ± 4	15 ± 3
RDI, event/h	37.3 ± 4.3	23.7 ± 6.7*
Mean awake SaO$_2$, %	94.2 ± 0.4	94.5 ± 0.5
Minimum asleep SaO$_2$, %	82.4 ± 1.3	82.7 ± 1.5
Mean pharyngeal area, cm^2	2.49 ± 0.09	1.83 ± 0.13*
Oropharyngeal junction, cm^2	1.49 ± 0.08	0.98 ± 0.13*

Data represent means ± SE; BMI, body mass index; and RDI, respiratory disturbance index; *$P < 0.05$ when compared with males.

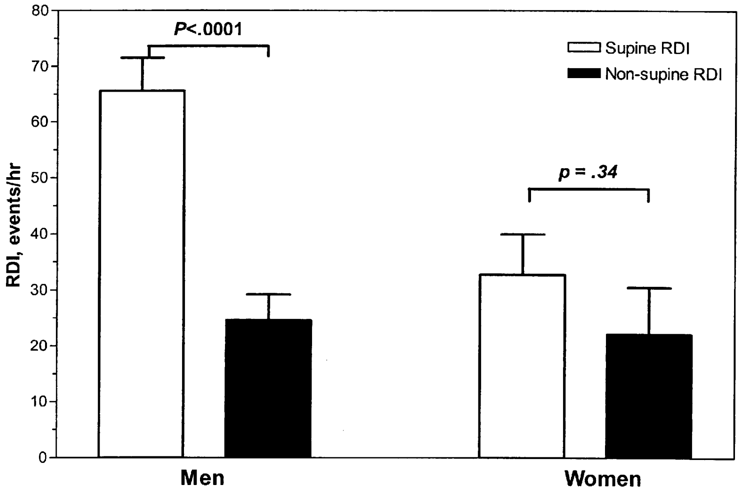

Fig. 2. Effect of sleep position on the respiratory disturbance index in men and women. Men have more severe OSA when supine versus on their side (non-supine) compared to women.

39.5 ± 3.0 kg m^{-2} ($P = \text{NS}$), respectively. The degree of daytime sleepiness, based on Epworth sleepiness scale, was comparable in men and women. Mean awake and minimum arterial oxygen saturations (SaO_2) during sleep were also similar. However, men had more severe OSA as demonstrated by a significantly higher overall RDI (37.3 ± 4.3 events/h) than women (23.7 ± 6.7 events/h), $P < 0.05$. The regression lines between BMI as an independent variable and RDI as a dependent variable in men and women were not significantly different, indicating that BMI was not a major factor explaining the gender difference in RDI. Fig. 2 shows the effect of body position during sleep on the severity of OSA. Men had a 63% reduction in RDI by moving from a supine to a side position in contrast to women who had only 30% decrease. The difference in RDI as a result of changing position from side to supine was 43.7 ± 5.2 events/h in males compared to 10.7 ± 7.6 events/h in females ($P = 0.0015$, unpaired Mann–Whitney U-test for in-between group comparisons). There was no difference in sleep time in supine or side positions between men and women. Moreover, there was no significant difference in non-REM and REM sleep distribution between the two groups. However, due to unequal sample size and variation in sleep architecture among the subjects only the overall RDI is reported as a function of position.

Women had significantly smaller oropharyngeal junction and pharyngeal cross-sectional area than men (Table 1 and Fig. 3). Adjustment of upper airway dimensions by dividing the cross sectional area by height or BMI did not eliminate the gender difference.

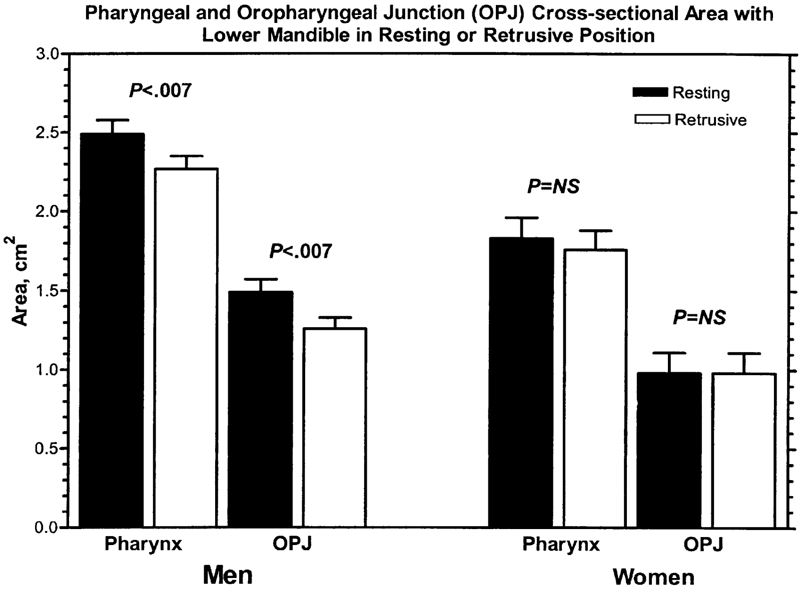

Fig. 3. Effect of retrusive mandibular movement on mean pharyngeal (Pharynx) and oropharyngeal junction (OPJ) cross-sectional areas in men and women. Retrusive mandibular movement resulted in a significant narrowing of upper airway in men but not women.

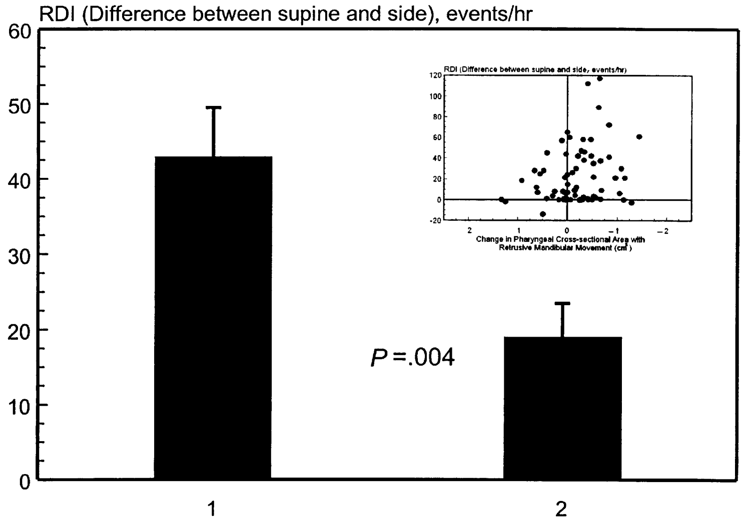

Fig. 4. Effect of change in pharyngeal caliber with retrusive movement of mandible on position-dependency of sleep apnea. Group 1 had a reduction in pharyngeal size with retrusive movement compared to Group 2 who had no change in pharyngeal size. The inset depicts the relationship between changes in the pharyngeal cross-sectional area with retrusive movement of the mandible and the severity of sleep apnea in supine position, the greater the reduction in pharyngeal area the higher the RDI in supine position.

The mean and range of retrusive mandibular movements using a George gauge were 2.5 mm (1–3 mm) for men ($n = 28$) and 2.6 mm (1–4 mm) for women ($n = 11$). There was no statistically significant difference in the retrusive range of movement of the mandible between men and women. However, the retrusive movement of the mandible resulted in significant decreases in pharyngeal (9%, $P < 0.007$) and oropharyngeal junction cross-sectional areas (15%, $P < 0.007$) in men but not in women (pharynx 3.8% and oropharynx 9%, respectively, $P =$ NS) (Fig. 3). To examine the effect of the degree of the mandibular movement on OSA, we divided the subjects into those with and those without a decrease in pharyngeal diameter during retrusive movement of the mandible and plotted the positional change in RDI for each group. Fig. 4 shows that the individuals with a decrease in cross-sectional area of the pharynx during retrusive movement of the mandible (Group 1) are more likely to have a higher RDI in supine position than those with more stable upper airways (Group 2). The change in airway size with retrusive movement of the mandible correlated with a higher RDI as a result of position change from side to supine. The inset of Fig. 4 shows the individual data points for the whole range of changes in the pharyngeal cross-sectional area in relationship to RDI change. This shows the clustering of individuals with side-position-dependent OSA and decreased airway caliber during retrusive mandibular movement. There was no correlation between airway caliber change and overall RDI (in all positions) in either gender. The study was not powered to examine the interaction between the influences of position and sleep stage on the frequency of respiratory events.

4. Discussion

The present study shows that: (1) OSA is more position-dependent in men than women; and (2) men have a greater reductions in upper airway dimensions with retrusive movement of the mandible than women and the worsening of sleep apnea in supine position appears, in part, be related to the degree of reduction in airway caliber with retrusive movement of the mandible.

Although there are lines of evidence to suggest the role of pharyngeal muscle tone, airway compliance and anatomic variables in control of upper airway patency, the critical factors responsible for pharyngeal patency during sleep remain to be elucidated. Two hypotheses have been proposed to explain the maintenance of pharyngeal airway during sleep. The neural hypothesis proposes the loss of wakefulness stimulus and diminished neural drive to pharyngeal dilator muscles during sleep, promoting the highly compliant pharynx to narrow or collapse [23]. The second hypothesis implicates the role of mechanical factors inherent in the pharynx as the mechanism of airway collapse. The proposed neural mechanism, however, does not explain the gender difference seen in OSA. There are some anatomic differences in the upper airway between the two genders. Direct measurement of the activation of pharyngeal dilator muscles in response to negative intraluminal pressure (analogous to increased airway resistance) has shown no significant differences between the genders, suggesting that the primary mechanism is due to mechanical rather than neural factors [8]. The magnetic resonance imaging of upper airway shows decreased proportion of parapharyngeal fat and soft tissue volume in the neck of obese females compared to obese males [24]. Measurement of pressure-flow relationship during sleep has shown that men generate almost twice as much pressure as women to achieve similar peak flow rates [25]. This is due to a progressive increase in upper airway resistance from wakefulness to sleep in both genders, but to a much greater extent in men than women [25]. Posture affects the upper airway caliber to a greater extent in men than women. A study by Martin et al. showed there was a 28% reduction in oropharyngeal junction area in supine position in awake men but only 19% change in women ($P < 0.02$) [6]. Likewise, Huang and colleagues demonstrated a 40% reduction in pharyngeal cross-sectional area from the sitting to the supine position in normal men compared to a 24% reduction in normal women [7]. Anatomic abnormalities in the form of regional neck obesity, increased soft tissue mass, enlarged tonsils and soft palate increase pharyngeal collapsibility [26–29]. In OSA patients, recumbency was associated with more than 50% decrease in pharyngeal area both at the level of the oropharynx and hypopharynx [30]. During sleep in supine position, the mandible tends to move inferiorly and posteriorly [12]. This vertical mandibular opening during sleep is larger in OSA patients than normal individuals. It has been suggested that the larger mandibular opening during OSA is due to augmented activity of the upper airway dilator muscles in response to increasing airway resistance during sleep [12]. The larger mandibular opening may impair the ability of the genioglossus and geniohyoid muscles to enlarge the upper airways because the distance between the mandible and the tongue/hyoid bone decreases [12]. Furthermore, since the lateral part of the soft palate connects to the base of the tongue through the palatoglossal arch, posterior displacement of tongue due to mandibular movement may relax the soft palate resulting in laxity of velopharyngeal segment and upper airway narrowing and possible collapse. In a similar study to ours, voluntary retrusive mandibular repositioning was associated with 40% reduction in the oropharyngeal cross sectional area [31]. Our data show that there are greater decrements in pharyngeal caliber in men than women with comparable retrusive movements of the mandible (2.5 mm in men versus 2.6 mm in women), suggesting that the geometry of the upper airway and its dynamic characteristics in relationship to mandibular movement are different between men and women.

These studies suggest that the gravitational changes in the upper airway as well as lung volume changes [32,33] in the supine position may play a significant role in increasing airway resistance and pharyngeal collapsibility during sleep. In the present study, the RDI was significantly higher in the supine position as opposed to the lateral recumbent position in men, which was not seen in women, suggesting a greater influence of gravity and position on upper airway patency in men. Conversely, the advancement of the mandible with an oral appliance resulted in a proportional decrease in the apnea-hypopnea index [34]. In this study, an 18 and 25% increase in the pharyngeal and velopharyngeal cross sectional areas was associated with a 71% decrease in apnea-hypopnea index.

The aforementioned studies suggest that narrowing of the upper airway during sleep is, in large part, related to differences in tissue linkage, anatomic factors and gravitational effects on soft tissue. Isono et al. reported improvement in oropharyngeal airway patency with mandibular advancement in both obese and non-obese subjects [35]. Mandibular advancement during sleep is more effective in reducing the apnea-hypopnea index in position-dependent OSA than position-independent OSA [36].

In conclusion, there is a gender difference in sleep-disordered breathing in adults, with males having a more severe and predominantly position-dependent OSA. This is, in part, due to a higher tendency for airway collapse with retrusive mandibular movement. Women, on the other hand, experience less severe OSA that tends to be less position-dependent. The expression of OSA appears, in part, to be related to differences in tissue linkage and inherent airway stability between men and women. Further studies are necessary to examine the effect of gender on anatomic changes in the upper airway during sleep and the efficacy of mandibular repositioning devices in women with sleep apnea.

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