8 Immunologic and Physiologic Effects of Dental Sleep Appliance Therapy

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Abbreviations

AASM	American Academy of Dental Sleep Medicine
AHI	Apnea-hypopnea index
BMI	Body mass index
CGRP	Calcitonin gene-related peptide
CKD	Chronic kidney disease
CPAP	Continuous positive airway pressure
CPH	Craniofacial Pain Handbook
CT	Computerized tomography scan
GERD	Gastroesophageal reflux disorder
GPT-9	Glossary of Prosthodontic Terms Ninth Edition
HTR	Hormone replacement therapy
IBS	Irritable bowel syndrome
ICSD-3	International Classification of Sleep Disorders Third Edition
LES	Lower esophageal sphincter
MA	Microarousals
MRI	Magnetic resonance imaging
OAT	Oral appliance therapy
ODI	Oxygen desaturation index
ODS	Obsessive daytime sleepiness
OFPG-4	Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management, Fourth Edition
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PAS	Posterior airway space
PGP 9.5	Protein gene product 9.5
PM	Portable monitors
PSG	Polysomnogram
RAAS	Renin angiotensin-aldosterone system
RDI	Respiratory distress index
REM	Rapid eye movement
RME	Rapid maxillary expansion
RMMA	Rhythmic masticatory muscle activity
RPS	Retropharyngeal space
SB	Sleep-related bruxism
SP	Substance P
TAD	Temporary anchorage device
TCR	Trigemino-cardiac reflex
TMD	Temporomandibular joint disorder
TST	Total sleep time
TTH	Tension-type headache
VDO	Vertical dimension of occlusion

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8.1 Introduction

Obstructive sleep apnea (OSA) is characterized by episodes of oropharyngeal obstruction due to repetitive collapse of the oropharyngeal tissues

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during sleep [1]. The oropharyngeal collapse is due to several factors. It is associated with sleep fragmentation, hypoxemia, hypercapnia, marked swings in intrathoracic pressure, increased sympathetic activity, and cardiovascular complications [2]. The prevalence of OSA in the adult population is estimated to be between 2 and 4% [3, 4], with the major factors being age [5, 6], sex [7], and weight [8]. The Wisconsin Sleep Cohort Study reported the prevalence of AHI greater than 5 per hour among 30–60-year-old men is 24% and women is 9% [4].

There are multiple forces that contribute to oropharyngeal collapse, including the elongation of the soft palate and uvula from the pulling forces that have been put on it from snoring; loss of vertical dimension resulting in a shortening of the lower 1/3rd of the face (can be due to bruxism resulting in attrition of teeth, clenching or extraction of teeth causing a loss in jaw support) [9]; increase in tongue size due to fat deposition in the tongue [10], which is due to weight gain [11]; and constriction of dental arches [12] due to extraction of first bicuspids when in braces and headgear and negative transmural pressure gradient and tissue weight.

8.2 Causes of OSA

Oropharyngeal patency depends on the balance between collapsing and dilating forces. The contraction of dilator muscles cause a stiffening of the oropharyngeal tissues resulting in dilation. However, an increase in oropharyngeal dilator muscle activity can still occur in patients with OSA during an obstructive event [13, 14]. In vitro studies show that dilator muscle activity and tension produced are higher due to OSA [15].

It has been shown that uvular stiffness is higher in subjects with OSA compared with non-OSA subjects who snore [16]. Recurrent OSA can lead to the development of an inflammatory process causing histologic alterations of oropharyngeal tissues, which can alter the integrity of the extracellular matrix and also interfere with the mechanical properties of soft tissues [1]. There are a few studies that have examined the inflammation of the oropharyngeal tissues in OSA [17] and the inflammation of the mucosa of the uvula [18]. The treatment with CPAP has become the standard of care for moderate to severe OSA. The primary aim of this chapter is to show the correlation and improvements on immunologic and physiologic effects of dental sleep appliance therapy based on the improvements seen with CPAP therapy.

Obstructive sleep apnea (OSA) is the most common forms of sleep apnea. There are various forms of sleep apnea, which are obstructive, central, and complex sleep apnea. OSA is a chronic clinical syndrome characterized by snoring, periodic apnea (episodes of oropharyngeal collapse during sleep), hypoxemia during sleep, and daytime hypersomnolence [19, 20]. OSA is prevalent among 4% of men and 2% of women [21]. The disorder is characterized by repetitive collapse (apnea) or partial collapse (hypopnea) of the pharyngeal airway during sleep [22]. OSA is classified as cessation of breath for ≥10 s. In 2007, there were some changes made by the task force in the respiratory scoring rules. Apnea in adults is scored when there is a drop in airflow by ≥90% from normal airflow for ≥10 s. A hypopnea in adults is when there is a drop in airflow by ≥30% for more than ≥10 s in association with either ≥3% arterial oxygen desaturation or an arousal. The numbers of both event types such as apnea and hypopneas are ultimately combined to compute an apnea-hypopnea index [23]. OSA is defined as apnea-hypopnea index (AHI) or respiratory distress index (RDI) greater than five events an hour and associated with symptoms such as excessive daytime sleepiness, impaired cognition, mood disorders, insomnia, hypertension, ischemic heart diseases, or history of stroke. The presence of respiratory efforts during these events suggested that they are predominantly obstructive [24].

There are multiple risk factors for patients who may be diagnosed with OSA. Some are genetic factors, while others are social factors. Roughly 84% of all apnea sufferers are diagnosed with OSA [25]. Patients with OSA have a small pharyngeal airway which is commonly due to being overweight in adults and enlarged tonsils in

children. While a subject is sleeping, the muscles are relaxed and therefore causing the pharyngeal airway to narrow and the upper airway to collapse for intervals [26].

8.3 Risk Factors

8.3.1 Obesity

Obesity is the most common risk factor of obstructive sleep apnea. Those who are overweight have a higher chance of developing symptoms for OSA. Obesity relates to OSA due to the excess fatty tissue, thickening of the walls, and decreased lung volume [27]. If a subject is overweight, the thickness of the lateral walls compromises the air to pass through which may cause the subject to choke during sleep or have fragmented sleep. The thickness of the lateral walls can be seen in a computerized tomography (CT) scan or magnetic resonance imaging (MRI) scan. With weight increase, excess fat starts to develop on muscular tissue which, in return, narrows the airway. Obesity also contributes indirectly to upper airway narrowing, especially in the hypotonic airway present during sleep, because lung volumes are markedly reduced by a combination of increased abdominal fat mass and the recumbent posture [28].

8.3.2 Narrow Airways

Narrow airways hinder the subject from breathing normally during sleep, which leads to increased hypopnea and apneas. The primary factor, which can predispose to a narrow airway and development of OSA, can be a result of restriction in the size of the bony compartment because of the deficient craniofacial skeleton. The maxillary and mandibular micrognathism of the jaw size results in a narrow airway [27]. A narrowed airway causes snoring, a common symptom of OSA. An airway can be narrowed by increase of soft tissue. Enlargement of soft tissue structures both within and surrounding the airway contributes significantly to pharyngeal airway narrowing in most cases of OSA [28]. A narrowed airway can also be caused if the subject is aging. An aging subject tends to have sagging muscles which may increase pharyngeal compliance and in turn cause their airway to be narrowed. Additionally, a narrow airway may be caused by hormonal factors such as the presence of testosterone or the absence of progesterone [27].

8.3.3 High Blood Pressure

Hypertension is another risk factor of OSA [29]. Many patients with OSA also have high blood pressure. Researchers have found that adults with severe apnea were more than twice as likely to have hypertension, while moderate OSA patients also had increased risk for high blood pressure [25]. OSA episodes produce surges in systolic and diastolic pressure that keep mean blood pressure levels elevated at night [30]. If OSA is able to be controlled, then blood pressure levels may also be lowered. Patients with pulmonary hypertension and OSA tend to have more profound nocturnal hypoxemia but may also have daytime hypoxemia as well [31].

8.3.4 Chronic Nasal Congestion

Nasal congestion causes the upper airway to narrow, which increases the risk of both snoring and OSA. Breathing through the nasal airway is important and idealistic for improved sleep. If the nasal airway is congested, then the subject is forced to breathe through their mouth [32]. Nasal congestion is a risk factor due to allergic rhinitis or an acute upper airway infection. Nasal congestion is commonly related to anatomical abnormalities such as septums, conchal hypertrophy, or nasal polyps [33]. Nasal breathing is better for the patient as the lungs will absorb more nitric oxides, due to the back pressure from the resistance air flowing out of the sinuses, compared to no resistance when breathing through the mouth [34].

8.3.5 Smoking

Smoking puts a subject at higher risk of being diagnosed with OSA and has greater changes in the upper airway. The airway becomes inflamed which makes it difficult to breath. Nicotine, an ingredient in cigarettes, is a stimulant. Smoking can refrain a subject from getting a restful sleep and may deter a subject from falling asleep as well. According to a 2011 study, people who currently smoke are 2.5 times more likely to also suffer from OSA, the most common type of sleep apnea caused by the collapse of muscles in the back of the throat during sleep. Smokers experience this repeated cessation of breathing more often because the smoke they inhale irritates the tissues in the nose and throat, causing swelling that further restricts airflow [35].

8.3.6 Diabetes

Diabetes and OSA are common disorders that often coexist. In one study of middle-aged men, the prevalence of sleep-disordered breathing (AHI > 20) was 36% in patients with diabetes compared with 15% in normoglycemic subjects [36]. Diabetes is a risk factor of OSA due to insulin resistance in subjects. There is a growing body of evidence from numerous human and animal studies that suggests an association between OSA and insulin resistance, glucose intolerance, and type 2 diabetes mellitus (DM2) [31]. Subjects who suffer from OSA have a higher chance of also suffering from insulin resistance. Most studies have demonstrated impaired glucose tolerance, higher fasting glucose, and insulin resistance in patients with OSA compared with patients without OSA irrespective of weight, presence of visceral fat, and age [31].

Whether a subject is male or female may also be a risk factor. In the general population, sleep-disordered breathing is estimated to occur in 9% of middle-aged women and 24% of middle-aged men. Only 2% of women and 4% of men also complain of daytime sleepiness and therefore may be at risk for OSA [36]. Generally, being a male is a risk factor for OSA itself [37]. Men are 2–3 more likely to have OSA. However, after menopause, women start to get OSA more than men due to their hormones. OSA will be more prevalent especially in women who are not getting hormone replacement therapy [19]. The male population tends to have an increased amount of fat around the upper airway as they age or it may also be due to obesity. In fact, the upper airway in men is frequently greater in length than women, which affects the airway collapsibility. Since the upper airway is longer in men, they are more susceptible to having their airway collapse. Additionally, hormones play a role in being associated with OSA as well. For instance, the presence of testosterone (higher in males) is a factor leading to the collapse of the upper airway [27].

8.3.7 Genetics

Genetics are a prominent risk factor for OSA. Upper airway anatomy, neuromuscular activity, and ventilatory control stability are determined based on genetics. OSA is more prevalent in specific ethnic groups due to their genetics. Craniofacial abnormalities are most common in Asians who have OSA, and an enlarged soft palate is more common in African Americans [27]. As mentioned previously, obesity is a risk factor of OSA. Interestingly, studies have shown that there are specific genes which increase the probability of obesity and OSA [19].

8.3.8 Asthma

Asthma has accumulating evidence suggesting a bidirectional relationship between asthma and OSA, where each disorder has a harmful influence on the other [38]. Alkhalil showed in cross-sectional studies that the prevalence of sleepiness, snoring, and OSA was significantly higher in participants with asthma [39]. Similarly, in clinical studies, OSA symptoms were frequently reported by patients with asthma than by the general population [40]. Furthermore, in a polysomnographic-based study, asthma was reported difficult to

control in almost 90% of OSA patients [41, 42]. Nighttime oropharyngeal narrowing in asthma patients is often associated with episodes of nocturnal and early morning awakening, difficulty in maintaining sleep, and daytime sleepiness [43]. A polysomnographic study showed no statistical differences between the two groups of OSA and non-OSA, except for changes in the percent of time spent in stages I and IV. Asthmatic patients with OSA had a higher percent of time in stage I and a lower percent of time spent in stage IV compared to patients without asthma. Therefore, sleep is superficial and poorer in quality for asthmatics with OSA. Whether CPAP can treat asthmatic nighttime symptoms and improve the pulmonary function test is questionable. A study conducted by Ciftci TU, on patients with asthma, concluded that after 2 months of continuous usage of nCPAP, there was no significant difference in the pulmonary function test. However, there was a significant improvement in the asthma nighttime symptom scores, which are quite evident in asthmatic patients with OSA [43].

8.4 Signs and Symptoms of OSA

8.4.1 Excessive Daytime Sleepiness

In patients with OSA, frequent arousals during the night lead to sleep fragmentation, depletion of slow-wave sleep (N3), and rapid eye movement (REM), which leads to excessive daytime sleepiness [44]. Excessive daytime sleepiness occurs if a subject is feeling tired or groggy in the morning or if the subject requires multiple naps throughout the day and is unable to perform regular day-to-day tasks. This may occur if a patient is unable to stay asleep during the night and wakes up multiple times. It may also occur if the patient is not getting enough sleep or restful sleep. Excessive daytime sleepiness can also occur if the subject is using drugs and alcohol, lacks physical activity, and/or is leading an unhealthy lifestyle. If the subject is unable to perform regular duties during the day due to excessive daytime sleepiness, this can lead to an impact on their lifestyle and work performance. OSA can be an underlying cause of excessive daytime sleepiness. In severe cases, patients fall asleep during stimulating activities, such as driving, or during conversation or meals. More frequently, they fall asleep during passive activities, such as watching TV or reading [36]. The Epworth Sleepiness Scale is a good tool to assess daytime sleepiness. Subjects are asked to fill out a questionnaire with eight questions and rate their activities. The higher the score, the higher the subjects sleep propensity in daily life [33].

8.4.2 Loud Snoring

Snoring is a symptom of OSA that often occurs with men who are overweight, but that isn't always the case. Up to 95% of patients with OSA snore. Normally, patients are unaware of their snoring and only realize they snore when their bed partner or someone else tells them. Snoring occurs when the flow of air through the mouth and nose is physically obstructed. Furthermore, airflow can be obstructed due to nasal airways, poor muscle tone, throat tissue, and/or a long soft palate [27, 45]. Loud snoring is a common complaint and symptom by patients suffering from sleep apnea [46].

8.4.3 Nighttime Sweating

Nocturnal sweating has been associated with cardiovascular disease, hypertension, and sleepiness, which are all symptoms of OSA. Based on a study conducted in 2013, inclusive of both OSA patients and the general population, it was noted that those diagnosed with OSA were much more likely to excessively sweat at night. Nocturnal sweating occurred more than three times per week in patients with OSA. Statistically, 30.6% of males and 33.3% of females with OSA suffered from nighttime sweating versus 9.3% of males and 12.4% of females in the general population. When the OSA patients were treated with PAP therapy, nocturnal sweating decreased from 33.3 to 11.5%, which was the general population [47]. Thermoregulation regulates the body

temperature by heat conduction. An increase in heat conduction will maintain thermoregulation, thus leading to a decrease in the core body temperature and further leading to a deeper level of sleep; an increase in the core body temperature can lead to increased nocturnal awakenings and lighter stages of sleep. Thermoregulation has a different pattern of mechanism between various sleep stages. For instance, thermoregulation is less prevalent during REM sleep vs. non-REM sleep. This is why the nighttime sweating is decreased during REM sleep as compared to non-REM sleep. There has been enlightening literature on the sleep-related perspiration as a consequence of OSA. In a study conducted in 2009, patients with untreated, moderate to severe OSA were evaluated for parameters such as temperature and electrodermal activity (EDA) to evaluate the perspiration in patients. All of the patients were medically managed with continuous positive airway pressure (CPAP) for a period of 3 months, and surprisingly, the electrodermal activity levels, along with systolic and diastolic blood pressure, decreased significantly after CPAP therapy. Not only this, there was a significant increase in REM sleep patterns in these patients. There is a future scope of research the hypothesis that high blood pressure found in OSA patients has a correlation with nocturnal sweating [47].

8.4.4 Decreased Libido

Sleep apnea does not only interfere with sleep, but after continuous research, it is becoming prevalent that sleep apnea is also leading to decreased libido in females and erectile dysfunction with males. There is a speculation by scientists that a decreased sex drive may be due to a decrease in testosterone. Testosterone increases when a subject gets enough sleep and the opposite happens if sleep is lacking. If an OSA patient has multiple arousals at night, they are unable to have a deep sleep. Based on a study conducted in 2011 with females who have untreated OSA, it was indicated that their libido was negatively affected when compared to the general population [48]. Budweiser mentions in a study with 401 male patients that sleep apnea independently decreases libido and causes erectile dysfunction [49]. In a randomized trial done on 40 patients with severe apnea, patients were made to wear a CPAP for a period of 1 month. Pleasantly, after the medical management of severe OSA over the period of a month, the International Index of Erectile Function improved from 15.71 ± 5.12 to 19.06 ± 3.94, which lead to a remarkable improvement in the sexual performance of the patients. According to the study done by Perimenis et al., the medical management of OSA with erectile dysfunction, one group was made to try CPAP solely, and another group tried CPAP along with pharmacological management of erectile dysfunction using sildenafil. The results were better with the latter group who tried CPAP and sildenafil vs. CPAP alone [50].

8.5 OSA Correlation to Medical Conditions

8.5.1 Diabetes

OSA is highly associated with insulin resistance. Evidence suggests that OSA is involved in the development of glucose metabolism alterations [51]. Several studies have shown that subjects with OSA have increased glucose levels and increased insulin resistance, which makes them genetically predisposed to developing type 2 diabetes [52]. Evidence suggests that OSA causes sleep loss and hypoxia, which elevates sympathetic activity. The inflammation caused by OSA, in combination with elevated sympathetic activity and weight gain, leads to insulin resistance and diabetes [53].

Bialasiewicz and collegues found in a study that continuous monitoring of interstitial glucose during a polysomnography (PSG) showed an increase in interstitial glucose concentrations and there was no effect during NREM sleep [54], whereas Grimaldi's findings support OSA in rapid eye movement (REM) sleep has a strong and clinically significant association with glucose levels in subjects with type 2 diabetes. Since

REM sleep is dominant during the second part of the night, REM-related OSA often remains untreated with 4 h of CPAP use. He recommends that in order to achieve significant improvement in glucose level in patients with type 2 diabetes, CPAP should be used over 6 h per night [55]. The level of hemoglobin A1C is correlated with the severity of hypoxemia in OSA and decreased with the use of CPAP for 3–5 months [56].

8.5.2 Blood Pressure

There is a very strong association demonstrated to date between OSA and hypertension, but a direct etiologic link between the two disorders has not been established definitively [57]. In his animal study, Brooks demonstrated that obsessive daytime sleepiness (ODS) produced sustained daytime hypertension and recurrent arousals from only sleep and cannot account for daytime hypertension observed in OSA. Early studies have shown conflicting results in the association between OSA and hypertension [8, 13].

OSA episodes cause surges in systolic and diastolic pressure, which maintains the mean blood pressure levels elevated at night. The blood pressure remains elevated during the daytime, when breathing is normal in many patients. Contributors to daytime hypertension include overactivity of the sympathetic nervous system, alterations in vascular function and structure caused by inflammation, and oxidative stress [30]. In the Wisconsin Sleep Cohort Study by Peppard, it showed the correlation between incidences of hypertension with severity of OSA in middle-aged patients. In contrast, the Sleep Heart Health Study, by O'Connor GT and his group, failed to show an association between OSA and the risk of incidence in hypertension [58].

The presence of OSA was associated with increased risk of incident for hypertension; however treatment with CPAP therapy was associated with lowering the risk of hypertension. Observational findings suggest that OSA appears to be a modifiable risk factor for new-onset hypertension [59]. In a study, Litvin and his group showed that effective CPAP use for 3 weeks resulted in a significant decrease in blood pressure and improvement in arterial stiffness in a group of hypertensive patients with OSA [60]. CPAP treatment in patients with difficult-to-control hypertension and OSA showed a significant reduction in diurnal and nocturnal systolic blood pressure, with no significant variations in diastolic blood pressure. This led to more patients who recovered to their normal nocturnal dipper pressure pattern [61].

8.5.3 Gastroesophageal Reflux Disorder

There is no causal link between gastroesophageal reflux disorder (GERD) and OSA, but they share common risk factors. Morse suggests that reflux medications may have a role in helping a selected population sleep better [62]. This effect likely is caused by controlling arousals secondary to gastroesophageal reflux [63].

Several investigators have concluded that there is a greater prevalence of GERD in patients with OSA based on reported symptoms of GERD and based on measurements of esophageal pH [64, 65]. Several studies have shown that the CPAP use for the treatment of OSA has reduced the occurrence of GERD [66–69]. The correlation between OSA and GERD remains unclear and controversial [62].

Several factors may increase GERD in patients with OSA, such as alterations in the function of the lower esophageal sphincter (LES), transdiaphragmatic pressure gradient increase, and decrease in the defenses against gastroesophageal reflux, due to reduction of esophageal clearance. The phrenoesophageal ligament may pull on the LES, creating an opening during an apnea event caused by an increase in diaphragmatic activity [70].

The transdiaphragmatic pressure may also increase due to abdominal pressure caused by obesity or when turning in bed during an OSA arousal [68]. In a study where acid reflux was simulated, the group with OSA had an impaired swallow reflex almost twice as long, when compared to the normal group [71]. Impaired clearance of gastric juices increases the contact time, causing an

irritation of the mucosa resulting in inflammation, further aggravating the obstruction and worsening the OSA [72–74]. Furthermore, the gastric acid also causes destruction of the dentition, wearing away enamel and dentin, known as attrition.

Science has yet been determined the amount of contribution that repetitive acid reflux has on OSA. Several studies using a PSG and a 24-h monitoring of esophageal pH were unable to show a bidirectional causal relationship between gastroesophageal reflux and OSA [66, 75, 76]. Several studies have shown that treatment with CPAP reduced the frequency of acid reflux events and nocturnal awakenings due to heartburn [63, 66–68]. When proton-pump inhibitor (PPI) therapy was initiated, AHI was reduced by 31%, and treatment with a histamine type 2 receptor antagonist (H_2RA) decreased arousals, but did not affect OSA [63, 66]. CPAP and OAT treat OSA by opening the oropharyngeal airway, stopping paradoxical breathing, and allowing the LES to function normally, thereby controlling the acid reflux while sleeping.

8.5.4 Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is characterized by recurring abdominal pain in conjunction with irregular bowel movements. The prevalence of IBS is about 8–20% among adults, and it is one of the most common diagnoses used by gastroenterologist [9]. The study conducted by Kumar D supports the hypothesis that IBS may be a disorder of inappropriate brain-gastrointestinal interaction which can lead to the motor abnormality of the small bowel only during the waking state. The cause and effect relationship between sleep disturbance and IBS is not definitive [77]. The studies conducted in the past confirm the finding that IBS patients are considered to have poor sleep functioning. The study done by Rotem AY with the aid of a sleep questionnaire, actigraphy, and the polysomnography findings supports the hypothesis that IBS patients have more difficulty in falling asleep and have lots of movements while asleep. The polysomnography findings show a significant shorter total sleep time (TST), indicating compromised sleep efficiency. Patients were found to have more than 70% decreased proportion of slow-wave sleep stage, and as a result, stage II sleep was significantly longer. The arousal index was found to be twice as greater in patients with IBS versus the control group. Similarly, subjects with IBS witnessed more events of shifting to lighter sleep when compared to the control group. Please refer to Fig. 8.1. Findings also

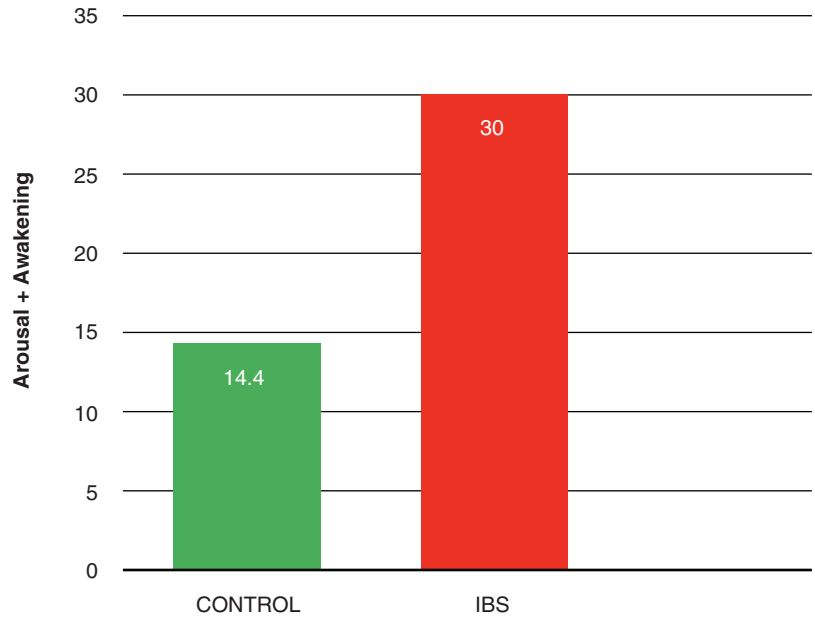

Fig. 8.1 Sleep Fragmentation in IBS Patients. Sleep fragmentation is doubled in subjects with IBS, as arousals and awakening was measured per hour [9]. Figure created by Mr. Haig Demerjian

suggested the increased proportion of REM sleep and longer wake period after sleep onset. A sleep questionnaire leads to the conclusion of greater excessive daytime sleepiness and higher Epworth Sleepiness Scale, thus leading to poor quality of life. All of these can lead to exacerbation of gastrointestinal abnormalities such as IBS [9]. Whether CPAP can aid in the treatment of IBS is a matter of debate, perhaps due to the limited number of studies. There is lack of evidence indicating that patients with IBS have poor quality of life; they were reluctant in trying CPAP therapy for the control of IBS symptoms. However, if patients were educated on how sleep disorders can be a risk factor for IBS and vice versa, then they may be willing to consider CPAP as an effective treatment to relieve symptoms and feel better. There is a lack of evidence supporting a direct cause and effect relationship between sleep disorders and IBS. Hence, we cannot conclude that CPAP can effectively treat patients with IBS. A future scope of study is required [78].

8.5.5 Cardiovascular System

Obstructive sleep apnea affects the cardiovascular system in multiple ways. OSA causes central hemodynamic effects. Episodes of OSA produce arterial oxygen desaturation, elevated carbon dioxide levels or hypercapnia, intrathoracic pressure oscillations, and possibly disrupted sleep [28]. Several studies have shown an independent association between OSA and increased cardiovascular morbidity [4, 59, 79].

In cases where the OSA is severe (AHI over 30), there is a higher predictability of mortality [80]. OSA treatment with CPAP improves quality of life, but there is no published study that has adequately showed a mortality benefit [81]. In echocardiographic studies, systolic and diastolic dysfunction occurred when AHI was increased [82, 83]. Possible mechanisms include the effects of hypoxia and the repetitive intrathoracic pressure changes that accompany obstructive apneas [84]. Studies have shown that negative intrathoracic pressure causes an increase in left ventricular afterload and impairs left ventricular relaxation [85, 86]. Cardiac contractility is also reduced, and left ventricular volumes rise, both at end-systole and end-diastole [87]. Hypoxia and arousals may induce tachycardia and peripheral vasoconstriction, further increasing ventricular afterload, caused by sympathetic nervous system activation [88].

CPAP use reduces the need for intubation during acute exacerbations in heart failure patients while providing symptomatic relief [89, 90]. In trials, it has been demonstrated that CPAP therapy has an improvement in exercise capacity, quality of life, and ventricular afterload [90–92]. Left ventricular ejection fraction had improved when on CPAP therapy but worsened when the CPAP was removed [93]. Furthermore, CPAP therapy has improved pulmonary hypertension and arrhythmias [94, 95].

8.5.6 Chronic Renal Failure

Renal failure also known as kidney failure is an important issue with patients who suffer from OSA. Patients who already have chronic kidney disease (CKD) are likely to also have OSA. OSA is also associated with proteinuria or protein in urine and hypertension. Proteinuria is a symptom of renal disease. If OSA is corrected with therapy, then renal outcomes may also be cured or improved [37]. As reported by one study from 2015, OSA can lead to decrease of kidney functionality. Furthermore, if moderate to severe OSA is treated, then the treatment also improves kidney filtration by minimizing glomerular hyperfiltration as sustained OSA is also associated with glomerular hyperfiltration [96]. The prevalence of OSA in patients with end-stage renal disease ranges from 40 to 60% [97]. The complete pathophysiology and background of disease mechanism are beyond the scope of this article. However, a brief introduction may be helpful. OSA mediates the renal damage via several mechanisms. In fact, the relationship between OSA and chronic renal failure is a complex system as illustrated in Fig. 8.2. The OSA patients are associated with hypoxia and sleep fragmentation which can contribute to the origin

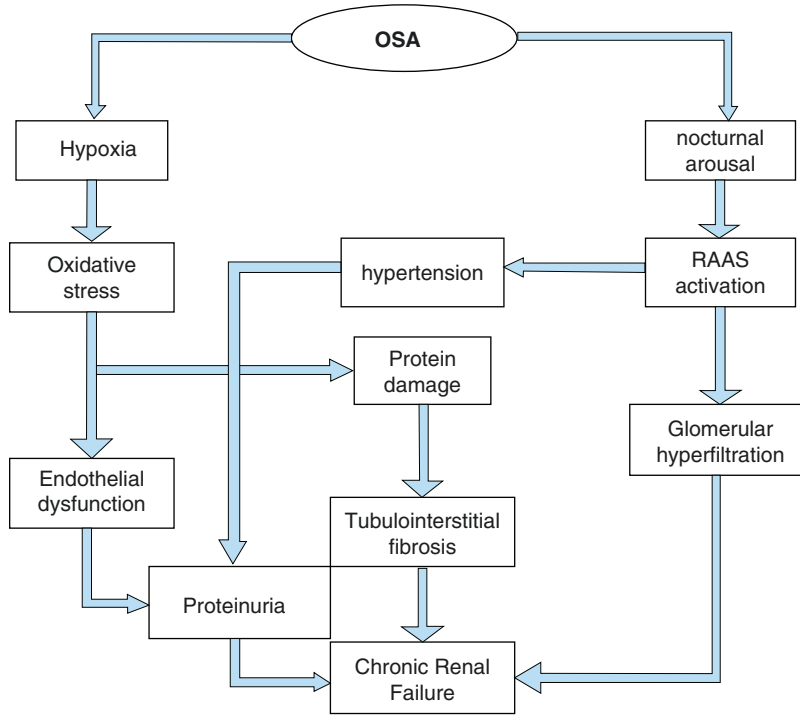

Fig. 8.2 Relation of OSA and chronic renal failure. Provided by "Dr. Pooja Goel". Pathophysiologic links between OSA and CKD. The figure is depicting the link between OSA and CKD. The flow is indicating how the elevated blood pressure during repetitive cessation of breathing during OSA can contribute to sympathetic nerve discharge to the renal vascular bed. Once the renal vascular bed is affected, renal failure occurs through different mechanisms

of chronic renal disease by activating renin-angiotensin-aldosterone system (RAAS) and elevation in the blood pressure as a result of activated sympathetic nervous system and via glomerular hyperfiltration. The following predictors of chronic renal failure can be improved with CPAP therapy: endothelial function, levels of circulating apoptotic endothelial cells, attenuates free radical production from neutrophils, inflammatory mediators, vasodilator levels, and mediates a decline in vasoconstrictor levels in patients with sleep apnea. A further study is required to support the hypothesis that chronic renal failure can be reversed back with CPAP therapy [37].

8.5.7 Stroke

Stroke is the fifth leading cause of death in the USA, with one person dying every 4 min as a result. Strokes occur due to problems with the blood supply to the brain; either the blood supply is blocked or a blood vessel within the brain ruptures, causing brain tissue to die. Stroke is a condition of acute injury to central nervous system tissue arising either from ischemia or hemorrhage [31]. The three main types of stroke are ischemic, hemorrhagic, or transient ischemic attacks (also known as mini-strokes). The narrowing or blocking of arteries to the brain causes ischemic strokes. Hemorrhagic strokes are caused by blood vessels in and around the brain bursting or leaking [98]. OSA has an independent correlation with cardiovascular disease, with stroke being one of them [37]. Since snoring is a symptom OSA, both have been known to increase incidence of stroke. Additionally, as the severity of sleep apnea increases, so does the risk of developing a stroke incident [31]. Whether or not CPAP can definitively decrease the chance of stroke is still a matter of debate. The current literature suggests that the medical management of OSA in a timely manner with CPAP can alter the severity of stroke by not leading to brain damage. In a recent editorial, there is a widespread belief that medical management of moderate to severe OSA associated with cardiovascular mortality by the use of CPAP can lead to a better prognosis but lacks the strong supportive evidence. However, CPAP treatment will prevent subjects from

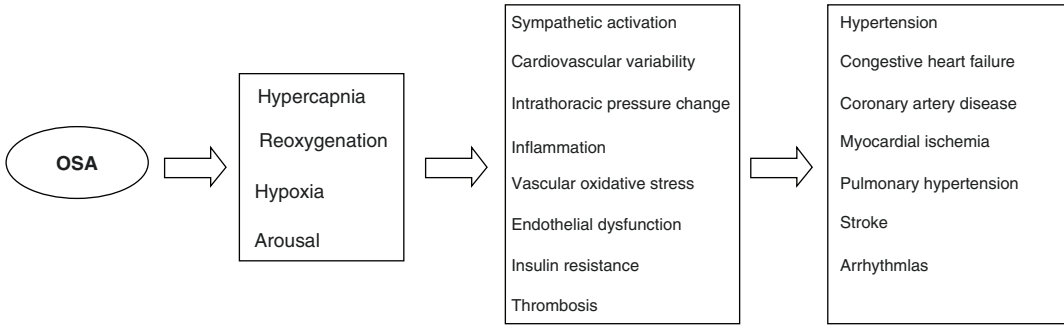

Fig. 8.3 OSA and cardiovascular consequences. Adapted from Vrints H et al.

getting hypoxia and cerebral flow fluctuation and thus in turn can prevent stroke occurrence [99]. According to a randomized trial, some enlightening considerations surfaced that there was correlation between CPAP therapy and a substantial reduction in cardiovascular morbidity. Thus, we can conclude that CPAP adherence in patients with OSA can reduce the severity of cardiovascular morbidity and cerebrovascular accidents but has not been found to be effective in recovering the patients from pre-existing stroke conditions [100] (Fig. 8.3).

8.5.8 Metabolic Syndrome

Metabolic syndrome, also known as syndrome X or the insulin resistance syndrome, is a condition where multiple factors lead to an increase for the risk of heart disease such as stroke and/or diabetes [36]. There are five conditions, which indicate that a subject may be diagnosed with the metabolic syndrome. If a subject has at least three out of the five conditions, then he or she may be diagnosed for the syndrome. The conditions are abdominal obesity, triglycerides, high-density lipoprotein cholesterol, blood pressure, and fasting glucose [31]. The interaction of the metabolic syndrome and OSA is known as syndrome Z [26]. In a study conducted in 2004, patients were examined to see the correlation between metabolic syndrome and OSA. Sixty-one male subjects were studied, and the findings were that people with OSA had the characteristics of the metabolic syndrome. The similar characteristics found among the subjects with OSA were that they were obese, had higher blood pressure, were resistant to insulin, had a lower HDL cholesterol level, and, finally, had an increased chance of diagnosis of the metabolic syndrome. Subjects, who have OSA, were 9.1 times more likely to also be detected with the metabolic syndrome [101]. Similarly, in another study it was concluded that patients with metabolic syndrome have a high chance of also having OSA and therefore should be tested with a PSG [102]. There is an independent association between sleep apnea and insulin resistance [103]. Metabolic syndrome may be treated with CPAP therapy as concluded in a study conducted in 2011. Subjects with metabolic syndrome were tested with CPAP therapy for 2 months. Before and after tests were conducted for several components, which are highly predictive of metabolic syndrome such as blood pressure, blood glucose (while fasting), insulin resistance, blood lipid profile, and visceral fat. It was concluded that patients with OSA, who were treated for 3 months with CPAP, had lower blood pressure and metabolic factors were also normalized [104]. As OSA leads to lack of sleep, treatment with CPAP will help patients to recover from sleep loss and thus may result in bringing the metabolic parameters to the normal levels, including glucose levels, blood pressure, blood lipid profile, and visceral fat [26].

Leptin, called a satiety hormone, is released by fat cells. It provides information about status of energy to the hypothalamus [105, 106]. Lepton level becomes elevated at night, partly as a

response to food ingestion during the day and to sleeping [107, 108], but decrease during the day when energy and calories are dimensioning [109]. When sleeping during the daytime, leptin levels stay elevated in subjects receiving continuous nutrition, which indicates leptin regulation is affected by sleep [110]. Leptin crosses the blood-brain barrier via saturation transport [111]. Leptin resistance is a common finding among subjects who are obese and have metabolic syndrome [112]. Based on many studies, leptin levels increase in subjects with OSA, and effective CPAP therapy decreases leptin levels in the long run [113].

Ghrelin, known as the hunger hormone, is necessary for body functions having to do with energy and appetite. In a study conducted in 2003, OSA patients were tested for ghrelin levels, both before and while using the CPAP machine. It was noted that OSA patients have higher levels of ghrelin as a baseline after fasting. After going through with CPAP therapy for 2 days, the levels of ghrelin had reduced significantly and remained only slightly higher in OSA subjects [114]. Another study conducted in 2010 on 55 OSA patients concluded that there is a positive relationship between the apnea-hypopnea index (AHI), Epworth Sleepiness Scale, and ghrelin levels [115].

8.5.9 Headaches

Previously there were not enough studies to establish a clear connection between OSA and headaches, perhaps due to the lack of evidence [116]. Recently, however, there are numerous studies which have mixed conclusions about OSA and headaches being directly related. There are two major findings for sleep-related headaches distinguished by the International Classification of Headache Disorders, one is "sleep apnea headache" and the other is "hypnic headache." Another type of primary headache which is known to be perpetuated with sleep-related headaches is tension-type headache (TTH) [117]. The most commonly described sleep apnea headaches are the recurrent morning headaches found to be three times more prevalent upon awakening in heavy snorers and OSA patients [118]. Although repetitive episodes of sleep apnea result in hypoxemic events, sleep fragmentation and nocturnal awakenings may be potential causes of recurrent morning headaches; however hypoxia is not an independent risk factor [51]. Additional studies support the established relationship between sleep apnea and other neurological and neurodegenerative disorders such as stroke, epilepsy, and headaches. Furthermore, OSA is known to exacerbate Alzheimer's disease and may be a sole cause of Parkinson's disease [119]. Sleep apnea, due to sleep loss and poor quality of sleep can lead to stimulation of nociceptive receptor system through different mechanisms and lead to an increase in various inflammatory markers such as proinflammatory cytokines, IL-6, and PGE_2 and exacerbates chronic pain conditions such as fibromyalgia, myofascial pain, temporomandibular joint disorder (TMD), and headaches [27]. There is evidence of dysfunction of serum serotonin levels in patients with OSA. In a study conducted in 2015, 4759 patients who were diagnosed with OSA were tested for TTH. TTH were noticed in 10.2% of patients with OSA and 7.7% of patients without OSA. The study concludes that patients who have OSA also have higher chances of getting tension-type headaches [117]. There is no definitive study on confirming the cause and effect relation between cluster headache and sleep apnea, but sleep apnea has been suggested to be a stimulus for cluster headache [120]. The oxygen desaturations caused by sleep apnea can lead to inappropriate functioning of carotid body activity perpetuated because of the dysfunction of the hypothalamus vasomotor system; and if it can lead to cluster headaches, it is not definitive. We need further research to see the cause and effect relationship [121]. CPAP treatment and other treatment modalities such as a dental oral appliance to treat sleep apnea have led to resolution and improvement in headaches from time to time. Treating OSA might not only improve headaches but also leads to decreased comorbidity [122].

8.5.10 Effects of Hormones

Hormone levels have always been a probable culprit in the propensity of OSA. It has been an intriguing matter of discussion that what leads to more prevalence of OSA in women after menopause. How do levels of progesterone, estrogen, testosterone, and hormones like calcitonin gene-related peptide (CGRP) affect the physiology of airway? As discussed previously, the collapse of the upper airway is a key issue in patients with OSA. A recent study concluded that a progressive lesion in the nervous system can be caused by the mechanical trauma due to snoring, leading to a collapse of the upper airway. This trauma is caused by the constant and repetitive low-frequency vibration of tissues from snoring. As a result of the trauma, there will be a sprouting effect leading to an increase in the number of varicose nerves and number of afferent nerve fibers. Eventually because of constant trauma, the sprouting effects fail to compensate and lead to the development of a degenerative neurogenic lesion. Such nerves contain specific hormones known as protein gene product 9.5 (PGP 9.5) and possibly substance P (SP) and CGRP. Whether the upper airway is unobstructed is dependent on both anatomical and neuromuscular factors, such as the negative intrapharyngeal pressure created during inspiration. Both afferent and efferent nerves mediate the reflex mechanism by stimulation of the mechanoreceptors located in the mucosa and submucosa of the pharynx, which causes the dilator muscles to react through the hypoglossal motor neurons. Oxygen desaturation index (ODI) is the number of time when the oxygen level in the blood drop below baseline measured in an average hour of sleep. Patients with severe OSA and significant increased ODI seemed to have a lower number of varicose nerves. Because of the degenerated nerves and significant depletion in the CGRP-immunoreactive small unmyelinated nerve fibers (C fibers), there are depleted levels of neuropeptides such as SP and CGRP, and the progressive degenerative neurogenic lesion can lead to injury of efferent nerve fibers and will lead to collapse of airway [123]. There is no linear relationship between the hormone levels and their repercussions on the central and neural respiratory mechanism, but the current literature is suggestive of the fact that increased level of progesterone/estrogen and lower levels of testosterone play a protective role against the development of OSA in women and men. The supporting fact for the suggestion mentioned can be that postmenopausal women without hormone replacement therapy (HRT) tend to have fourfold risk of development of OSA, as compared to the ones with HRT [124]. OSA per se is not directly related to the low levels of testosterone, but inadequate or exorbitant amounts of testosterone can alter sleep. The supporting fact is that people who are deficient in testosterone levels of hormones (hypogonadal) with poor sleep quality get benefited with HRT; however excessive doses of testosterone replacement therapy can lead to abnormal sleep quality and architecture as well [125].

8.5.11 Sleep Homeostasis

Sleep has many benefits. Sleep is a necessity for energy conservation, restoration, brain temperature regulation, modulation of neurochemistry, hormonal regulation, memory consolidation, and other neurocognitive functions. Sleep is not a well-defined entity, which is controlled independently or has a definite purpose. Sleep represents the process of meta-regulation which internal/external factors following the history and current hemostatic needs. Although sleep is a common practice and is a major component in the maintenance of the body functionality, it is intricate to comprehend easily and simply the effect of sleep deprivation as it's a multifactorial entity. Whether the regain of sleep loss will lead to an efficient functioning of specific physiological variables in the same way is a matter of debate. Homeostatic regulation is a crucial function of sleep physiology. An increase in the number of hours awake is equivalent to an increase in the homeostatic drive. This process will increase the metabolic demands and will lead to an increased intracellular adenosine. Adenosine inhibits wakefulness maintaining

neurons and promotes sleep. An increased level of adenosine will bring the homeostatic drive down and patient will. Hence, the main concept remains that the longer one stays awake, the deeper/longer they will require to maintain the integrity of the tissues and regulation of brain metabolism and synaptic plasticity. A common enlightening thought is that prolonged wakefulness can result into detrimental effects such as molecular, cellular, network, physiological, psychological, and behavioral levels [126]. During a 24-hour day, there is a bidirectional flow between catabolism and anabolism; one end is driven by the wakefulness which enhances the more intracellular breakdown of tissues and cells and thus is depicted as catabolism, while the other end, which offsets the catabolism, is known as anabolism and is represented by sleep. The sleep keeps the balance between catabolism and anabolism by decreasing the secretion of cortisol, catecholamines, releasing more growth hormones which in turn will lead to more production of protein and will metabolize the free fatty acids to provide energy and will eventually lead to the more synthesis of bone and increased number of red blood cells production. In a nutshell, this balance between catabolism and anabolism helps to get better sleep and relieve patients of sleep debt. In the latest practice, modern hypnotic drugs prevent the sleepiness and thus help in attaining better sleep and relieve the patient's anxiety and help in the restoration and normalization of the tissues [127].

8.5.12 Trigeminal Cardiac Reflex

The trigeminal nerve (V) is the fifth cranial nerve. It exits to pons and enters Meckel's cave, forming the gasserian ganglion. The gasserian ganglion divides into the three major divisions that contain sensory impulses eyes, face, and cranium. The ophthalmic division is purely sensory, which supplies sensation to the eyes and forehead. The maxillary branch is purely sensory also. It supplies the midface, including the nose, nasopharynx, upper lip, maxilla, maxillary teeth, palate, soft palate, and tonsils. The mandibular division consists of a large sensory root and a minor motor root. The sensory root supplies the lower face, including the tongue, mandible, mandibular teeth, lower lip, lateral surface of the ears, temples, and TMJ. The motor root supplies the muscles of mastication, which consists of masseters, temporalis, lateral pterygoids, medial pterygoids, anterior digastric, tensor-veli tympani, and tensor-veli palatini.

As sensory impulses are transmitted via the trigeminal nerve, they enter the trigeminal spinal nucleus, within the pons. The trigeminal spinal nucleus has numerous collateral and longitudinal connections to other cranial nerve nuclei and to the reticular formation. The rostral trigeminal sensory nucleus has neurons that convey information to the thalamus [128].

The trigemino-cardiac reflex (TCR) is a powerful autonomic reflex that helps the body to autoregulate by conserving oxygen and reducing the heart rate under challenging situations [129, 130]. Any stimulation of the trigeminal nerve anywhere along the nerve will result in sympathetic withdrawal and parasympathetic over activation via the vagus nerve, thus resulting in apnea, bradycardia, bradypnea, and hypotension. TCR has various manifestations, which include central TCR, peripheral TCR, the diving reflex, and naso-cardiac reflex [131–133]. TCR is linked to sleep-related bruxism (SB) as a probable cause [134] and has been hypothesized to play a role in sudden infant death syndrome (SIDS) [135]. It is reported that sudden microarousals (MA) occurring in the brain due to airway obstruction during sleep cause tachycardia, which stimulates rhythmic masticatory muscle activity (RMMA) and SB, that activate the TCR resulting in bradycardia [128, 134, 136]. When breathing is normal during waking or sleep, the heart rate remains stable. When breathing becomes labored due to airway obstruction such as a hypopnea or apnea, the oxygen level drops in the blood causing the body to put extra effort in obtaining oxygen [128]. This will lead to MA of the brain. MA episodes are characterized by an increase in brain activity, heart rate, and muscle tone during sleep [137]. Sleeping in the supine position causes oropharyngeal obstruction, due to the gravita-

tional pull on the tongue, soft palate, and mandible. Therefore, the frequency of SB increases an effort to get more oxygen [138].

Before SB occurs, activation of the TCR causes a sequence of physiological changes starting with an increase in respiratory rate, followed by an increase in EEG activity and then an increase in heart rate [139]. Brunelli demonstrated that when using a spring device that keeps the teeth apart and performing partial jaw movements, it caused prolonged reduction of blood pressure and heart rate [140]. Chase identified the specific neurons in the medullary reticular formation that are responsible for the inhibition of the postsynaptic trigeminal motor neurons during active REM sleep, which caused masseter muscle atonia [141]. In a study using transcranial magnetic stimulation, Gastaldo found data suggesting that the trigeminal motor system has a group of interneurons that modulate. The alteration in excitability of these interneurons can increase the firing of the trigeminal motor neurons during sleep arousals, causing excessive masseter muscle contractions, seen in SB [142].

8.6 OSA Correlation to Dental Conditions

8.6.1 Sleep Bruxism

Bruxism is of great interest to researchers and clinicians in the dental, neurology, and sleep medicine communities. Common clinical symptoms associated with bruxism are craniofacial pain, tooth wear, tooth sensitivity or pain, and failing dental restorative treatments [143].

There are four definitions of bruxism based on the perspective from organizations defining the term. The definition of bruxism formulated in the *Glossary of Prosthodontic Terms Ninth Edition (GPT-9)*; in the Craniofacial Pain Handbook (CPH) published by the American Academy of Craniofacial Pain; in the *Orofacial Pain Guideline for Assessment, Diagnosis, and Management, Fourth Edition (OFPG-4)*, published by the American Academy of Orofacial Pain; and in the *International Classification of Sleep Disorders Third Edition (ICSD-3)*. These four definitions have been critically scrutinized by these organizations, after which a new definition of bruxism was proposed.

The *Glossary of Prosthodontic Terms Ninth Edition (GPT-9)* has two definitions for bruxism: "(1) the parafunctional grinding of teeth; (2) an oral habit consisting of involuntary rhythmic or spasmodic nonfunctional gnashing, grinding, or clenching of teeth, in other than chewing movements of the mandible, which may lead to occlusal trauma; nocturnal bruxism, occlusal neurosis, tooth grinding" [144].

The *Craniofacial Pain Handbook (CPH)* defines bruxism as "Grinding or gnashing of the teeth when not masticating or swallowing. Gnashing and grinding of teeth. An unconscious habit usually limited to the sleeping period but sometimes occurs under the strain of mental or physical concentration. Diurnal or nocturnal parafunctional activity including clenching, bracing, gnashing and grinding of the teeth. In the absence of subjective awareness, can be diagnosed from presence of clear wear facets that are not generated by masticatory function. Diurnal or nocturnal parafunctional activity including clenching, bracing, gnashing and grinding of the teeth. In the absence of subjective awareness, past bruxism can be inferred from presence of clear facets that are not interpreted to be the result of masticatory function, and contemporary bruxism can be observed through sleep laboratory recordings. (1) The parafunctional grinding of teeth. (2) An oral habit consisting of involuntary rhythmic or spasmodic nonfunctional gnashing, grinding or clenching of teeth, in other than chewing movements of the mandible, which may lead to occlusal trauma- called also tooth grinding, occlusal neurosis" [145].

The *Orofacial Pain Guidelines for Assessment, Diagnosis, and Management, Fourth Edition (OFPG-4)* defined bruxism as: "Diurnal or nocturnal parafunctional activity including clenching, bracing, gnashing, and grinding of teeth; in the absence of subjective awareness, past bruxism can be inferred from the presence of clear wear facets that are not interpreted to be the result of masticatory function, and contemporary bruxism can be observed through sleep laboratory recordings" [146].

The International Classification of Sleep Disorders Third Edition (ICSD-3), defines bruxism "as a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or bracing or thrusting of the mandible. Bruxism has been divided into its two circadian manifestations known as sleep bruxism and awake bruxism" (ICSD-3).

ICSD-3 classifies sleep bruxism among the sleep-related movement disorders which was previously among the parasomnias. The *International Classification of Sleep Disorders Third Edition* defines bruxism as "an oral activity characterized by grinding or clenching of the teeth during sleep, usually associated with sleep arousals" [147].

When sleeping, frequently repeated jaw muscle contractions occur and are referred to as rhythmic masticatory muscle activity (RMMA). When looking at electromyographic tracings, RMMA has two forms, phasic and tonic contractions. Phasic contractions are repetitive jaw muscle activity, and tonic contractions are an isolated sustained jaw clenching. The tooth grinding sounds are referred as sleep-related bruxism [147].

This can lead to abnormal tooth wear, tooth pain, jaw muscle pain, and headaches. Sleep bruxism may also result in sleep disruption in association with sleep arousal. The sounds made by friction of the teeth can be quite loud and disturb the bed partner or others nearby [147] (Fig. 8.4).

8.6.2 Malocclusion

Malocclusion is the misalignment of teeth and the jaw. In obese patients, hyperplastic soft tissue is one of the predisposing factors causing OSA. Whether the same holds true for nonobese patients is questionable. There is no substantial literature supporting the statement that malocclusion is an independent risk factor of OSA. The editorial study conducted in 2008 on 97 male patients with the help of diagnostic tools such as cephalometric and dental analysis concluded that increased overjet and overbite are related to the propensity of OSA severity in nonobese patients. Malocclusion is such an irregularity that tends to make a subject breathe through their mouth more prominently as compared to nasal breathing. Furthermore, evidence is increasing which demonstrates that OSA patients have dentofacial/skeletal characteristics associated with a narrow upper airway [148]. In turn, that leads to the downward and backward rotation of the mandible, tongue, and occlusion into the retropalatal (velopharynx) and retroglossal (oropharynx) [148–152]. Please refer to Fig. 8.5. If a person has an increase in overjet and overbite, then they will tend to breathe through their mouth and that in turn leads to retro-inclination of maxillary and mandibular incisors and hence increases the severity of malocclusion. Please refer to Fig. 8.5. We can conclude that overjet in nonobese subjects may possibly occur due to mandibular hypoplasia or

Dental clinical signs of bruxism

Worn dentition	Due to the forces placed on the teeth
Fractured restorations	Due to the forces placed on the teeth
Abfractions	Due to concavity of the tooth structure at the gum line caused by lateral forces placed on the teeth
Tori	Overgrowth of bone typically seen in the lingual aspect of the teeth, either at the middle of the palate or on the premolar section of the mandible
Buccal exostosis	Overgrowth of bone on the cheek side of the teeth
Loosening of teeth	Caused by trauma from bruxism
Tooth sensitivity	Due to the trauma caused by bruxism
Gingival recessions	Caused by a response to the forces placed on the periodontium
Muscle pain	Caused by overworked muscles
TMJ-related symptoms	Internal derangement, clicking, popping, crepitus, capsulitis, arthralgia, ear pain or fullness, dizziness, myalgia, cephalgia, pain or tenderness of the neck and shoulder, pain or pressure behind the eyes, pain or sensitivity of the dentition

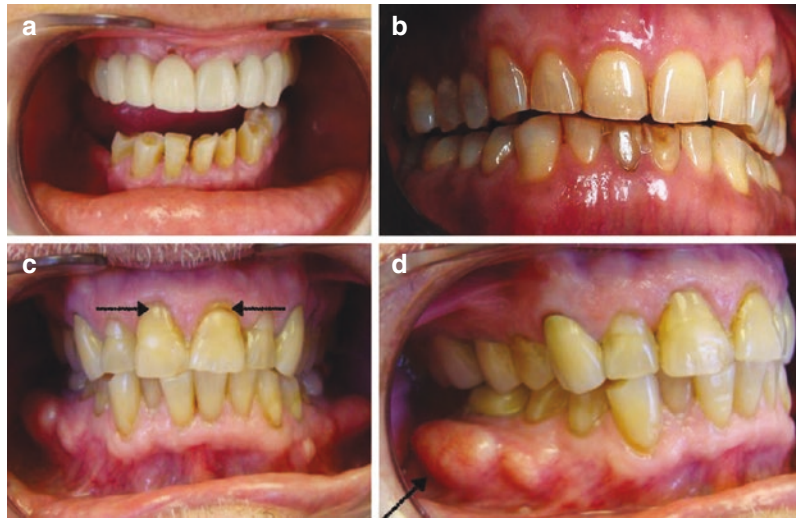

Fig. 8.4 (**a**) Attrition associated with sleep bruxism. Notice the wear of the lower teeth. Image provided by "Dr. G. Gary Demerjian". (**b**) Severe attrition seen in sleep bruxism. Notice the flat edges of the upper and lower teeth. Image provided by "Dr. Pooja Goel". (**c**) Severe recession and abfraction. Abfractions are indentations of the teeth at the gum line, as seen in this photo where tooth-colored fillings have been placed. Image provided by "Dr. G. Gary Demerjian". (**d**) Buccal exostosis. Overgrowth of bone indicated by the arrow. Image provided by "Dr. G. Gary Demerjian"

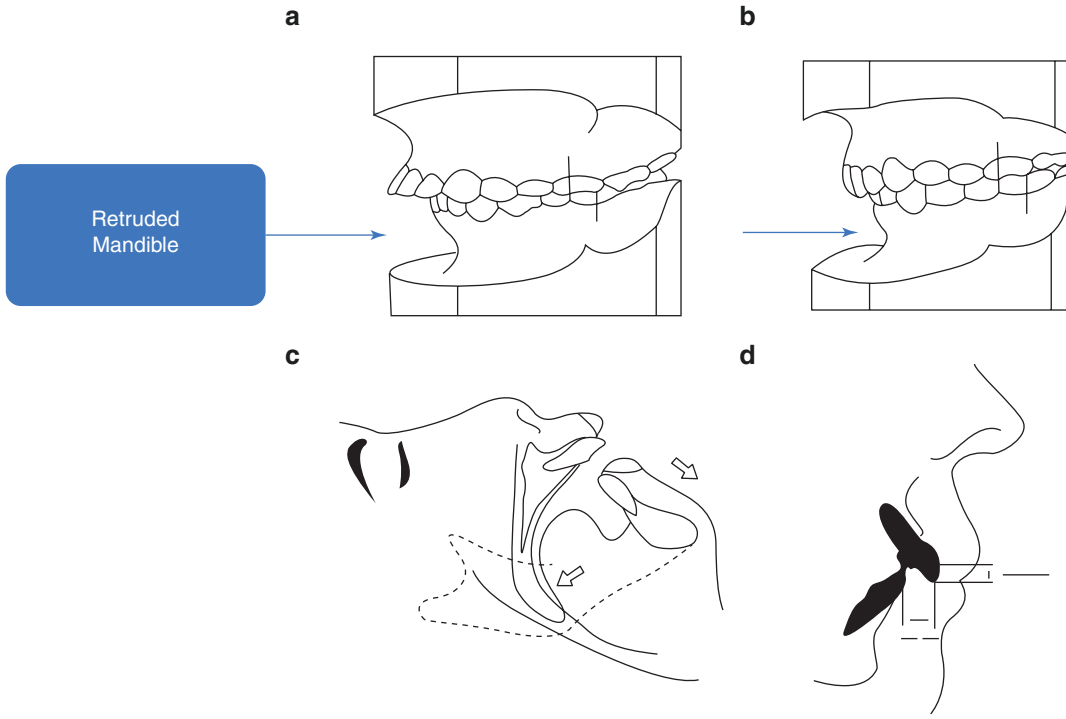

Fig. 8.5 Maxillary and mandibular relationship. Adapted from Miyao E et al. (**a**) Maxillary protrusion/mandibular retrusion, (**b**) deep overbite, (**c**) upper airway and protrusion of maxillary anterior teeth during sleep in a patient with mouth breathing, (**d**) measurement of overbite and overjet

a retrognathic placed mandible and can lead to OSA. Also, the Sella-Nasion to B point angle (SNB) is smaller, less than 80°, in nonobese patients according to this study and is a bony irregularity which can lead to the propensity of OSA. The lateral cephalometric steiner analysis depicts a recessive mandible. Please refer to Fig. 8.6 [150, 153]. The hypothesis is that maxillofacial anomaly, also known as malocclusion, may play a critical role in increased propensity of OSA. The supportive fact for the hypothesis is that the inability of the lip closure around an increased overjet/overbite in subjects can eventually lead to increased tension in the orbicularis oris muscle, which will lead to the imbalance of pressure in the ring of muscles of orbicularis oris, buccinator, and constrictor superior muscles. The ring of muscles mentioned above plays a crucial role in the physiology of breathing in human beings. Any unwanted increase in the tension of these muscles can lead to a narrowing of the airway and decrease the posterior airway space and contribute to OSA in patients [154]. The effects of oral appliances on OSA and the upper airway, involving alterations in the dentofacial morphology, have been investigated extensively by the dental field of orthodontics [155–158].

Class I

Class I is known as normal occlusion. When the jaw and the molars are in normal alignment, however the teeth may be crowded/rotated or missing. Normal position of the tongue rests against palate posing a balancing force on the teeth between the tongue and cheek muscles.

Class II

Class II is known as retrognathia of the mandible. An overbite occurs when the mandible is deficient, and therefore the maxilla protrudes over the mandible.

It has been accepted for decades that dental arches in mouth breathers can be influenced by an imbalanced muscular function [159]. Nasal breathing due to obstruction can impact the facial growth was acknowledged, by Schendel described as a long face [160]. The dental relationship is mostly determined by genetics [161] and adaptation to breathe; therefore mouth breathing is a secondary etiological factor to class II development.

Several observational studies found that a class II malocclusion seen in permanent dentition had an underlying skeletal imbalance which can be detected as a distal step in the primary or deciduous dentition [162–164]. Baccetti et al.

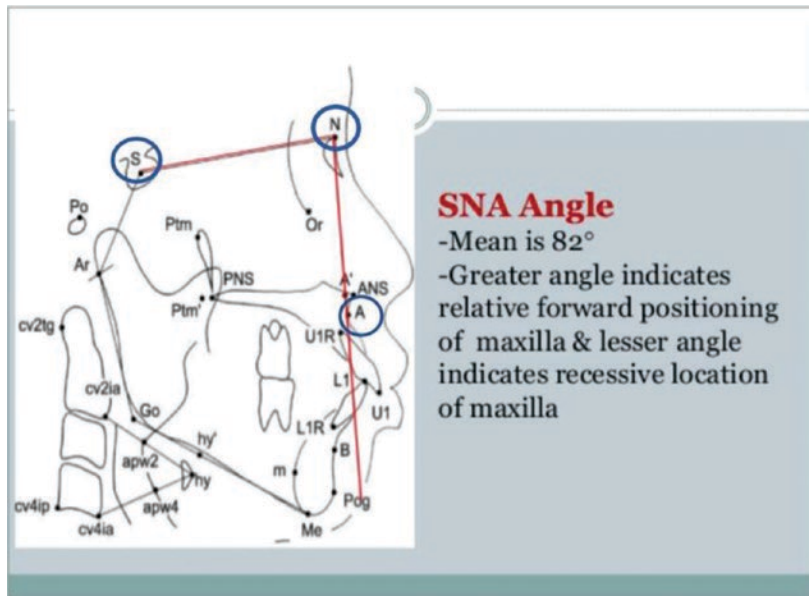

Fig. 8.6 SNA angle. Adapted from Nabil et al. SNA landmarks from the lateral cephalometric analysis are circled

concluded that in the primary dentition, when looking at the dental relationships in the sagittal plane, the mandibular teeth will have a distal step, the canine will be in a class II relationship, and an excessive overjet will be seen. A transverse interarch discrepancy is due to a narrower maxillary arch which is a common feature of early class II malocclusion. Skeletal findings of class II malocclusion in children is clinically seen as mandibular retrusion and shorter total mandibular length [162]. When looking at the transition during mixed dentition, class II occlusal characteristics are either maintained or even worsen. Treatment to correct the class II malocclusion should be initiated in all three planes of space by expanding the maxilla and using mandibular repositioning to aid in the skeletal development.

As the mouth stays open to breathe, the tongue does not rest against the palate to resist the forces of the facial muscles; thus the maxillary arch can become narrow, and the mandible rotates back and down, causing an anterior open bite and a posterior crossbite. Environmental factors such as sucking habits (fingers or pacifier) and mouth breathing work as a secondary cause in creating an anterior open bite [74, 165]. Mocellin et al. found palatal constriction in 63% of mouth breathers and 5% of nasal breathers. This demonstrated the correlation of posterior crossbite to be significant factor for mouth breathers in relation to the general population [97]. Souki BQ and colleagues concluded in their study that children in primary dentition with nasal obstruction have a higher prevalence of posterior crossbite than the general population. Subjects in mixed and permanent dentitions, who present as mouth breathers, were more likely to present with an anterior open bite and class II malocclusion. There is also a sample of mouth breathers with the presence of rhinitis, adenoid, and tonsillar hyperplasia where there is no association with the prevalence of class II malocclusion, anterior open bite, and posterior crossbite [97].

According to a study by Banabilh conducted on 120 adults, the class II malocclusion patients are significantly more prevalent in the OSA category. The subjects with OSA, when compared to the control group, had a larger number of candidates with a convex profile, class II malocclusion, and the V-shaped palate [166]. Similarly, another study conducted in 2008 supports the hypothesis that malocclusion and OSA are linked in nonobese subjects. Specifically, those with an overjet bite had increased chances of OSA [150].

Class III

Class III is when the mandible is larger than the maxilla that causes the anterior teeth to be edge to edge or an underbite [70]. Most cases of skeletal discrepancy are due to insufficient growth of the maxilla or an overgrowth on the mandible. The tongue position in class III subject is resting at the lower dental arch. If the tongue is not filling the palate to balance the buccal forces of the facial muscles, that can cause a narrowing the maxillary arch. This author believes that due to the tongue position and the need to breathe, the patient will subconsciously protrude the jaw, thus causing a dental and skeletal class III.

Iwasaki et al. compared the cephalometric of class I to class III regarding the position of the maxilla, the mandible, and the oropharyngeal airway. The class III group had mandibles more anterior than the class I group. There was no difference in the nasopharynx, but the oropharyngeal airway was significantly larger in the class III group, indicating a low tongue position [167]. Also, the difference of the oropharyngeal width was wider in the class III, indicating hyperplasia of the palatine tonsil. In class III children, the hypertrophy of the palatine tonsils and the lower position of the tongue affect both occlusal relationships and upper airway space [70, 168–170]. With the use of CBCT, children with class I malocclusion had a square oropharyngeal airway 84% of the time, and children with class III malocclusion had a relatively flat rectangular shape 70% of the time, either in the lateral direction (55% wide) or anteroposterior direction (15% long) [167].

Cross-sectional area of the oropharynx tends to be wider in proportion to the severity of the class III malocclusion, thus indicating the class III children have less occurrence of OSA. Several

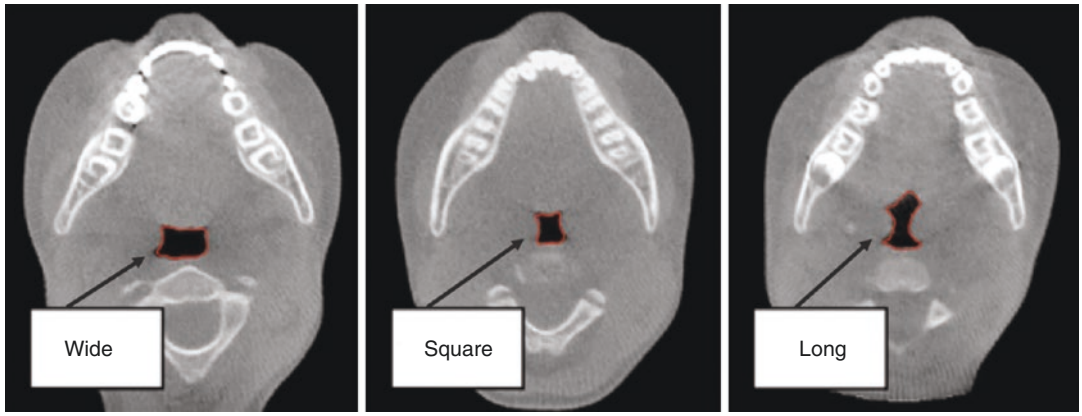

Fig. 8.7 Oropharyngeal airway shapes. Adapted from Iwasaki T et al. The arrows are pointing to the oropharyngeal airway

studies found that the base of the tongue is 3.0 mm inferior in patients with severe OSA than in those with mild to moderate OSA [171] (Fig. 8.7).

Breastfeeding and Non-Nutritive Sucking Habits

There is considerable body of literature indicating the link between breastfeeding and non-nutritive sucking patterns such as thumb-sucking and pacifier into the proper development of dental arches. There is concrete evidence suggesting that non-nutritive sucking habits can lead to an increased propensity of malocclusion such as anterior open bite in the primary dentition. In the study conducted by Romero, it was concluded that consistent breastfeeding for 12 months decreased the chances of an anterior open bite by 3.7 times. Comparatively, consistent yearly non-nutritive sucking habits increased chances of malocclusion development by 2.38 times. Interestingly enough, there was another finding having to do with the length of duration of breastfeeding. If an infant was breastfed for less than 6 months, their chances of developing an improper dental arch was increased by 5.35 as compared to infants who were breastfed for more than 12 months. The anterior open bite and development of malocclusion lead to dental skeletal alterations which caused improper swallowing pattern, improper speech, and improper posture of tongue in the position [172]. Certain congenital conditions such as ankyloglossia (tongue-tie) can pose difficulty occasionally in breastfeeding neonates and infants. Approximately 4.2–10.7% newborns are affected with tongue-tie. Tongue-tie is a condition where mobility of the tongue is limited due to an exceptionally short lingual frenum. The research conducted by Rowan-Legg on 36 neonates with ankyloglossia showed that there is evident incidence of latching difficulty ranging from 19% when compared to a control group where there was 0% difficulty. Furthermore, breastfeeding was overall proven to be difficult with neonates suffering from ankyloglossia by 25% when compared to the control group who had 0% difficulty. A procedure known as frenotomy can be performed if there are major breastfeeding issues caused by tongue-tie to relieve in neonates [172]. When there is a tight maxillary frenum, the newborn will have improper latching of the breast, creating a difficulty with breastfeeding [173].

If the newborn cannot breastfeed, the tongue will not function properly and be trained for proper swallow patterns. During suckling, the tongue places forces on the breast to extract the milk and to move it from the front of the mouth to the posterior of the mouth to swallow. The mandible also moves forward and back with the tongue to move the bolus of milk. This movement of the tongue will develop the palate, and the mandibular movement will develop mandibular growth. Therefore, releasing the maxillary and

lingual frenum requires an early diagnosis and treatment. This can potentially prevent developmental problems [173].

However, according to Sum there is research suggesting certain parafunctional habits; nonnutritive sucking habits such as digit sucking and pacifier have detrimental effect on dental occlusion and dental arches. According to this 2015 study conducted on 851 children, between the ages of 2 and 5, these habits can lead to the development of anterior open bite, decreased overbite, increased overjet, posterior cross bite, and constricted arches. Narrow maxillary arches are quite frequently associated with digit sucking. Breastfeeding more than 6 months can lead to a proper development of dental relationship by developing the arches into anterior sagittal and transverse dimensions. Constant breastfeeding in children for more than 6 months leads to a lower frequency of development of class II incisal relationship, less increased overjet, and a wider intercanine and intermolar widths. Hence, we can conclude that proper development of arches will lead to proper swallowing function, speech function, and proper posture of the tongue and the correct balance of forces between orofacial musculature [174]. In conclusion, getting rid of parafunctional habits and following proper breastfeeding way of nutrition for neonates will lead to less craniofacial development abnormalities and help the children to develop a normal airway leading in proper breathing.

Bi-Extractions and Narrow Dental Arches

There is controversy regarding the effects of four premolar (bicuspid) extractions on the oropharyngeal airway. In orthodontic premolar extraction cases, the treating dentist or orthodontist is looking at trying to correct issues of crowding or bimaxillary dentoalveolar protrusion. In a study of adolescents, orthodontic treatment was done in combination with extraction of four premolars, resulting in no influence on oropharyngeal airway volume [175]. Germec-Cakan reported a narrowing of the oropharyngeal airway in orthodontic cases following four bicuspid extractions, where maximum anchorage was used in retraction of the anterior teeth. Conversely, when the anterior teeth were not distalized and the molars were medialized, the airway dimension was increased [176]. In a study, 14 children were chosen who had a malocclusion and OSA confirmed with a PSG. Ten of the subjects completed rapid maxillary expansion (RME) over a 12-month period. Two of the children had a fail result. Of the other eight subjects, the apnea-hypopnea index (AHI) decreased by the end of the treatment period, and the symptoms had resolved. Two years after the end of RME, there were no significant changes in the AHI [177]. Any changes in the position of incisors and soft tissue can potentially affect tongue position and oropharyngeal airway [175]. In bimaxillary protrusive patients, extraction of four premolars and retraction of the incisors affected velopharyngeal, glossopharyngeal, hypopharyngeal, and hyoid position [178]. In a systematic review, Hu Z concluded that based on the current evidence, more trials are needed with reliable evidence. In cases of extractions, followed by retraction of the anterior teeth (reducing the inclination of the incisor) causes upper airway narrowing by reducing the tongue space and causing retraction of the tongue. Mesial movement of the molars increased the posterior tongue space enlarging the oropharynx dimensions [148].

If we treat OSA cases in the early developmental phase, we can potentially help develop patients skeletally in the dentofacial region when they are in mixed dentition, to possibly avoid extraction of permanent teeth and widen the dental arches to create more room to the tongue in the long term. When looking at skeletal discrepancy cases, such as class II or class III, there is usually underdevelopment of mandible or maxilla [166]. If there is any underdevelopment, we believe that when teeth are extracted in order to close that space, the anterior teeth have to be retracted, thus resulting in reduction of space for the tongue. Furthermore, as the subject grows into adults, all of the hard and soft tissues continue to grow and develop except the size and shape of the teeth. We need long-term studies showing the relationship between dentofacial airway development, respiratory function, and oropharyngeal collapsibility (Fig. 8.8).

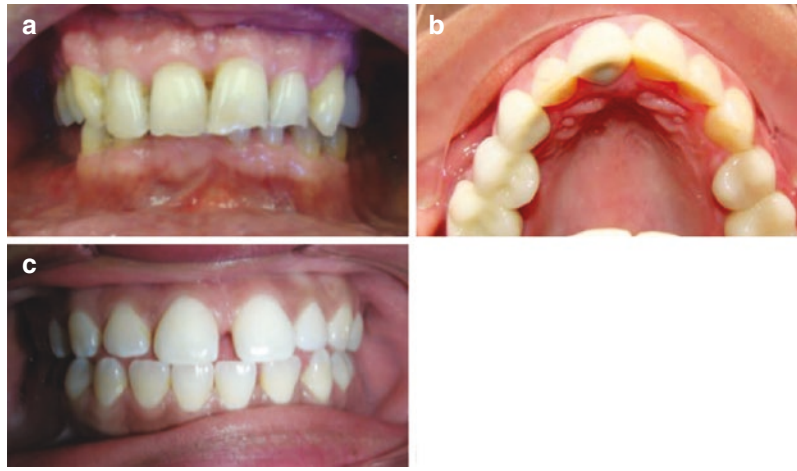

Fig. 8.8 (**a**) Deep bite malocclusion. A deep bite occurs when the upper anterior teeth cover most of lower front teeth. Image provided by "Dr. G. Gary Demerjian". (**b**) Missing first premolars. Extraction of bicuspids causes a shortening and narrowing of the Dental arch resulting in less room for the tongue. Image provided by "Dr. G. Gary Demerjian". (**c**) Interproximal spacing. Notice the spacing between the teeth. Four premolars were extracted on this person, and tongue is pushing when swallowing due to the limited tongue space. Image provided by "Dr. Chetan Parikh"

Tori

There is insufficient of evidence directly associating maxillary and mandibular and tori to OSA. The concept of bone remodeling or growth as it adapts to mechanical forces is called Wolff's law. However, this is not always true and is comprised of various processes [179]. According to Drs. Prehn and Simmons, parafunctional habits such as clenching and grinding can be secondary to offset the restricted or reduced airway caliber to prevent its collapse. Patients with sleep bruxism as a result of sleep-disordered breathing such as OSA are prone to lead to formation of buccal exostoses and the mandibular tori [180]. Mandibular tori are more frequently found bilaterally on the premolar area onto the lingual aspect of the mandible. Overgrowth of bone in the oral cavity can lead to narrowing of the oral cavity volume and will leave minimal space for the tongue to rest in the floor of mouth. Hence, the tongue will have a tendency to fall back into the upper airway due to gravity. Eventually, the oropharyngeal region will crowd and cause upper airway obstruction. Upper airway narrowing can lead to OSA. There is no cause and effect relation with tori and OSA. The surgical removal of tori has led to improvement of OSA in many cases. Once the tori are removed, the oral volume is increased which then allows the tongue to have more room and open airway. Although there is not a direct relation between tori and OSA, there is an indirect link [181]. In another 2016 recent study, it was concluded that if the tori are larger than 2 centimeters, then the possibility of OSA in a patient may be present [182]. If a patient has these kinds of malformations of bone morphology and has associated sleep-related issues, he/she should be asked to get a sleep study done by the sleep physician to rule out the possibility of sleep apnea. In children if parents do bring out the concern of habitual snoring, clenching, and grinding and evident wear and tear on the primary dentition noticed by the dentist, they should be given a referral for the sleep physician or the ear, nose, and throat specialist to rule out the OSA. Tori and nocturnal bruxism are not the telltale symptoms for the diagnosis of sleep apnea but can be a valuable diagnostic tool in the armamentarium of dentist to rule out the classic triad of TMD, sleep-disordered breathing, and malocclusions [180] (Fig. 8.9).

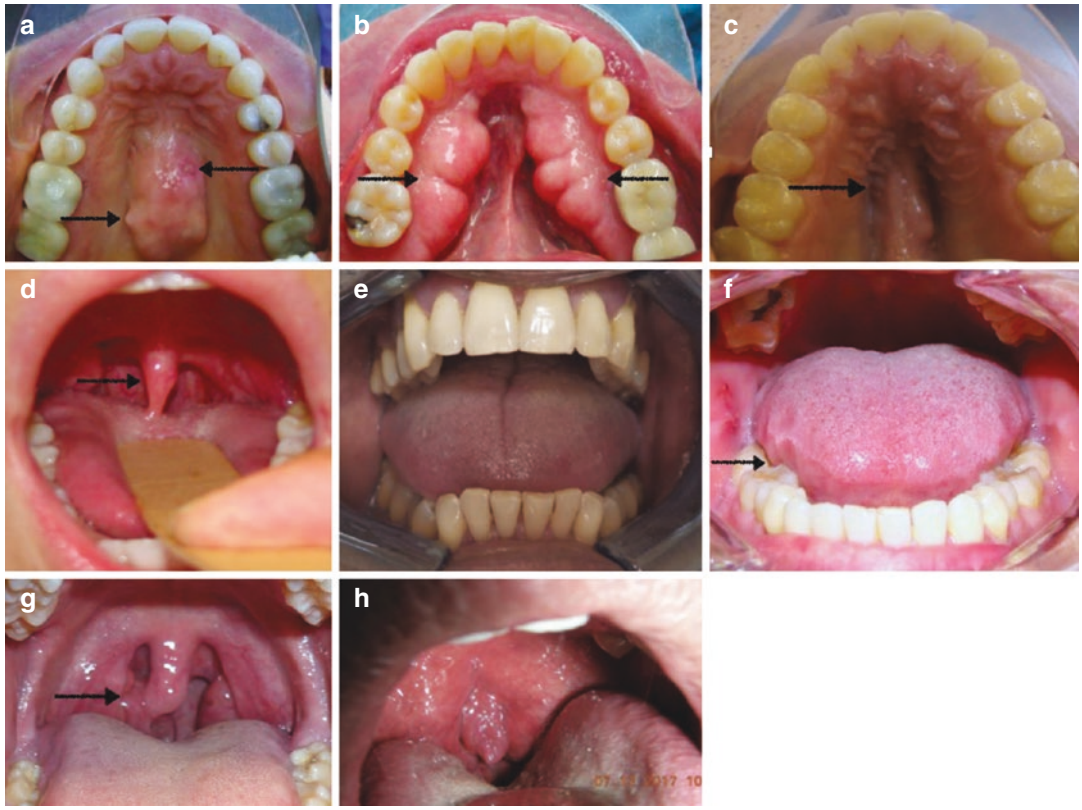

Fig. 8.9 (**a**) Maxillary tori. Notice the overgrowth of bone at the center of the palate. Maxillary tori are due to the stimulation and flexion of the maxillary sure caused by bruxism. At the right arrow is a sore spot which is healing due to abrasion from eating hard food. Image provided by "Dr. G. Gary Demerjian". (**b**) Bilateral lingual mandibular tori. Mandibular lingual tori are the overgrowth of bone cells (osteoblasts) due to stimulation from bruxism. Image provided by "Dr. G. Gary Demerjian". (**c**) Narrow maxillary arch and high-vaulted palate. Clinical symptoms seen in patient with snoring and sleep apnea. Image provided by "Dr. G. Gary Demerjian". (**d**) Elongated uvula. Due to the pulling of the uvula during snoring. Image provided by "Dr. G. Gary Demerjian". (**e**) Enlarged tongue. Large tongue placed above the occlusal plane of teeth. Image provided by "Dr. Pooja Goel". (**f**) Scalloped tongue. The side of the tongue is scalloped taking the shape of the teeth, indicated by the arrow. Image provided by "Dr. G. Gary Demerjian". (**g**) Enlarged tonsils. Notice the uvula touching the tonsil on the left and the tonsil on the right is half way between the pharyngeal wall and the uvula. Image provided by "Dr. Mayoor Patel". (**h**) Elongated and edematous uvula and soft palate. Image provided by "Dr. Chetan Parikh"

8.7 Dentofacial Changes Via Orthodontic/Orthopedic Treatments

8.7.1 Maxillary Expansion

The term maxillary constriction refers to a narrow maxilla, in the lateral dimension relative to the mandible. Maxillary arch width was significantly smaller in the groups of OSA and snoring children than in the control group [12]. Based on clinical observations, many clinicians suggest that maxillary constriction may also play a role in the pathophysiology of OSA. The maxillary arch width is measured by the distance between the first molars [183]; this can be seen clinically in OSA patients [184]. It is known that subjects with narrow maxilla have increased nasal resistance causing one to mouth breathe [185] and causing the tongue to acquire a low posture [186, 187]. A low tongue posture can result in retroglossia, causing oropharyngeal narrowing and possibly affecting OSA

[188, 189]. In cases of Marfan's syndrome, which is characterized as having a high palatal arch with maxillary constriction, they are known to have a high prevalence of OSA, where the degree of sleep apnea is correlated with the measurements of the maxilla [190].

Several studies have investigated the radiographic changes after maxillary expansion of the nasal cavity using a posterior-anterior cephalometric radiograph [185, 191]. Acoustic rhinometry was used before and after expansion, which revealed an increase in the nasal volume and minimum cross section and a decrease in nasal resistance [71, 192, 193]. Due to the variations in the individual response to the expansion, the degree of reduction of nasal resistance cannot be predicted [194, 195], but over 50% of patients with maxillary expansion subjectively reported an improvement of breathing [194].

Maxillary expansion has been studied for years and recently with the use of mini-implants (MI), also known as temporary anchorage device (TAD). Maxillary expansion separates the mid-palatal suture and cause less tipping of the teeth, depending on the type of expander being used [196]. The use of TADs has expanded to include various clinical applications: correction of deep bite and occlusal cants; closure of extraction spaces; dental midline alignment; intrusion, extrusion, and uprighting of teeth; retraction of anterior teeth; medialization and distalization of posterior teeth; and correction of sagittal discrepancies and vertical skeletal discrepancies which traditionally require orthognathic surgery [197–202]. Several investigations have evaluated the failure rates and success rates of MIs and risk factors associated with their use as temporary anchorage devices (TADs) for orthodontic purposes. According to these studies, the success rates of MIs have significantly increased to between 75.2 and 90.7%. Researchers believe that MIs have already become efficient anchorage devices for orthodontic purposes and suggest them as the conventional anchorage devices of future everyday clinical practice [199–201].

8.7.2 Hyoid Bone

The connection of the hyoid bone to the surrounding musculature has been implicated in maintaining oropharyngeal patency. Various studies have demonstrated that changes in mandibular position can result in changes to the hyoid position [203]. Several studies reported that patients with mandibular retrognathia had a posterior position of the hyoid bone and an association with narrowing of the oropharyngeal airway [204, 205]. In a cephalometric study of skeletal class I compared with class III subjects, Adamidis and Spyropoulos found a significant difference in the position of the hyoid bone [206]. The contraction of the hyoid muscles caused a reduction of airway resistance as a response to chemical, vagal, and negative-pressure stimuli [76]. There is also a correlation between the length of the hyoid bone muscles, head position, and upper airway volume [207]. In an orthodontic study, Parisella V found in cephalometric analysis that the hyoid position was modified by maxillary arch expansion, reconditioning tongue posture and function. Orthodontic treatment resulted in the skeletal improvement of class II malocclusion of the skeletal class I [208]. In surgical studies, surgical advancement or setback of the mandible influences the hyoid position. The hyoid bone is typically described as being inferiorly positioned in OSA patients [154, 209]. The oropharyngeal airway was shown that mandibular advancement resulted in a forward displacement of the hyoid with minimal widening of the pharyngeal airway [210], whereas in surgical mandibular setback cases, the opposite was true [203, 210]. The mechanics of an oral appliance for the treatment of OSA is mandibular advancement to cause tension of the pharyngeal muscles in order to keep the airway patent. Therefore, when advancing the mandible with an oral appliance, the hyoid position can be a determining factor of airway patency.

8.8 Dental Orthopedic Jaw Position: Loss of Vertical Dimension/Bite Collapse

Pharyngeal narrowing can occur at the oropharynx, at the level of the tongue and soft palate or hypopharynx. Several structural changes in craniofacial morphology have been associated with

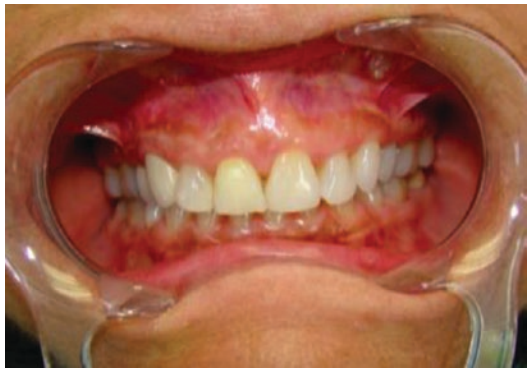

Fig. 8.10 Deep overbite. Image provided by "Dr. G. Gary Demerjian"

OSA pathogenesis, such as retrognathia of the mandible, posterior placed pharyngeal walls, macroglossia, and soft palate collapsibility [211]. Loss of vertical dimension due to loss or absence of teeth produces prominent anatomical changes that influence oropharyngeal size and function, therefore resulting in reduction of the lower face height and mandibular rotation [212]. In several studies, Bucca and his colleagues show a worsening of OSA with the extraction of teeth where the subject slept without their dentures. They observed the retropharyngeal space (RPS) and posterior airway space (PAS) to be reduced. Anatomical changes were caused by the decrease in vertical dimension of occlusion (VDO) resulting in the collapse of orofacial structures [213]. In same edentulous subjects, after wearing complete dentures and having an acceptable VDO, the RPS and PAS were found to increase, resulting in an improvement of the OSA, due to restoration of the VDO [214]. This also applies to patients with deep overbite, where the tongue has no room but to retract into the oropharyngeal airway (Fig. 8.10).

8.8.1 American Academy of Dental Sleep Medicine (AASM)

8.8.1.1 Recommendation on Dental Sleep Appliance Therapy

Whether or not the oral appliance is an effective treatment modality for the treatment of OSA used to be a matter of debate, perhaps owing to fewer number of studies. There is a wealth of literature on the efficacy of oral appliances in the treatment of OSA in the past few years. A task force of seven members, three physicians board certified in sleep medicine, two dentists, and two AASM research staff members were put together to develop the guidelines stated below [215].

8.8.1.2 Suggested Recommendations

1. Sleep physicians should prescribe oral appliance therapy, rather than no treatment, for adult patients who do not have OSA and want treatment for primary snoring. (*Standard*)

   When we weigh the benefits over risk, certainly the benefits are lot more in controlling the health consequences of snoring by providing the treatment for it. If the primary snorers have tried the other treatment modalities such as weight loss and positional therapy and want another treatment, then they should be prescribed for an oral appliance by the sleep physician, to be fitted by a qualified dentist [215].
2. When sleep physicians prescribe oral appliance therapy (OAT) for adults with OSA, qualified dentists should fabricate custom, titratable appliances over prefabricated appliances. (*Guideline*)

   An evidence-based systematic review clearly shows that the custom titratable oral appliances are effective in improving the sleep physiologic sleep parameters such as decreasing the AHI index, decreasing the arousal index, increasing the oxygen saturation, and possibly also improving the daily function and quality of life. Therefore, OAT should be considered as treatment of choice for the patients who are suffering from OSA and cannot tolerate CPAP or prefer alternate therapy [215].
3. Sleep physicians should consider prescribing OAT, for patients diagnosed with OSA who are CPAP intolerant or prefer alternative treatments, rather than no treatment. (*Standard*)

   Although some of the sleep physiologic parameters such as AHI, arousal index, ODI, and oxygen saturation levels are better improved by CPAP as compared to OA, the adherence is better with OA. Hence an oral appliance outweighs the efficacious nature of CPAP and should be offered to adult patients

who are intolerant to CPAP and prefer alternative therapy [215].

4. Qualified dentists should regularly monitor OAT outcomes for OSA patients to minimize the occurrence of undesirable side effects. (*Guideline*)

   The side effects caused by the use of OAT are not permanent or major in nature. All the therapies have pros and cons, and having said that OAT for the treatment for OSA is no different. With the proper supervision and constant follow-up by the dentist, the impact of undesirable side effect can be superseded [216].

5. Sleep physicians should perform follow-up sleep testing to confirm or improve OAT efficacy. (*Guideline*)

   In many instances, after the subjective relief of symptoms, patients might have residual OSA and high AHI. The follow-up sleep testing with sleep physicians can allow the dentist to redesign or further titrate the appliance to achieve better efficacy and success with the oral appliance [216].

6. Sleep physicians and qualified dentist should instruct adult OSA, who are being treated with OAT, to return for periodic follow-up visits. (*Guideline*)

   For a chronic condition like OSA, even after the successful treatment, the recommendation is to do 6-month follow-up for the first year followed by yearly follow-up visits. This proposal is made to make sure that dentist can oversee the condition of oral appliance such as excessive wear and tear, cracks, discoloration, and lack of retention. Also, if the patient's symptoms have come back, then further sleep testing can be done by sleep physician, and depending on the results, either a new appliance can be made or the old appliance can be titrated further [216]. All of this is possible only if the protocol is followed for the periodic visits after rendering the treatment.

8.9 Medical Intervention

8.9.1 Diagnosis

Whether a patient has OSA or is at risk of developing the complications of OSA is a complex, multifold method. The most important step in the diagnosis of OSA is to start with a complete sleep-oriented history and a physical examination carried out by a sleep physician. Following the initial exam, if a patient falls into a high pretest probability of suffering with sleep-disordered breathing, then they should be referred for further objective testing conducted by an acceptable method in order to have an established diagnosis of OSA. The two commonly used methods for objective testing are an in-laboratory PSG and with portable monitors (PM). The two out of many major AASM practice parameters to be diagnosed with OSA with PSG and PM are as such: PSG is routinely indicated for the diagnosis of sleep-related breathing disorders (Standard). PMs may be used to diagnose OSA when utilized as a part of comprehensive sleep evaluation in patients with a high pretest likelihood of moderate to severe OSA (Consensus). PM testing is not indicated in patients with major comorbid conditions including, but not limited to, moderate to severe pulmonary disease, neuromuscular disease, or congestive heart failure or those suspected of having a comorbid sleep disorder (Consensus) [1].

8.9.2 Treatment Options

A long-term, multidisciplinary course of medical intervention should be considered for a chronic disease like OSA. There are behavioral/medical/surgical options along with some very effective adjunctive therapies such as weight loss, positional therapy, myofunctional therapy, or pharmacological intervention which are used along with the major primary treatment rendered for the treatment of OSA for better success and improvement of results. The patient should be completely engaged in the discussion of the commonly offered treatment options, including their associated modalities, risks, and benefits. OSA management is evaluated by looking at several factors such as decrease in daytime sleepiness, improvement in the oxygen saturation, improved quality of life measures, patient and spousal satisfaction, adherence to the therapy, and long-term management of sleep apnea. While fractional improvement may be of

significant benefit, achievement of the threshold level of apnea severity at which there is no significant morbidity or mortality would appear to be the desired goal [1].

8.9.3 CPAP

The gold standard of care for the treatment of OSA is with positive airway pressure (PAP) therapy. PAP is a treatment modality which leads to the pneumatic splinting of the upper airway. PAP can be of various kinds such as CPAP (continuous positive airway pressure), bi-levels of pressure in PAP, auto-PAP, or servo ventilation PAP. Depending upon the severity of OSA, the initiation management and follow-up of PAP therapy should be approached by a multidisciplinary team. The patient should be well taught about the functionality, adherence, and maintenance of their equipment to make it a success by their disease management team. After the initial PAP setup, active follow-up by the appropriate trained health providers is indicated yearly and as needed to troubleshoot PAP mask, machine, or usage problems [1].

8.9.4 Oral Appliance

Over the past decade, oral appliances have emerged as a well-proven alternative in the treatment of OSA. Oral appliance therapy (OAT) works by modifying the position of the mandible, the tongue, and the pharyngeal structures. A proper diagnosis of OSA should be made by a sleep physician followed by a prescription of oral appliance before the initiation of OAT. A complete dental examination, including the condition of teeth, periodontal tissues, and TMJ, is crucial prior to therapy. The AASM guideline is that custom-made titration appliance should be considered over non-custom appliance for better efficacy [215]. The meaningful definition of response must include outcomes such as improved sleep, improved oxygen saturation, decreased AHI, improved sleep architecture, improved EDS (excessive daytime sleepiness), and improved quality of life [217]. Additional cardiovascular and neurobehavioral outcomes should also be improved. A regular follow-up is required to make sure adherence is there and no recurrence symptoms and also to evaluate no breakage or wear/tear of appliance [216].

8.9.5 Surgical Treatment

Patients who cannot tolerate or failed PAP and OAT or patients with established diagnosis of OSA who have severe obstructive anatomy that is surgically correctable (e.g., tonsillectomy) or maxillary and mandibular deficiency and have a preference for surgery should be given an option of upper airway surgery [218]. Upper airway can be an important treatment option in patients and can help to resolve the concern of patient compliance to treatment modalities such as PAP and OAT therapy [219]. In order to be successful, upper airway surgeries require the proper patient selection, proper procedure selection, proper procedure execution, and proper skill set of the surgeon, recognizing the primary site of correctable probability, which is causing the OSA [218]. There are three main subdivisions for surgery alternatives. The first one is to reconstruct the upper airway including procedures such as nasal operations, uvulopalatopharyngoplasty (UPPP), expansion sphincter pharyngoplasty (ESP), palatal implants, tonsillectomy, tongue volume reduction, genioglossal advancement, and maxillomandibular advancement (MMA). The second surgical alternative is the use of a hypoglossal nerve stimulator. The stimulator is implanted in the chest and acts like a pacemaker, and the lead wire is implanted under the tongue at the hypoglossal nerve. The hypoglossal nerve innervates the tongue muscles (genioglossus, hyoglossus, and styloglossus). It sends signals to the tongue muscles causing a contraction of the tongue muscles, thereby keeping the oropharynx open. The third surgical alternative is to bypass the upper airway by doing the surgery such as tracheostomy [217]. With all the recent advancements in the technology and new surgical approaches, there is a data suggesting a satisfactory success rate of about 70 to 99% with combined surgical procedures [218].

8.9.6 Adjunctive Therapy

Adjunctive therapies include weight loss, bariatric surgery, positional therapy, myofunctional therapy, and pharmacological intervention. These therapies can be an immensely effective tool in your armamentarium, along with the primary treatment of OSA to improve the results drastically.

8.9.7 Bariatric Surgery

Bariatric surgery is indicated in patients with a body mass index (BMI) greater than or equal to 40 kg/m^2 or with BMI greater or equal to 35 kg/m^2 with potential comorbidities. Bariatric surgery can lead to reduction in the 75% of RDI [220]. When speaking of BMI, 35 kg/m^2 is equivalent to at least a height of 58 inches with a weight of 167 pounds. 40 kg/m^2 is equivalent to at least a height of 58 in. with a weight of 191 pounds ("body mass index"). A close and active follow-up with these patients is absolutely critical. According to a study conducted on 600 subjects, it concluded that a 10% weight gain predicted in a 32% increase in AHI and a 10% loss of weight predicted a 26% decrease in AHI [221]. According to the study conducted by Maree when a proper 16-week diet and exercise program was tailored for patients with mild to moderate OSA, the results showed significant improvement in variables such as neurobehavioral and cardiometabolic outcomes but no significant changes in sleep-disordered breathing [222].

8.9.8 Pharmacological Management

The exacerbation of existing OSA can be prevented by the avoidance of sedatives and alcohol. AHI and apnea length increased significantly resulting in greater hypoxemia in subjects with severe OSA [223]. There is insufficient literature supporting the role of drug therapy in OSA. Drug therapy is not much of clinical value [217]. Certain medications such as SSRI, strychnine, nicotine, progesterone, protriptyline, and acetazolamide have been used in the past to increase the upper airway tone but are no longer used [44]. Supplemental oxygen has limited role in treatment of OSA. Some of these medications that have been shown to have beneficial effects on the treatment of OSA have been constrained because of their side effects. In patients with residual sleepiness after CPAP, FDA-approved drug such as modafinil, which is a wake-promoting agent, can be of beneficial use [224]. Thyroxine can be beneficial in patients suffering with OSA with hypothyroidism [44].

8.9.9 Myofunctional Therapy

There is evident literature supporting the role of myofunctional therapy as a very effective adjunctive tool in healthcare provider's armamentarium to treat OSA. The severity of OSA can be reduced by 50% reduction of AHI in adults and 62% in children according to the study conducted by Camacho M [225]. Upper airway patency is a result of complex interplay of the balancing forces between negative inspiratory intraluminal suction as a result of diaphragm constriction and dilating forces of the pharyngeal muscles [219]. There have been unsuccessful attempts in improving the neuromuscular control of the abnormal pharyngeal dilator muscles with the aid of medications and nerve stimulators [219]. The myofunctional therapy is comprised of isotonic and isometric exercises that train the oropharyngeal structures such as soft palate, tongue, and facial muscles and the dilator muscles. The goal behind the myofunctional therapy is to increase the tonicity of the abovementioned muscles of oropharyngeal tissues and is to train the tongue to be positioned in the oral cavity at the right place, which is to place the tip of the tongue at the incisive papilla as the rest of the tongue is resting on the palate to encourage the nasal breathing as compared to mouth breathing. The results according to the study done by Camacho M were impressive. The results were as such; myofunctional

therapy reduced the snoring both subjectively and objectively. There was improved reduction in Epworth Sleepiness Score (ESS). Regardless of heterogeneity in the muscles of oral cavity and the nature of oropharyngeal exercises, there was a consistent improvement in the AHI and the subjective sleepiness scales [225].

8.9.10 Positional Therapy

There is wealth of data supporting the fact that the severity of OSA and the frequency of AHI events are far less in the lateral and non-supine positions as compared to supine position in OSA patients. What exactly happens in the lateral position that leads to increased activity of dilator muscle activity and opens up the airway is questionable. According to the study conducted by Matsuzawa Y, the constriction of the oropharyngeal was more severe in the supine posture [226]. The hypothesis was supported by the fact that gravity plays an evident role in it and the tongue will fall backward leading to stenosis of the oropharyngeal airway. According to the research study Tsuiki S, the velopharynx is the main contributing culprit site of obstruction and is the narrowest anatomical site in the pharynx and does keep changing with the different sleep positions [227]. The positional therapy thus can play a very important role as an adjunct therapy in addition to the primary treatment for OSA. By avoiding the supine posture, one can improve the subjective sleepiness and reduce the severity of AHI events in patients who have more events in the supine-related OSA [228]. Approximately 30–50% of patients with OSA can be treated with positional therapy alone [229]. A very interesting finding is that supine-dependent apnea is more prevalent in young, lean, and lower BMI patients. The same study suggested that non-positional obese patients became supine dependent after losing weight [228]. The various positional therapy methods are such as the use of the sleep position trainer [86], positional pillows such as cervical pillows, various bumper belts such as slumber belt and Rematee belts, and lastly the elevation of the head by 30°.

Conclusion

It has been an intriguing matter of debate which treatment option is better than the other. Our primary aim of this chapter was to show the correlation and improvements on immunologic and physiologic effects of dental sleep appliance therapy based on the improvements seen with CPAP therapy, and according to a randomized control study conducted by Phillips, it concluded that CPAP is more efficacious in reducing the objective variables such as AHI, arousal index, oxygen desaturation index, and respiratory distress index (RDI), but the adherence and compliance was better with OAT. The 24-h mean arterial pressure response was similar with both OAT and CPAP. However, neither one of the treatment options overall were able to improve the blood pressure. Similarly, other variables such as subjective sleepiness, driving simulator performance, and analysis of improved quality of life responded in a similar manner with both the treatment options. OAT was noted to be efficient in improving four general quality-of-life domains [230]. In a long-term study ranging 2.5–4.5 years, OAT remained effective in improving RDI, fatigue, sleepiness, sleep quality, blood pressure, cardiac rhythm, and quality of life [231]. We can conclude from the study that even though CPAP and OAT both work hand in hand in the treatment of OSA, the adherence and better compliance with OAT offsets the efficacy of CPAP because of inferior compliance eventually resulting in the similar effectiveness. Therefore, considering the comorbidities associated with OSA and being improved with CPAP, the treatment with OAT should also improve these OSA-related comorbid conditions.

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