Obstructive Sleep Apnea

A Multidisciplinary Approach

Peter M. Baptista
Rodolfo Lugo Saldaña
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Editors

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To my parents and sisters for their guidance and love.

To my wife, children, and grandchildren for their unwavering love, support, patience, and inspiration.

To all those patients and physicians with whom I have learned so much.

Peter M. Baptista

Dedicated to my dear parents and brother. Because I know they are always with me. My wife and my children, they are my engine, and lastly, all my former fellows, who are the fuel of that engine.

Rodolfo Lugo Saldaña

To my family for their constant warmth. My fellow editors, Peter and Rodolfo, for their great work and friendship.

Steve Amado

Foreword

With almost a billion people suffering from obstructive sleep apnea (OSA) worldwide, the enormous scientific output on all aspects of OSA, published in sleep journals, general medical journals, and textbooks, is not surprising. Scientific papers include original papers, systematic reviews, consensus documents, and guidelines.

Textbooks have covered all aspects of OSA that you can think of: epidemiology, pathophysiology, medical history, general and OSA-specific examination, diagnosis, sleep studies both in a sleep lab and at home, drug-induced sleep endoscopy, imaging, and all forms of nonsurgical and surgical treatment that are out there: CPAP, MAD positional therapy, myofunctional therapy, upper airway surgery, maxillofacial surgery, and upper airway stimulation. The authors of this book have done a great job by updating the current literature.

This book, however, offers much more. It is new and original by approaching OSA from a completely new perspective. This is the reason that I am so enthusiastic about it. It fills a gap, an unmet need. Allow me to explain.

OSA caregivers are increasingly confronted by patients and have patients referred by primary care physicians and by specialists from other disciplines with questions as to how far their other disease could be related to OSA. In addition, therefore, would it be a good idea to screen for OSA and treat it?

For instance, an ophthalmologist might refer a patient with glaucoma with the specific question: Is it useful to screen for sleep apnea in such a case? Similarly, a cardiologist who sees a patient with difficult-to-treat high blood pressure or arrhythmia poses the question: Should this patient be screened for OSA? A neurologist who has a patient who has suffered a cerebrovascular accident asks if this could be related to OSA and whether the patient in that case needs to be treated, even if he/she is asymptomatic. A general orthopedic surgeon who is seeing a patient for hip surgery needs to know if this patient has OSA and, if so, is this OSA a risk for general anesthesia. Should the surgery be postponed, with a sleep study done first before the surgery is performed? It is a known fact that patients undergoing bariatric surgery will suffer from OSA in up to 56% of cases. Is it needed to screen all the patients in the bariatric population for OSA and treat those with severe OSA with CPAP or not? In addition, should all patients with OSA who have had bariatric surgery have a repeated sleep study after their weight loss? In all these situations, is it needed to perform the most comprehensive form of sleep study (polysomnography) or are less comprehensive forms of sleep study (polygraphy) or even yet simpler

forms of screening sufficient? In this approach, one accepts that by using simpler screening devices, early-stage OSA might be missed, but these are not the patients who are at perioperative risk. Those are just examples; there are many relevant questions for doctors of other disciplines that we as OSA experts can help with.

The potential other manifestations of OSA in women are highlighted. The potential effect of OSA in urologic disease, in particular erectile dysfunction, is another factor so far not sufficiently studied. Should all men with erectile dysfunction be screening for OSA? Many psychiatric patients suffer from sleep disturbances; here, it might be difficult to distinguish between cause and effect. A recent theory for instance is that Vincent van Gogh, who wrote in many letters to his brother Theo about his sleep disturbances, suffered from sleep apnea, due to his retrognathia.

Another excellent chapter in this book deals with the role of OSA in metabolic disturbances. The chicken or the egg question is: Are patients with OSA often obese due to their disease or have they developed OSA because of their overweight? OSA caregivers see increasingly frequently children with OSA. Should we as ENT doctors screen all kids with hypertrophic tonsils for OSA before we remove them?

In sum, I regard this book as a highlight and a valuable addition to what we already have in OSA textbooks. We need to congratulate the editors Dr. Peter Baptista J., Dr. Steve Amado, and Dr. Rodolfo Lugo for this hallmark. They are to be congratulated for putting together a group of well-published international authors from all relevant disciplines. Read this book!

Amsterdam, The Netherlands Nico de Vries

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Introduction

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Peter M. Baptista and Guillermo Plaza Mayor

1.1 Introduction

Obstructive sleep apnea (OSA) is one of the most prevalent sleep disorders in the general population, with important pathophysiological sequelae that worsen the quality of life of patients, leading to an increase in traffic accidents and a higher mortality rate [1]. Therefore, early diagnosis and adequate treatment of OSA are of vital importance.

1.2 Sleep Disorders

Sleep is a physiological state to which the human being dedicates a third of his life. It is an active state, different from wakefulness, in which a series of physiological processes occur to maintain physical and mental balance.

Sleep is made up of a series of phases in 4–6 cycles that repeat throughout 7–8 h during the night. These phases are called REM (Rapid Eye Movement or rapid eye movement) and non-REM (non-Rapid Eye Movement). The representation of these is called hypnogram and is obtained by recording the brain electrical activity (electroencephalogram or EEG), eye movements (electrooculogram or EOG) and muscle activity (electromyogram or EMG).

Each sleep cycle consists of about 60–90 min of non-REM sleep and 15–30 min of REM sleep. By the age of 60, deep non-REM sleep starts to decrease, especially

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in men, until it disappears, while REM sleep remains stable throughout life. Each phase of sleep has specific functions, and therefore, its deprivation entails a series of consequences.

Sleep-related disturbances have been observed in up to 15% of the current population. Given the progressive impact on health and the difficult management of all sleep disorders, the American Academy of Sleep Medicine (AASM) in 2004 considered necessary a revision of the initial international classification of 1979 (ICSD international classification of sleep disorders [2].

This classification subdivided all disorders into two large blocks based on the patient's main symptomatology: dyssomnias, for all those disorders that lead to insomnia or excessive daytime sleepiness, which may be caused by intrinsic or extrinsic factors, and parasomnias, disorders that occur during sleep, sleep without producing the two previous symptoms. The ICSD-2 already describes seven large blocks, one of them dedicated exclusively to sleep-disordered breathing, and the last changes of the ICSD in 2014 gave rise to a third edition (ICSD-3) with minimal differences from the previous one [3].

International classification of sleep disorders (ICSD-3 2015)

1. Insomnia
2. Sleep-associated breathing disorders (SBD)
3. Hypersomnia of central origin
4. Sleep-wake circadian rhythm disorders
5. Parasomnias
6. Sleep-related movement disorders
7. Other sleep disorders, subclassified in:
   (a) Medical and neurological disorders associated with sleep
   (b) Substance-induced sleep disorders

1.3 Sleep Breathing Disorders (SBD) and Their Differential Diagnosis

In the previous ICSD classifications, SDBs belonged to the group of intrinsic sleep disorders. Currently, they constitute the second group of the ICSD-3 and can be summarized as follows [2, 4]:

1. Central sleep apnea syndromes
   (a) primary
   (b) secondary
2. Obstructive sleep apnea syndromes or Obstructive Sleep Apnea (OSA), previously known as OSAHS (obstructive sleep apnea–hypopnea syndrome)
   (a) in the adult
   (b) in the child
3. Hypoventilation disorders
   (a) idiopathic

   (b) central congenital
   (c) secondary
4. Sleep hypoxemia
5. Other nonspecific sleep-disordered breathing:
   (a) snoring
   (b) catathrenia

All these SBDs have in common a respiratory failure during sleep, which generally leads to continuous oxygen desaturations and a series of clinical manifestations that will give rise to severe metabolic, neurological and cardiovascular sequelae [5].

Polysomnography (PSG) is considered the reference or gold standard sleep test [6–14]. It consists of recording neurophysiological and cardiorespiratory parameters during sleep. It allows us to classify the different respiratory events, distinguish pathological from physiological apneas, obstructive from central apneas, or demonstrate the transition from apnea to breathing, in any sleep position [14].

Currently the relatively high and increasing prevalence of OSA [15] and consequent economic burden and limited access to PSG has led to the development of less costly procedures like home sleep apnea testing (HSAT) for patients with suspected obstructive sleep apnea (OSA) and has become widespread [16–18]. Clinical studies have shown that HSAT when used in uncomplicated patients with a high probability of moderate to severe OSA may provide similar diagnostic accuracy as PSG for moderate and severe OSA [19, 20]. Also, health care insurance companies and third-party payers accept HSAT diagnostic findings for payment of treatment for OSA with CPAP in many countries [16, 21, 22].

Therefore, according to the AASM (American Association of Sleep Medicine), HSAT is recommended as an alternative to PSG for diagnosis of OSA only in medically uncomplicated adult patients with a high pretest probability of moderate-to-severe OSA [23, 24]. With "medically uncomplicated" adult patients being defined as those with an absence of conditions associated with increased risk of nonobstructive sleep-disordered breathing (SDB), including significant cardiopulmonary disease, potential respiratory muscle weakness due to neuromuscular conditions, history of stroke or chronic opioid use, and no potential indications of a significant central sleep disorder, such as central sleep apnea, parasomnia, narcolepsy or severe insomnia [25].

1.4 Pathophysiology of OSA

Under normal conditions, during sleep, there are changes in the caliber of the upper airway (UA) that lead to a reduction in airflow with a stable airway in healthy patients but with a collapse in OSA patients with variable manifestations (Fig. 1.1). These changes are due to three main factors [26–30].

1. During non-REM sleep, hypotonia appears in the dilator muscles of the pharynx, which are the ones that while awake, maintain the caliber of the upper airway. In

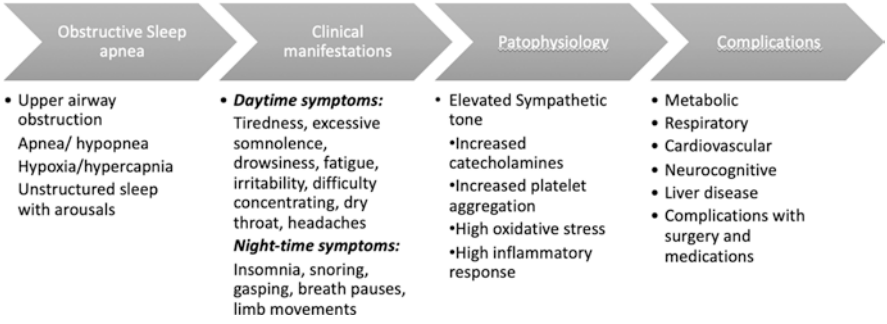

Fig. 1.1 Summary of consequences of OSA

patients with OSA, there is an airway collapse during inspiration, called dynamic collapse, due to negative pressures, and during expiration (static collapse) caused principally by muscular hypotonia.

2. Ventilatory function, lung volume and ventilatory response to hypoxia and hypercapnia decrease. In the OSA patient, airway collapse produces a state of hypoxemia and hypercapnia, which stimulates chemoreceptors. This produces overexertion of the inspiratory muscles, which stimulate the mechanoreceptors, activating the CNS, ending in microarousals or arousals as a defense mechanism to resume correct breathing. These states of hypoxemia, hypercapnia and continuous microarousals will give rise to a series of serious clinical consequences.
3. The anatomical reduction of the upper airway due to excess fat or small bony structure, or other anatomical factors cause a reduction in the caliber of the airway, and more so in a supine position. In patients with OSA, these anatomical factors, associated with general and functional characteristics, predispose to the collapse of the UA during sleep. Any structure of the UA that reduces the size of the pharyngeal lumen is also a factor that favors OSA. However, a narrower pharynx is not synonymous with OSA since women have a smaller UA than men and suffer from this problem less frequently, in a 2:1 ratio.

1.5 Phenotypes and Endotypes of OSA

In the last decade, Eckert et al. have made progress in understanding the pathophysiology of OSA, describing at least four phenotypes/endotypes that contribute to its pathogenesis and opened new therapeutic alternatives aimed at more personalized medicine [30–58].

The increased collapsibility of the UA is mainly due to the narrowing of the upper airway (anatomical factor). However, the fact that OSA does not occur during wakefulness demonstrates that it is not just an anatomical problem [30]. Thus, functional (nonanatomical) factors include:

- A lack of efficient muscle contraction during sleep (muscular factor).

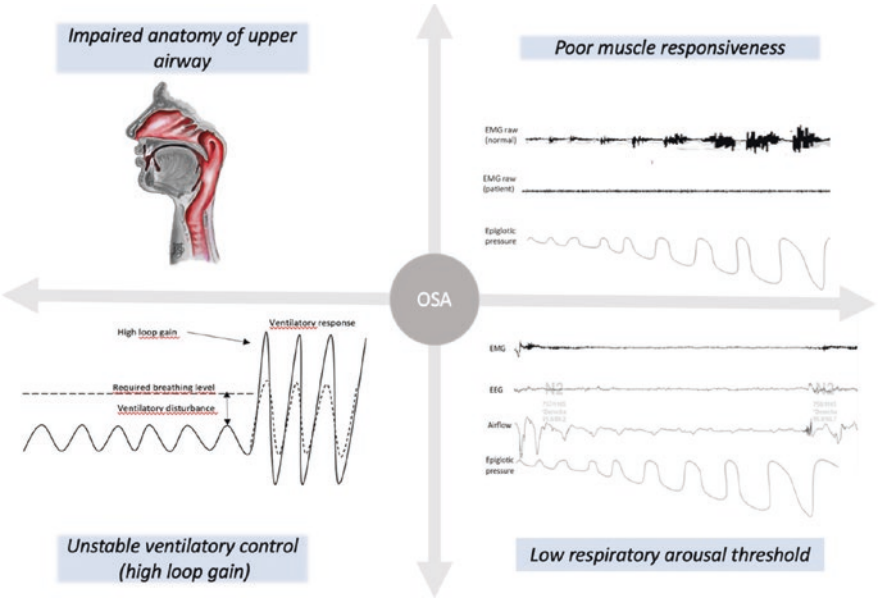

Fig. 1.2 Modification Eckert et al. [30–35]: four types of phenotypes/endotypes

- Instability of respiratory control (respiratory control or loop gain).
- A low threshold for arousal (Fig. 1.2).

The standard reference for quantifying airway alteration is done by calculating the collapse-inducing tissue pressure, the so-called critical collapse pressure (P_{crit}) [29]. It is defined as the minimum intraluminal pressure necessary to keep the collapsible segment of the UA open. However, a negative critical pressure characterizes normal UA. This P_{crit} value is lower in normal subjects than in snorers and OSA. The increase in P_{crit} may be due to anatomical abnormalities or functional or nonanatomical abnormalities.

1.5.1 Anatomical Phenotype

The factors that reduce the caliber of the UA involve an increase in its resistance, generating negative pharyngeal pressure during inspiration that predisposes it to collapse. Undoubtedly, altered UA anatomy is a critical factor in OSA. Anatomical factors range from nasal obstruction (nasal valve, septal deviation, turbinates), craniofacial anomalies (size and shape), anomalies of the oral cavity (macroglossia, tonsillar hypertrophy, abnormal hard and soft palate configurations), alterations of the pharynx at its three levels (nasopharynx, oropharynx and hypopharynx) and laryngeal alterations.

In addition, anatomical factors have an impact on other factors (muscular and neurological response). Micrognathia, for example, moves the base of the tongue backward and interferes with the genioglossus's muscular efficiency. Obesity is the leading cause of decreased pharyngeal space since adipose tissue deposition in the regions surrounding the UA directly reduces pharyngeal space. Additionally, it has been shown that fatty deposits in specific places, such as the tongue, can play an essential role in the collapsibility of the UA. Obese individuals also tend to have lower lung volumes and significantly lower functional residual capacity, which decreases the caudal traction of the trachea and predisposes to the collapse of the UA and its narrowing. Fat deposits between muscle fibers have also been described in obese subjects, reducing their contractile capacity.

The UA's size and shape also influence the pharynx's cross-sectional area. The smaller size of the craniofacial structures has shown to be a critical anatomical factor in OSA patients of Asian descent. Additionally, other nonanatomical factors, such as edema, may be involved in the collapsibility of the UA and, consequently, in the appearance of obstructive events.

1.5.2 Muscle Factor

Far from being a rigid structure, the UA's permeability depends mainly on its muscles' dilator activity. Within the muscle factor, three key elements have been defined in the pathophysiology of OSA: Neural control, response and muscle efficiency.

Given its location and participation in multiple functions (speech, swallowing and breathing), the neural control of the muscles is highly complex. The onset of sleep dramatically influences the neural drive of these muscles. The primary dilator muscle of the UA, the genioglossus muscle, is mainly cyclically activated and receives neural input from the brainstem, the UA mechanoreceptors and changes in hypoxia and $PaCO_2$. The sum of these impulses results in the activation of the genioglossus muscle during inspiration to counteract the negative pressure exerted by the inspiratory muscles and thus to prevent the collapse of the UA. The onset of sleep and changes highly influence this activity during the different sleep phases (progressively decreases during N1, N2 and REM, increases in N3). Other muscles, such as the tensor veli palatine, have a more tonic activity that decreases at the onset of sleep and is not as phase dependent. Apart from the neural response to sleep onset and its different sleep phases, the pharyngeal musculature can increase its activity in response to $PaCO_2$ and pressure changes. This concept refers to muscle response. It has been reported that muscle activity does not increase in the face of obstruction in a third of patients with OSA. Finally, muscular efficiency converts the neural input received by the airway dilator muscles into a contraction that will increase flow in response to an obstructive event.

Additionally, it has been shown that even within OSA patients, there are different patterns of muscle efficacy. While some patients have an adequate increase in muscle activity against obstruction (good muscle response) and good effectiveness in dilating the UAW, others show a low muscular response to obstruction and therefore

fail to open the UA (low muscular efficiency). Additionally, there are patients who, despite having an excellent muscular response, do not have UA dilation and therefore have low muscular efficiency.

In addition, the predominance in patients with OSA of type IIA muscle fibers has been described, compared to type I, which presents little resistance to prolonged anaerobic efforts, significantly reducing their performance during hypoxemia [50].

Therefore, a therapeutic option would be the "training" of these muscles through exercises proposed with myofunctional therapy. Other therapeutic options would be the hypoglossal implant or myotonic drugs such as desimipramine [51] or atomoxetine/oxybutynin [52, 53].

1.5.3 Loop Gain

After an obstructive event, there is a hyperventilation of a variable amplitude that depends on the individual. An elevated response to hypoxia and hypercapnia secondary to apnea due to hypersensitivity of the chemoreceptors will lead to hyperventilation, decreased $PaCO_2$ and the efferent impulse of the respiratory centers that will give an excessive response (very often present in the patients with severe OSA) and that will determine the instability of the respiratory system, in an increase in collapsibility and therefore favor the appearance of new obstructive apneas. Alternatively, postapnea hyperventilation can decrease $PaCO_2$ and favor central apneas, which explains the coexistence of obstructive and central episodes in the same patient [32].

The sensitivity of the respiratory center can be quantified as the increase in ventilation in response to an alteration and return to homeostasis (loop gain). Therefore, a high loop gain is considered a negative aspect of UA collapsibility, while a low loop gain, by stabilizing respiration, can prevent the collapse of the UA and is therefore considered positive. One-third of OSA patients are considered to have increased loop gain. Like the concept of decreased muscle efficiency, it may be especially important in patients with mild-moderate OSA.

In cases like these, CPAP may not be effective [55], and there will be a need for other therapeutic options like respiratory re-education [49], additional oxygen therapy [55], or UA surgery [56].

1.5.4 Awakening Threshold

Apneas produce a transient or arousal awakening that creates the characteristic fragmentation of sleep but favors the opening of the UA due to muscle activation. However, despite this effect, which has been considered protective until now, it has been shown that it can have a harmful effect for the patient. Awakening produces hyperventilation that can promote ventilatory instability and thus promote collapse. Each person has a different threshold for awakening, which can change depending on the stage of sleep. Usually, the N3 phase has a high wake-up threshold, implying

little respiratory variability and, as has been explained, greater activation of the UA muscles; therefore, fewer obstructive events occur. Thus, in general, a high arousal threshold is considered protective of the UA's patency.

This is why, in some cases of OSA, mild hypnotics such as zopiclone or zolpidem can reduce the awakening threshold without modifying muscle tone [57].

1.6 From Phenotypes to Endotypes

Although initially described by Eckert as phenotypes, in OSA, there are underlying endotypes following the PALM (P_{crit}-arousal-loop-muscle) classification, which are the ones that will determine the most appropriate treatment for each patient, following increasingly personalized methods.

As we determine each patient's endotype, we can offer a more precise and personalized treatment, increasing adherence to CPAP and the supply of surgical and pharmacological treatments.

However, for this personalized approach, it is necessary to determine the P_{crit}, the loop gain and the awakening threshold through certain studies that, at this moment, may be complex [58–63].

1.7 Factors Defining Severity of OSA

In OSA, the most widely accepted marker of the severity of disease is the apnea–hypopnea index (AHI), which represents the number of apneas and hypopneas per hour of sleep. The AHI is used not only to diagnose OSA (AHI > five events/h together with daytime hypersomnia or other clinical manifestations) but also to classify the severity of the condition: mild OSA (AHI between 5 and 15), moderate OSA (AHI between 16 and 29) and severe OSA (AHI equal to or greater than 30).

It has been argued that this classification is arbitrary because there are scarce data to assess the relationship between AHI and the importance of daytime signs and symptoms. However, the usefulness of AHI as a predictor of cardiovascular morbidity and mortality has recently been demonstrated in long-term cohort studies [64–70].

Oxygen desaturation, sleep interruption and total sleep time are important pathological parameters associated with apnea episodes. However, it is possible that these factors could serve as biomarkers of OSA severity, but there is still little data in the literature. However, until a specific "pattern marker" is widely accepted, the AHI can be considered the best option to define the severity of OSA as sleep-disordered breathing.

OSA is considered part of an uninterrupted pathophysiological process in which the upper airway (UAV) presents a high resistance to airflow [71] (Fig. 1.3). Initially, this dysfunction does not present symptoms or manifests through snoring (susceptibility stage). Subjects predisposed to develop OSA probably have a high burden of

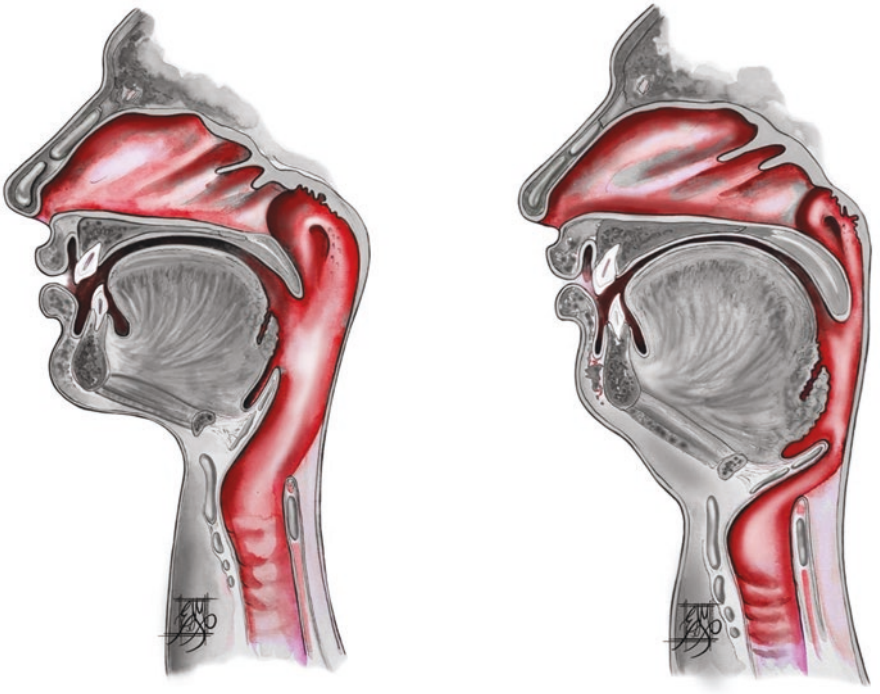

Fig. 1.3 Observe the smaller airway in the right figure of a patient with OSA compared to a normal patient, due to collapse of the airway, enlarged palate and tongue

susceptibility of unknown origin. As individuals age and reach adulthood, in addition to weight gain, epigenetic factors may accentuate the collapsibility of the UA.

In the presymptomatic stage, snoring worsens and nocturnal apneas appear; however, the individual may not report any limitations in his daily activities.

If there isn't any interruption, the patient develops nocturnal clinical manifestations (e.g., nonpositional snoring, bed partner reported apneas, nocturia) and daytime (morning headache, asthenia, excessive sleepiness) that are increasingly disabling (stage of the clinical disease). At this phase, comorbidities may develop at an early age compared to populations without OSA, in a context that we can consider accelerated aging. If the illness is not identified and treated, the natural evolution is directed toward disability and premature death (recovery stage, disability or death), mainly due to cardiovascular problems.

Most adults with OSA are overweight or obese [72]. Obesity is related to decreased thoracic cage distention capacity, reduced lung volumes and increased upper airway resistance. Furthermore, cervical fat also facilitates the collapse of the upper airway during sleep. These factors increase the frequency and duration of nocturnal respiratory events. On the other hand, there is a linear relationship between body weight and AHI. However, it has been mentioned that since obesity itself leads

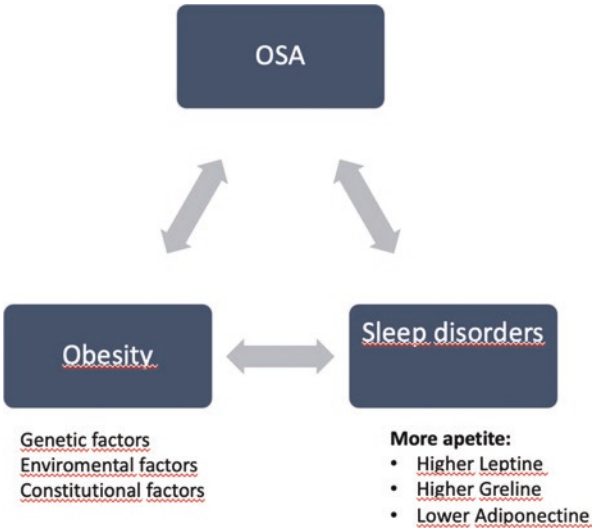

Fig. 1.4 Relationship between OSA, obesity and sleep disorders

to increased cardiovascular morbidity and mortality, it is most likely that excess weight and not the AHI value is responsible for the increased morbidity and mortality in patients with OSA.

The prevalence of OSA in obese patients exceeds 30%; in cases of morbid obesity, it reaches 98%. It is estimated that a 10% weight gain increases the AHI by 32%, while a 10% reduction can improve the AHI by 26% [72]. Numerous studies have shown that weight gain is related to the development of OSA or its worsening [73]. Obesity aggravates OSA because the increase in fat in the UA favors the collapse of its lumen. The cervical circumference has been shown to be a better predictor of OSA severity than body mass index (BMI); also, adults with OSA have high levels of leptin (a satiating hormone in thin individuals) and ghrelin (appetite-stimulating hormone) and lower levels of adiponectin (an anti-inflammatory cytokine that increases insulin sensitivity). A vicious circle exists where obesity and OSA worsen each other (Fig. 1.4).

The following chapters of this book will review in a comprehensive way the main medical consequences of suffering from OSA in adults in diverse fields of medicine.

1.8 Mortality

Death is the most determining "result" or final effect of the natural history of any chronic medical entity. Premature death, however, comes to represent the sum of "unhealthy" risk factors that aggravate the progression of the index disease, in this case, OSA (Fig. 1.5). In sleep medicine, some clinical signs or symptoms, such as drowsiness or snoring, are easy to measure in routine practice and the development of a clinical trial. However, cardiovascular events and death are subject to comorbid conditions that make it more challenging to establish the definitive role of OSA.

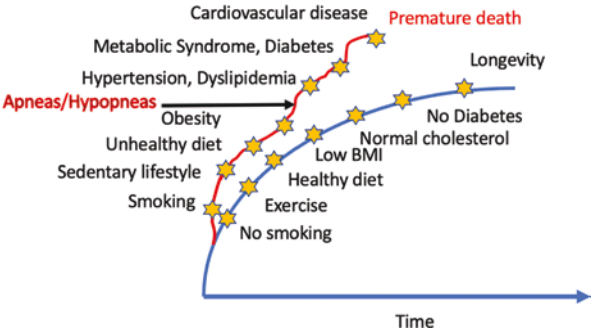

Fig. 1.5 Healthy life path vs. unhealthy trajectory that shortens lifetime

In clinical trials, death is the event with the most significant weight, so various studies conducted in the field of cardiology with antihypertensives have shown that these drugs produce a slight decrease in blood pressure without modifying the function of the left ventricle. Since these drugs have been shown to increase survival, they have been included in heart failure treatment guidelines, not so much because they lower blood pressure, but because of their effect on the most potent health outcome, death. In the field of sleep medicine, these studies designed to evaluate the impact of OSA treatment on mortality still need to be defined [74].

With time, we will have better knowledge of this disease, and death, even though inevitable, will be postponed.

Take-Home Message

- Obstructive sleep apnea (OSA) is one of the most prevalent sleep disorders in the general population, with critical pathophysiological sequelae that worsen patients' quality of life, leading to increased traffic accidents and a higher mortality rate.
- Sleep-related disturbances have been observed in up to 15% of the current population.
- These disorders have in common a respiratory failure during sleep, which generally leads to continuous oxygen desaturations and a series of clinical manifestations that will give rise to severe metabolic, neurological, and cardiovascular sequelae.

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Pathophysiology of Obstructive Sleep Apnea

2

Sara Op de Beeck, Eli Van de Perck, and Olivier M. Vanderveken

2.1 Introduction

Although several risk factors are known to be related to the development and severity of obstructive sleep apnea (OSA), the true underlying causes (endotypes) of OSA remain unknown [1, 2]. OSA characterization can be based on five different data levels [3]:

1. *Risk factors and environment*: obesity, medications, allergens, alcohol. This data level can be treated with, e.g., lifestyle modification such as weight loss or alcohol reduction.
2. *Clinical features*: cardiovascular disorders, age, metabolic disorders, cancer, gender, OSA symptoms, neurocognition. This data level can be targeted using integrated care mechanisms, risk stratification, etc.
3. *Pathophysiology*: upper airway anatomy, muscle responsiveness, sleep stability, lung volume, ventilatory drive, arousal threshold. This endotypic group is the target of the current chapter.
4. *Biologic features*: neurohormonal changes, inflammation, fibrinolytic imbalance, oxidative stress, endothelial dysfunction and age. These features can partly be captured using different biomarkers such as IL-6, IL-10 and CRP.
5. *Genetics and genomics*: pharmacogenetics, epigenetics, RNA and DNA.

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In clinical practice, the data levels of "clinical features" and "risk factors and environment" are most commonly used. The current chapter will focus on the pathophysiological data level.

OSA pathophysiology can be subdivided into anatomical and physiological endotypic traits (Fig. 2.1). The site of upper airway collapse is an anatomical trait. The physiological traits are ventilatory control stability, pharyngeal muscle responsiveness and arousal threshold. Upper airway collapsibility can be categorized into both categories. The relative contribution of these traits varies between patients and determines the optimal treatment strategy for each patient [4, 5].

This chapter will discuss the measurement techniques (Fig. 2.2) for each of these traits and their influence on treatment outcomes (Table 2.2).

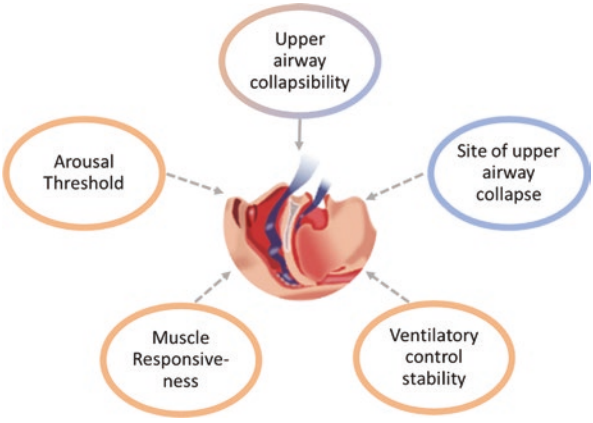

Fig. 2.1 Overview of obstructive sleep apnea (OSA) pathophysiology. The site of upper airway collapse is an anatomical trait (blue), while arousal threshold, muscle responsiveness and ventilatory control stability are physiological traits (orange). Upper airway collapsibility can be categorized into both categories

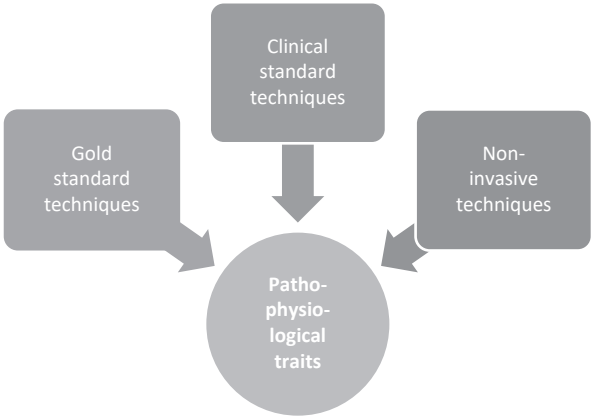

Fig. 2.2 Each pathophysiological trait can be measured using a gold-standard, clinical standard or noninvasive measurement technique

2.2 Site and Pattern of Upper Airway Collapse

The upper airway can collapse at different sites: at the level of the soft palate, tonsils, tongue base, lateral walls and/or epiglottis (Fig. 2.3). To assess the site of upper airway collapse, three different techniques can be used: natural sleep endoscopy (gold standard), drug-induced sleep endoscopy (clinical standard) and flow shape analysis (noninvasive measurement technique) (Fig. 2.4).

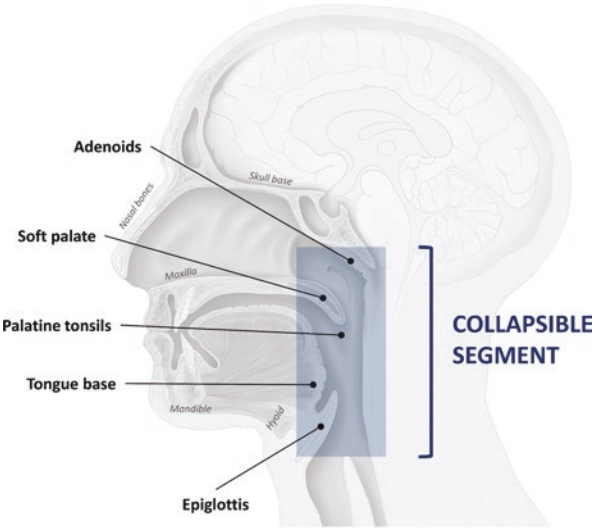

Fig. 2.3 The lack of a bony framework renders the upper airway susceptible to collapse, which can occur at different levels

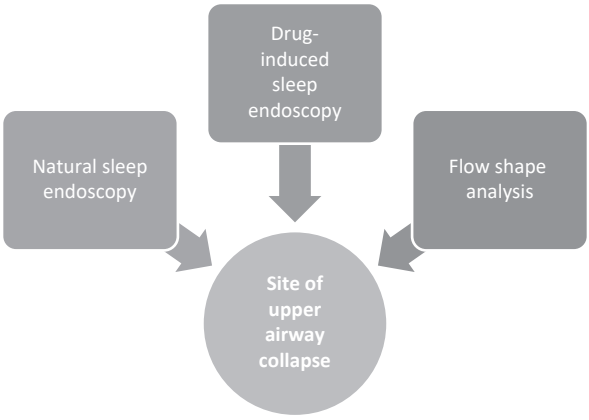

Fig. 2.4 The site of upper airway collapse can be assessed using three different techniques: natural sleep endoscopy (gold standard), drug-induced sleep endoscopy (clinical standard) and flow pattern analysis (noninvasive measurement technique)

2.2.1 Natural and Drug-Induced Sleep Endoscopy

The gold-standard measurement technique to assess the site of upper airway collapse is natural sleep endoscopy (NSE). During overnight sleep, the upper airway is assessed with endoscopy, and the site, pattern and degree of upper airway collapse are determined [6, 7]. As natural sleep endoscopy is labor-intensive, challenging to perform and unpleasant to undergo, this technique is not used in clinical practice. Instead, drug-induced sleep endoscopy (DISE) is used to determine the site of upper airway collapse.

During DISE, sleep is mimicked using sedative agents [8, 9]. Sedation is usually induced using an intravenous injection of midazolam and/or propofol [8]. A flexible endoscope is inserted through the nose to visualize the upper airway (Fig. 2.5). During the DISE procedure, heart rate and oxygen desaturation are continuously monitored. The procedure is started in the supine position. Several maneuvers such as a jaw thrust or lateral head rotation can be adopted to simulate therapeutic effects [10].

Upper airway collapse is scored using a predefined scoring system. Several scoring systems are currently used. A potential scoring system is shown in Fig. 2.6 [11]. At each level, the degree of collapse is graded as absent, partial or complete. If a

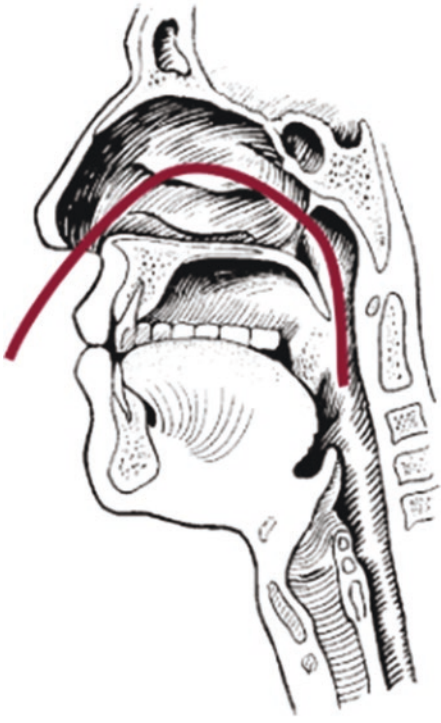

Fig. 2.5 During drug-induced sleep endoscopy, the upper airway is assessed during mimicked sleep with an endoscope inserted through the nose. (Adapted from Vroegop [12])

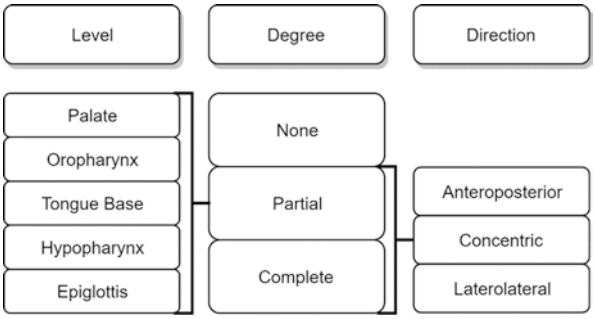

Fig. 2.6 Scoring system used in the Antwerp University Hospital (UZA). For each level (palate, oropharynx, tongue base, hypopharynx and epiglottis), the degree (no, partial or complete collapse) is determined. For partial and complete collapse, the direction is assessed as either anteroposterior, concentric or laterolateral. (Adapted from Verbruggen et al. [13])

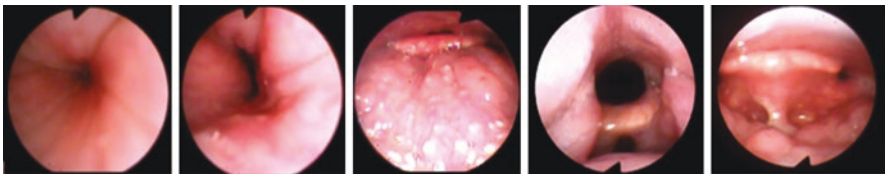

Fig. 2.7 Examples of DISE scoring. From left to right: complete concentric collapse (CCCp) at the level of the palate, complete laterolateral collapse at the level of the oropharynx, complete anteroposterior collapse at the level of the tongue base, partial laterolateral collapse at the level of the hypopharynx and complete anteroposterior epiglottic collapse

partial or complete collapse is present, the direction of collapse is scored as either anteroposterior, concentric or laterolateral. Examples of DISE scoring are shown in Fig. 2.7.

Agreement between NSE and DISE findings, only using a bolus injection midazolam, was found to be highest at the level of the epiglottis (92%), followed by the oropharynx lateral walls (89%), palate (77%) and tongue base (69) [14]. The collapse direction at the level of the palate and epiglottis showed an agreement of 89% and 92%, respectively. Complete concentric collapse at the palate level (CCCp) was seen more frequently during DISE than to NSE [14].

2.2.2 Flow Shape Analysis

Recently, noninvasive measurement techniques to determine the site of collapse were developed using the airflow signal.

Negative effort dependence (NED), defined as the percentage reduction in inspiratory flow from peak to plateau (characteristic of flow-limited breaths), is

associated with the upper airway collapse site [15]. A posteriorly located tongue, defined as narrowing of the airway due to posterior displacement of the tongue, is associated with a small NED, reflected by a somewhat "flat" flow shape. Isolated palatal collapse, i.e., collapse without the involvement of the tongue, and lateral wall collapse are associated with moderate NED, and epiglottic collapse with high NED, reflected by a large and sharp inspiratory peak [15]. The presence of high NED during epiglottic collapse has recently been confirmed during DISE [16].

Azarbarzin et al. [17] showed it is possible to identify epiglottic collapse and palatal prolapse using nasal pressure airflow shape. Epiglottic collapse was characterized by a rapid fall in inspiratory flow (discontinuity index), high variability in both inspiratory and expiratory flow (inspiratory and expiratory jaggedness) and reduced tidal volume (expressed as the ratio of peak expiratory flow and tidal volume). Palatal prolapse, defined as "ballooning" of the palate into the nasopharynx during expiration, was shown to be associated with expiratory flow limitation quantified using the expiratory flow limitation index (EFLi) [18].

Recent research could also demonstrate the potential of predicting the site collapse during DISE from a separate routine baseline PSG. In this model, CCCp and lateral wall collapse were characterized by scoopy, left skewed breaths and opposed to tongue base and epiglottic collapse [19].

2.3 Upper Airway Collapsibility

Upper airway collapsibility is the second pathophysiological trait and can be regarded as both an anatomical and physiological trait (Fig. 2.8). The higher the upper airway collapsibility, the easier the upper airway will collapse and the narrower the upper airway tends to be [20]. As such, patients with a higher collapsibility will be more prone to suffer from apneas and hypopneas and will inherently be at greater risk of developing OSA [21, 22].

Upper airway collapsibility is influenced by obesity [21] and greater in supine compared to lateral position [23–25], but the influence of sleep stage [23–27] and sex [28, 29] is ambiguous. Collapsibility was shown to differ between REM and NREM stages [26, 27], although other studies did not seem to find any differences [23–25]. Sex alone does not seem to influence upper airway collapsibility [28, 29]. However, if corrected for obesity, women tend to have a lower airway collapsibility [29].

In patients with small NED values, the upper airway likely behaves as a Starling resistor [30–33]. In a Starling resistor model, the upper airway is modeled as a collapsible segment surrounded by the noncollapsible nasal and tracheal segments [34]. If the upstream pressure at the nasal segment is lower than the critical closing pressure (P_{crit}), as defined by the surrounding tissue, the upper airway will collapse. Flow limitation will occur if the downstream pressure is lower than P_{crit}, [26, 32, 33]. However, in patients with large NED, the Starling resistor might not be the best model to describe the upper airway. Alternative models are thus needed, and the

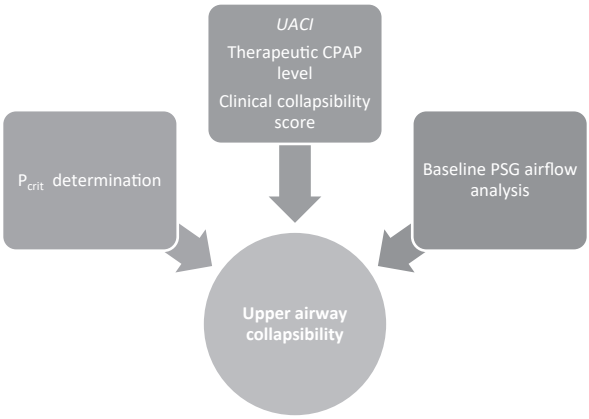

Fig. 2.8 Upper airway collapsibility can be assessed using different techniques: by determining the critical closing pressure of the upper airway or P_{crit} (gold standard) or using flow shape analysis (noninvasive measurement technique). Currently, there is no clinical standard measurement method that can be used for upper airway collapsibility assessment, yet the therapeutic CPAP level, clinical collapsibility score and determining the upper airway collapsibility index (UACI) using a wakefulness test holds promise for future clinical application

Starling resistor might not be usable as a universal model for upper airway collapsibility [30, 35, 36].

Upper airway collapsibility can be measured using the gold-standard technique, which involves determining the critical closing pressure using upper airway pressure drops. However, due to the rigorousness of this method, this technique is not used in routine clinical practice. Furthermore, it has been shown feasible to use brief negative airway pulses in awake patients to determine the upper airway collapsibility index [37, 38]. While this technique shows great potential for application in clinical practice, as it can be performed in awake patients, invasive techniques are still needed, including the catheter insertion. Regarding other potential clinical measures, the therapeutic CPAP level predicts upper airway collapsibility [39], and a clinical score was developed to distinguish between male patients with high and low collapsibility [40]. Recently, however, a new innovative, noninvasive technique was developed to estimate upper airway collapsibility using the airflow signal as recorded during diagnostic polysomnography (Fig. 2.8).

2.3.1 Critical Closing Pressure (P_{crit})

The gold-standard measurement technique involves determining the critical closing pressure (P_{crit}) using upstream (nasal) pressure drops. P_{crit} is defined as the minimal nasal pressure at which the upper airway remains patent [33]. To measure P_{crit}, the pressure at the nose is repeatedly lowered while simultaneously monitoring airflow. After several pressure drops, a linear regression line is fitted through the different

sample points. The physiological P_{crit} is defined as the zero-flow intercept from the linear portion of the flow-pressure curve [41].

P_{crit} can be measured under active (active P_{crit}) or passive (passive P_{crit}) conditions. The first reports on measurements of P_{crit} describe active P_{crit} [22, 32, 33]. To measure active P_{crit}, the pressure is first dialed up to the holding pressure, defined as the pressure at which all apneas, hypopneas and flow limited breaths are abolished, during steps of 5 min each [33]. The holding pressure equals the "effective continuous positive airway pressure (CPAP)" or "upper airway opening pressure" [26, 42]. In a next step, the critical closing pressure is determined. Active P_{crit} is determined by gradually lowering the upper airway pressure. At each pressure level, flow is measured. This is repeated until no stable breathing can be achieved anymore. The results are then plotted on a pressure–flow curve, and a linear regression line is estimated. The x-intercept of this line, where flow is zero, is the critical closing pressure [32, 33]. To assess passive P_{crit}, flow is dropped to different pressure levels from the holding pressure. After each pressure drop, the pressure is set back to the holding pressure [4, 43]. In contrast to the active method, the passive method minimizes the recruitment of upper airway muscles.

Upper airway collapsibility can also be quantified using ventilatory parameters. The higher the ventilation at a certain nasal pressure, the less collapsible the airway and vice versa [4, 43]. This method is based on the measurement methods that were previously described in the literature for P_{crit} [4, 25, 32, 33]. However, instead of measuring pressure, flow is measured. Briefly, to assess both passive and active V_0 (ventilation at 0 cm H_2O) in one run, the mask pressure is first dialed up to the holding pressure. Passive V_0 is determined by dialing down the pressure to 0 cm H_2O during 5 breaths. To determine active V_0, the pressure is lowered from the holding pressure until the minimal pressure level ($CPAP_{min}$) is achieved at which no arousals occur. Active V_0 is then determined by an active drop [43].

Recently, P_{crit} could be measured during DISE, showing a more reliable P_{crit} measurement using the ventilation method. Furthermore, patients with CCCp showed a wide range of P_{crit} values, indicating no clear association between P_{crit} and CCCp [44].

2.3.2 Clinical Techniques

In awake patients, upper airway collapsibility can be assessed with the upper airway collapsibility index (UACI). The UACI is measured by applying brief (250 ms) pulses of negative airway pressure (−12 cm H_2O) during awake early inspiration and is calculated as the pressure difference between the choanae and the epiglottis during the brief pulse [37, 38]. Although collapsibility in awake conditions is systematically lower compared to during sleep, the UACI is significantly correlated with P_{crit} measurements [38]. A recent study even showed that the UACI value could separate individuals with subatmospheric P_{crit} values from individuals with supraatmospheric values [37]. While this technique shows great promise as a potential clinical method, the invasiveness and used materials hamper its applicability.

Another method that could be applied in clinical practice was recently developed by Genta et al. [40]. Combining NREM-OAI/AHI, waist circumference, obstructive apnea duration and REM-AHI in a clinical score was able to predict a P_{crit} >2.5 cm H_2O. A clinical score ≥3 showed a sensitivity of 90.9% and specificity of 84.3%, highlighting the potential clinical value of this method. Furthermore, in patients (previously) treated with CPAP, the therapeutic CPAP level can also be used as a surrogate for collapsibility [39]. Specifically, a therapeutic CPAP level of ≤8 cm H_2O showed a sensitivity of 75% and specificity of 91% in an independent dataset for having a mildly collapsible upper airway.

2.3.3 Baseline PSG Airflow Analysis

Several problems arise in using the above explained gold-standard methods to measure $P_{crit,}$ including the requirement of specialized equipment, the invasiveness of the technique and the need for trained personnel overnight. No clinically applicable method is currently available in routine clinical practice.

A noninvasive method to determine collapsibility was recently developed by Azarbarzin et al. [45]. They showed that active P_{crit} was significantly correlated with both peak and mid-inspiratory flow (as measured during natural NREM sleep) as well as active $\dot{V}_{max}$, the maximal flow at atmospheric pressures under active conditions. The rationale of this study was based on the construction of the pressure–flow curve and the assumption that a change in pressure (*x*-intercept) is partly captured by the flow (*y*-intercept) [45].

Alternatively, ventilation parameters can be used to define collapsibility. The minimal ventilation at normal ventilatory drive is defined as passive ventilation ($V_{passive}$). $V_{passive}$ is the ventilation at which no additional muscles are recruited. By contrast, ventilation at maximal ventilatory drive, just preceding arousal, is defined as active ventilation (V_{active}). At V_{active}, upper airway muscles are optimally recruited. $V_{passive}$ thus reflects the inherent collapsibility of the upper airway during sleep, while V_{active} considers upper airway muscle activity [4, 43, 46].

2.4 Ventilatory Control Stability

The most commonly used ventilatory control parameter is loop gain, a measure of the sensitivity of the ventilatory chemical control system. Loop gain can be seen as a central component of sleep apnea and is calculated as the ratio of the ventilatory response and its associated ventilatory disturbance (Fig. 2.9) [47]. A loop gain at a phase angle of 180° between 0 and 1 will result in a stable system. A ventilatory disturbance will lead to a ventilatory response with a smaller magnitude than the initial disturbance, eventually returning to the original ventilation level. A loop gain closer to 0 will lead to a faster return to the initial ventilation level, signifying a more stable control system. A loop gain of 1 results in a cyclical ventilation,

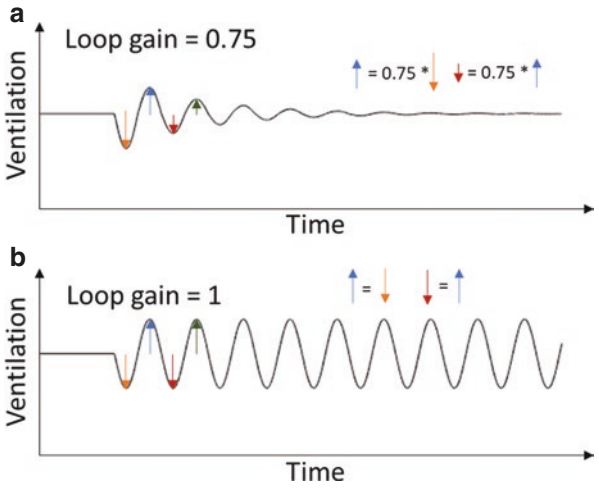

Fig. 2.9 Loop gain is defined as the ratio of a ventilatory disturbance and its associated ventilatory reaction. (**a**) Example of ventilation with a loop gain equaling 0.75. A ventilatory disturbance (orange arrow) causes a ventilatory reaction (blue arrow) with a magnitude of 75% of the initial (orange arrow) disturbance. In turn, the ventilatory response (blue arrow) becomes a ventilatory disturbance, causing a ventilatory reaction (red arrow) of 75% of its magnitude, finally resulting in a restoration of the initial ventilation. (**b**) Example trace of loop gain of 1. A ventilatory disturbance in a system with a loop gain of 1 will result in an unstable system. A loop gain of 1 will cause a ventilatory response (blue arrow) with the same magnitude as the initial disturbance (orange arrow). (Based on Wellman et al. [47])

fluctuating around the initial ventilation level. A loop gain higher than 1 will cause highly unstable breathing, as the ventilatory response will be higher than the ventilatory disturbance. If the loop gain is ≥1, a return to the initial ventilation is only possible with external measures (e.g., arousal).

The major determinants of loop gain are plant gain and controller gain. Controller gain determines the response to a change in concentration of CO_2, while plant gain is the amount that CO_2 changes for a given change in ventilation [48].

Loop gain can be measured using a gold-standard measurement technique or using recently developed noninvasive measurement methods (Fig. 2.10). Currently, no clinical standard method is available. However, recently Messineo et al. showed that breath-holding maneuvers during wakefulness is associated with loop gain [49]. Patients with a higher loop gain showed a shorter maximal breath-hold duration and a more significant ventilatory response to 20-s breath-holds [49]. This technique, as such, shows promise for future clinical applications.

2.4.1 Airflow Pressure Drops

The gold-standard measurement technique involves the use of airflow pressure drops. As the upper airway has a collapsible segment, the upper airway can be held

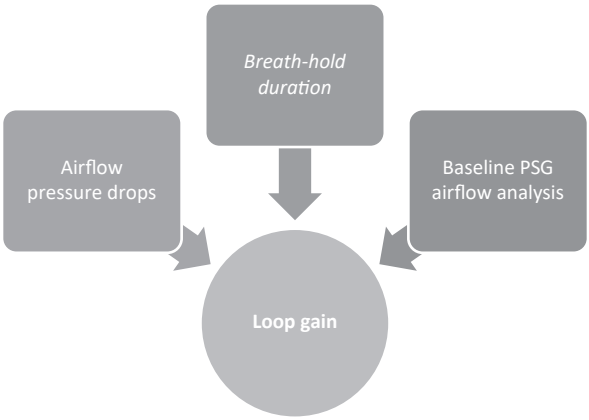

Fig. 2.10 Loop gain can be measured using airflow pressure drops (gold standard) or using PSG flow analysis (noninvasive technique). Currently, no clinical measurement method is available, but recently Messineo et al. [49] developed a new technique using breath holding

open using positive pressure. Like the gold-standard method to determine the P_{crit}, determination of loop gain also requires pressure drops.

To measure loop gain, the mask pressure (P_{mask}) is abruptly lowered by decreasing the applied pressure from the holding level, defined as the minimal pressure needed to keep the upper airway patent. After a minor delay, the upper airway muscles will be recruited to increase airflow and partially restore ventilation. Under the reduced pressure, a new steady-state ventilation will be achieved. The difference between the normal ventilation and the new steady state is called the disturbance. Due to this suboptimal new steady state, CO_2 will accumulate in the body and ventilatory drive increases. The mask pressure is dialed up again to the normal level to measure this ventilatory drive. The ventilatory sensitivity will cause an overshoot in ventilation (response). Loop gain is defined as the ratio of the response and the disturbance [4]. In general, loop gain is measured during NREM sleep and tends to be lower in REM compared to NREM sleep [50].

2.4.2 Baseline PSG Airflow Analysis

The rationale behind the noninvasive technique using flow signals to measure loop gain, is that the apneas and hypopneas that naturally occur during sleep, will cause disturbances in ventilation [51]. These disturbances will cause a change in the ventilatory drive. The magnitude of this change is determined by loop gain (ratio of response and disturbance). By fitting a ventilatory control model, adjusted for changes in ventilatory drive due to arousals and/or changes in chemical concentrations, loop gain can be calculated from a standard baseline polysomnography [51].

A second ventilatory control stability parameter is the ventilatory response to arousal, defined as the increase in ventilatory drive attributed to arousal from sleep [51, 52]. The ventilatory response to arousal cannot be explained by an increase in chemical drive, which is attributed to loop gain [46].

2.5 Pharyngeal Muscle Responsiveness

During the transition between wake and sleep, the odds of collapse are higher due to a decrease in muscle activity. Pharyngeal muscle responsiveness is defined as a patient's ability to prevent or overcome upper airway collapse by recruiting the upper airway muscles during sleep. In addition, high pharyngeal muscle responsiveness implies strong muscle recruitment to keep the upper airway patent, reducing the chances of upper airway collapse.

Pharyngeal muscle responsiveness can be measured using a gold-standard technique involving diaphragm EMG measurements using pressure drops or flow analysis techniques (Fig. 2.11).

2.5.1 Airflow Pressure Drops

As for the other traits, the gold-standard technique to measure pharyngeal muscle response requires pressure drops. By dropping the upper airway pressure from the holding pressure to suboptimal pressures, ventilation will also suddenly drop. This drop in ventilation will cause an increase in ventilatory drive achieved by an increase in pharyngeal muscle activity. In turn, the increased muscle activity will lead to rise in ventilation toward a new, suboptimal steady-state ventilation.

The gold-standard method to measure muscle activity uses intramuscular electrodes. In this way, muscular activity can be determined as the response to the intraluminal pressure associated with lowering the applied pressure from the holding pressure [53].

Alternatively, ventilation measures during airflow pressure drops can define upper airway muscle responsiveness. Using this technique, the difference between the ventilation immediately after the airflow pressure drop and the new, suboptimal, steady state is defined as the pharyngeal muscle responsiveness [4].

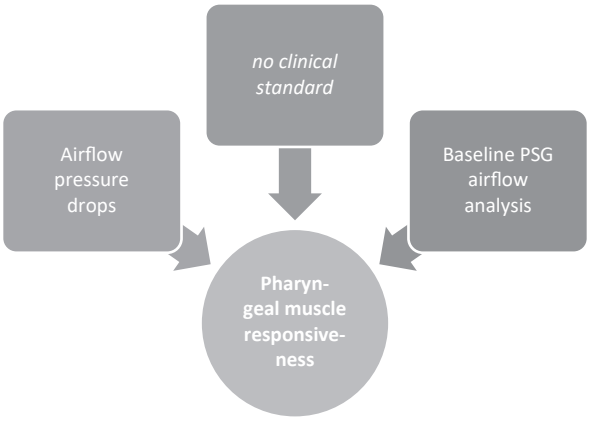

Fig. 2.11 Upper airway muscle responsiveness can be measured using airflow pressure drops (gold standard) or using PSG flow analysis (noninvasive technique)

2.5.2 Baseline PSG Airflow Analysis

Using polysomnography signal analysis, pharyngeal muscle compensation is calculated based on ventilatory parameters. As described earlier, passive ventilation is defined as the ventilation at which no additional muscles are recruited. Furthermore, active ventilation is the ventilation just before arousal, at maximal ventilatory drive and as such at maximal muscle recruitment. Therefore, compensation is defined by the difference between active ventilation (V_{active}) and passive ventilation ($V_{passive}$) [46].

2.6 Arousal Threshold

Arousal threshold is the threshold at which an arousal stimulus will lead to an arousal response [54]. This arousal stimulus can be external (e.g., noise) but can also be triggered by the central nervous system [55, 56]. An internal trigger can be an increased ventilatory drive to restore ventilation during a ventilatory disturbance. The arousal threshold is then defined as the ventilatory drive causing arousal.

An increased ventilatory drive will activate and stiffen the upper airway muscles. Therefore, a high arousal threshold allows the ventilatory drive to rise to levels needed for the upper airway muscles to restore ventilation [57]. However, a high arousal threshold is also associated with longer apneas/hypopneas and can cause deeper oxygen desaturations. By contrast, a low arousal threshold is associated with an increased propensity to wake up, preventing stable sleep and perpetuating cyclical breathing [57].

Arousal threshold can be assessed using invasive gold-standard techniques or noninvasive alternatives including flow analysis. Currently, there is no clinical standard method available; however, a model including clinical parameters was recently developed (Fig. 2.12).

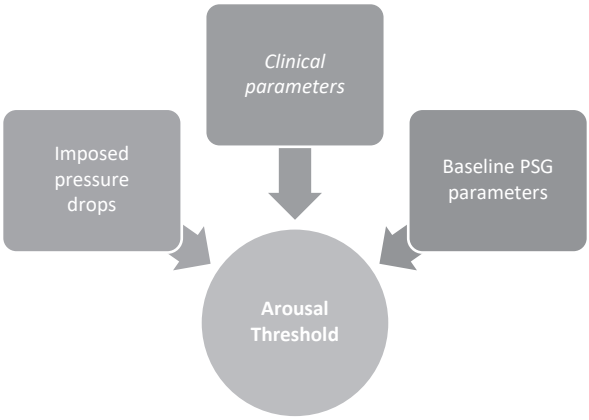

Fig. 2.12 The arousal threshold can be measured using airflow pressure drops (gold standard) or using baseline polysomnography (PSG) analysis (noninvasive technique). Currently, no clinical standard method is available; however, a model using clinical parameters shows potential for future clinical application

2.6.1 Airflow Pressure Drops

Like the previously described techniques, the gold-standard technique to determine arousal threshold includes pressure drops. To assess arousal threshold, adequate ventilatory drive measurements are needed. This can be achieved by measuring epiglottic pressure, diaphragm EMG or esophageal pressure or mathematical modeling.

Using an epiglottic catheter, the arousal threshold is determined as the epiglottic pressure immediately preceding an arousal [57]. Similarly, diaphragm activity can be measured using an intraesophageal diaphragm EMG catheter. Using esophageal pressure measurements, increasing or decreasing pressure swings reflect increasing or decreasing ventilatory drive [57–59].

In another method [4], ventilatory drive is determined using a mathematical model with parameters derived from the individual ventilation signal. An exponential decay characterizes ventilation after an arousal. The delay and time constant characterizing this exponential decay can be used to determine the ventilatory drive at each time point during a ventilatory disturbance. This method assumes that the delay and time constant of the increase in ventilatory drive (which is modeled) equals the time constant and delay of ventilation after arousal (which is observed). As such, these parameters can be used to model the ventilatory drive in time. The calculated ventilatory drive before arousal, is then defined as the arousal threshold.

2.6.2 Clinical Parameters

Alternative techniques to determine the arousal threshold have been developed. Edwards et al. [57] showed that combining the apnea–hypopnea index, oxygen saturation and the fraction of hypopneas could estimate the chance of a patient having a low arousal threshold (defined as less than −15 cm H_2O peak epiglottic pressure). However, this metric is not able to determine the exact arousal threshold.

2.6.3 Baseline PSG Airflow Analysis

Furthermore, recently, an algorithm to estimate the arousal threshold was developed by Sands et al. [58]. This algorithm was based on the method of Wellman et al. [4] in which the ventilatory drive was modeled based on the exponential decay of the ventilatory signal. However, instead of using external pressure drops to provoke airflow disturbances, the naturally occurring apneas and hypopneas in OSA patients are used.

2.7 Interplay Between the Different Pathophysiological Traits

To prevent OSA, the major traits of each OSA patient must interact to produce stable breathing during sleep that does not cause arousal [60].

To show the interactions between the different traits, the traits can be plotted on a graph of ventilatory drive against ventilation (Fig. 2.13) [4, 43]. When the airway is patent during resting breathing (eupnea), ventilation matches the ventilatory drive (V_{eupnea}). The arousal threshold is defined as the ventilatory drive at which a patient arouses and can be plotted as a vertical line (green dashed line). $V_{arousal}$ is the lowest ventilation that can be tolerated without arousal. Loop gain is then defined as the reciprocal of the slope connecting V_{eupnea} and $V_{arousal.}$. Passive collapsibility is reflected by $V_{passive}$, which is the ventilation that can be achieved through the upper airway

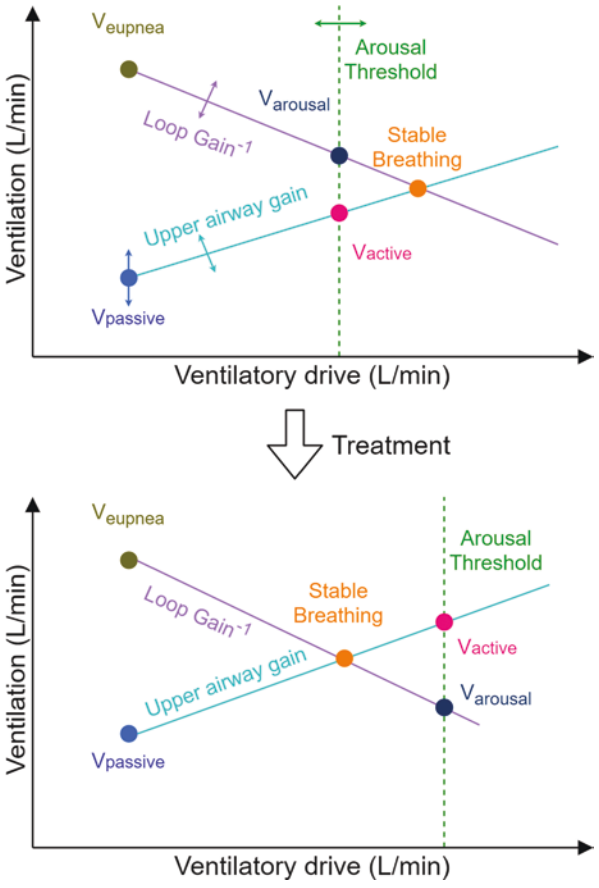

Fig. 2.13 Interplay between the different pathophysiological traits. The pathophysiological traits can be plotted on a graph explaining ventilation as a function of ventilatory drive. (Based on Wellman et al. [43])

Table 2.1 PALM classification scale

PALM category		Category cut-off	Definition
1	Severe anatomical deficit	$P_{crit} > +2$ cm H_2O	Anatomical deficit. Anatomical or mechanical intervention advised (e.g., CPAP)
2	Moderate anatomical deficit	-2 cm $H_2O < P_{crit} <$ $+2$ cm H_2O	Potential candidate for combination therapy
	2a	Minor nonanatomical vulnerability	Anatomic interventions advised (e.g., CPAP, MAD, positional therapy)
	2b	Nonanatomical vulnerability	Combination of anatomic and nonanatomical interventions (e.g., MAD + oxygen)
3	Minor anatomical deficit	$P_{crit} < -2$ cm H_2O	Nonanatomical interventions advised (e.g., oxygen)

Can be used to classify patients and as such define optimal treatment options for the individual OSA patient [5]

when the pharyngeal muscles are passive (i.e., not additionally activated). By definition, active collapsibility is the ventilation that can be achieved at maximal ventilatory drive (i.e., when ventilatory drive is at the arousal threshold and pharyngeal muscles are activated as much as possible). The upper airway gain, reflecting upper airway muscle activation, is the slope of the line connecting $V_{passive}$ and V_{active}. Stable breathing (orange) is achieved if the line representing "1/loop gain" and the line representing "upper airway gain" intersect. However, stable breathing can only be achieved if the ventilatory drive associated with this point is situated before (to the left of) the arousal threshold.

The goal in treating obstructive sleep apnea is to modify one or more of the traits (loop gain, arousal threshold, passive collapsibility or upper airway muscle compensation) to allow stable breathing without reaching the arousal threshold.

A potential patient classification scale is defined as the PALM scale [5] based on four pathophysiological traits: $\boldsymbol{P}_{crit}$, **A**rousal threshold, **L**oop gain and **M**uscle responsiveness (Table 2.1). According to this scale, OSA patients can be subdivided into three main categories The major determinant to define the category of each individual patient is the upper airway collapsibility, based on P_{crit} [5]. Patients with moderate anatomical deficits can be further subdivided into patients without nonanatomical vulnerability (group 2a) and patients with nonanatomical vulnerability (group 2b). Based on this classification scheme, optimal treatment actions can be defined for individual patients [5].

2.8 Association Between Treatment Outcome and Pathophysiological Traits

While the different traits will interact as shown in Fig. 2.13, the relative importance of each trait affects treatment outcome of different OSA treatment modalities (Table 2.2).

Table 2.2 The optimal treatment for OSA patients depends on the underlying pathophysiological trait distribution. Colored fields represent the most important traits for each OSA treatment. Importance of each trait is reflected in the height of the colored bars

	Upper airway collapsibility	Site, pattern and degree of upper airway collapse	Ventilatory control stability	Muscle responsiveness	Arousal threshold
Continuous Positive Airway Pressure (CPAP					
Mandibular Advancement Devices (MAD)					
Hypoglossal Nerve Stimulation					
Upper Airway Surgery					
Drug Therapy					

2.8.1 Continuous Positive Airway Pressure (CPAP)

CPAP treatment is characterized by a high efficacy across different patient cohorts. However, limited adherence might hamper overall efficiency. Assessing the underlying pathophysiology of patients and its associations with CPAP adherence might increase overall efficiency. A recent study on patients with coronary artery disease showed that a greater adherence to CPAP was found in patients with a higher arousal threshold and average muscle compensation [61].

2.8.2 Mandibular Advancement Devices (MAD)

Regarding MAD treatment, all pathophysiological, both anatomical and physiological, traits play a role in selecting the best candidates.

Regarding the site of upper airway collapse, an increase in velopharyngeal cross-sectional area with MAD correlates with treatment response [62–66]. Furthermore, an improvement in upper airway patency during DISE using a simulation bite predicts MAD response [63]. Recently, a posteriorly located tongue during natural sleep was also found to be associated with MAD treatment outcomes [67]. Similarly, tongue base collapse during DISE was found to be associated with increased odds of being a MAD responder. In contrast, CCCp and complete laterolateral oropharyngeal collapse were associated with increased odds for deteriorating during MAD treatment [68].

Regarding upper airway collapsibility, MAD treatment response is associated with a lower pharyngeal collapsibility, reflected in a lower P_{crit} and lower optimal CPAP level [67, 69–72]. Using finite element modeling and during clinical studies, mandibular advancement was shown to lower $P_{crit,}$ in a dose-dependent way [21, 23, 24, 73–77].

Loop gain affects both upper airway surgery outcomes and MAD treatment outcomes. For both treatment modalities, a lower loop gain, reflecting a more stable ventilatory control system, was associated with an increased probability of treatment response [52, 69].

Overall, using the noninvasive technique to assess the pathophysiological traits based on baseline PSG signals, a low loop gain proved to be the most critical physiological parameter [72]. However, lower collapsibility, higher arousal threshold, lower response to arousal and weaker muscle compensation were also favorable determinants [71].

2.8.3 Hypoglossal Nerve Stimulation

Complete concentric collapse at the level of the palate (CCCp), assessed during DISE, is a negative endotype and formal exclusion criterion for respiration-synchronized upper airway stimulation treatment [78, 79]. Furthermore, it has been shown that patients with complete anteroposterior or laterolateral palatal or epiglottic collapse might have increased odds for therapy failure [80].

Regarding the other traits, a recent study using the noninvasive methods described earlier showed that patients with a higher arousal threshold had increased odds of being a responder to HGNS treatment after 1 year [81]. Combining arousal threshold with the other physiological traits into one model showed that patients with a nonanatomical problem predisposing OSA (low arousal threshold, high loop gain, low pharyngeal compensation, mild collapsibility) tend to be nonresponders to HGNS treatment.

2.8.4 Upper Airway Surgery

Assessing the site of upper airway collapse is paramount before performing upper airway surgery. Therefore, DISE is routinely performed on each surgical candidate to define and fine-tune the treatment plan [82, 83].

In contrast to HGNS or MAD treatment, maxillomandibular advancement (MMA) surgery was shown not to be affected by the presence of CCCp. In addition, MMA tended to resolve CCCp [84].

Regarding the other traits, especially loop gain was shown to affect upper airway surgery outcomes. A lower loop gain was associated with an increased probability of treatment response [52, 69].

2.8.5 Pharmacological Treatment Options

Numerous drugs have been investigated, such as antidepressants, diuretics, antihypertensives, antiemetics, stimulants and sedatives, with some of them showing interesting properties [85].

Acetazolamide, a carbonic anhydrase inhibitor, may enhance respiratory drive by inducing metabolic acidosis, thus improving loop gain [86]. Other drugs have also been repurposed for the treatment of OSA. Spironolactone may improve upper airway collapsibility by reducing fluid retention and edema [87]. Several studies tried to mitigate OSA by modifying the activity of dilatory upper airway muscles. Initially, it was thought that sleep-related changes in muscle activity were primarily due to the withdrawal of serotonin at the hypoglossal neurons [88, 89]. However, more recent data suggest that drops in noradrenaline levels also play a key role. Therefore, noradrenergic stimulants, such as protriptyline and desipramine, can increase muscle activity and reduce upper airway collapsibility [90, 91].

A final potential target is the arousal threshold. Studies have indicated that sedatives such as eszopiclone and zolpidem increase the arousal threshold by 20–30% [92–95].

Regarding oxygen therapy, a correlation between response and lower collapsibility at baseline was found [96]. Furthermore, oxygen therapy lowers loop gain [47]. Pharyngeal muscle compensation affects the response to oxygen therapy; patients with a higher muscle compensation show increased response [96].

As OSA is a multifactorial disease, recent studies have looked at combinations of drugs. One of the most exciting studies in this field demonstrated that the combination of atomoxetine (noradrenergic) and oxybutynin (antimuscarinic) lowers the AHI by 63% [97]. This improvement was attributed to drastic changes in collapsibility and muscle compensation [98]. Notably, both drugs were ineffective when administered separately. Another exciting combination, eszopiclone and supplemental oxygen reduced the AHI by 43% via improvements in arousal threshold and loop gain [99].

2.9 Conclusion

Overall, we can conclude that assessment of OSA pathophysiology holds promise for playing a pivotal role in coming to precision medicine for obstructive sleep apnea patients. While until recently, these traits could only be assessed using rigorous, often invasive, and overnight measurements. However, the newly developed noninvasive techniques can make this information available in routine clinical practice.

Take-Home Message

- There are five critical pathophysiological OSA traits: site(s) and pattern(s) of upper airway collapse, upper airway collapsibility, ventilatory control stability (loop gain), muscle responsiveness, and arousal threshold.
- All these traits can be measured using a gold standard technique involving overnight measurements and/or upper airway pressure manipulations.
- OSA pathophysiological traits are helpful for treatment selection purposes. Besides DISE, especially the non-invasive techniques, e.g., based on sleep study data, hold promise as a patient selection tool.

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Sleep Related Breathing Disorders

3

Fausto Fernandes

3.1 Classification

Sleep pathologies are prevalent and frequent.

The classification of disorders plays several vital roles in Medicine. First, they are essential as a guide to clinicians in identifying the specific disease state. It provides them with information regarding numerous related factors, including pathogenesis, prognosis, course, heritability, and therapeutics necessary for precision diagnosis and treatment.

It also serves to define de domain of a given medical specialty.

The first classification for sleep disorders was made by the American Disorders Sleep Association in 1979. It was named the Diagnosis Classification of Sleep and arousal diseases.

This classification was reviewed in 2011, and the third edition was performed in 2014.

The concepts are based on the **International Classification of Sleep Disorders, AASM, ICSD 2014—Third Edition** (Table 3.1), [1] here we join the concepts of **The AASM Manual for Scoring of Sleep and Associated Events, 2.6 Version-2020** [1, 2].

These are the definitions adopted:

Apnea—There is a drop in the pick signal ≥90% of prevent signal, and last ≥10 s (recommended).

Hypopnea—The pick signal excursion drop by ≥30% of pre-event base line is ≥10 s, and PO_2 desaturation ≥3% (recommended).

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Table 3.1 Sleep-related breathing disorders

Obstructive sleep apnea disorders
Obstructive sleep apnea, adult
Obstructive sleep apnea, pediatric
Central sleep apnea disorders
Central sleep apnea with Cheyne–Stokes breathing
Central sleep apnea due to a medical disorder without Cheyne–Stokes breathing
Central sleep apnea due to a medication or substance
Central sleep apnea due to high-altitude periodic breathing
Primary central sleep apnea
Primary central sleep apnea of infancy
Primary central sleep apnea of prematurity
Treatment-emergent central sleep apnea
Sleep-Related Hypoventilation Disorders
Obesity hypoventilation syndrome
Congenital central alveolar hypoventilation syndrome
Late-onset hypoventilation with hypothalamic dysfunction
Idiopathic central alveolar hypoventilation
Sleep-related hypoventilation due to a medication or substance
Sleep-related hypoventilation due to medical disorder
Sleep-related hypoxemia disorder
Sleep-related hypoxemia
Isolated symptoms and normal variants
Snoring
Catathrenia

Obstructive—If it meets apnea criteria and is associated with continued or increased respiratory effort through the entire period of absent airflow (recommended).

Central—If it meets apnea criteria and is associated with absent inspiratory effort, throughout the entire period of absent airflow (recommended).

Mixed—If it meets apnea criteria, in the initial portion of the event absent inspiratory effort, followed by the reasumption of inspiratory effort in the second period of the event, without airflow [2].

3.2 Classification

3.2.1 Sleep-Related Breathing Disorders

The sleep-related breathing disorders are characterized by abnormalities of respiration during sleep (Table 3.1).

The disorders are:

Obstructive sleep apnea (OSA)

Central sleep apnea disorders

Sleep-related hypoventilation disorders

Sleep-related hypoxemia disorder
Isolated symptoms and normal variants
Summary:

In general, patients have a combination of obstructive and central sleep apnea. The diagnosis is often based on which disorder predominates; this may vary from night to night, and over time in individual patients.

On the other hand, OSA is different in adults that in children.

These disorders are characterized by upper airway narrowing or closure during sleep while respiratory effort continues.

We will essentially pay attention to the breathing disorders during sleep of the adult that are the most frequent.

We will reference central apnea due to neurologic or medical condition and cite a new entity—treatment-emergent central sleep apnea.

Sleep-related hypoventilation disorders are characterized by an abnormal increase in arterial PCO_2 during sleep (≥55 mm). Obesity hypoventilation syndrome is in this category.

A reference is made to the sleep hypoxemia disorders, which are characterized by sustained periods of significantly reduced oxyhemoglobin saturation during sleep.

Finally, a reference is made to hypoventilation syndrome, hypoxemias disorders, and normal variants like snoring or catathrenia.

3.3 Phenotypes and Sleep and Obstructive Apnea Syndrome

Beyond the classification, we must pay attention to the purpose of treatment on patient phenotypes. With these tools, we can do "tailor-made" treatment for the patient with sleep disorder breathing (SDB) [3].

Three phenotypes have been identified—position-dependent OSA (POSA), severe OSA in obese patients (OSA and Obese), and OSA and periodic limb movements (OSA PLM).

There are nine variables that should be looked for: (1) Body mass index (BMI), (2) Systolic arterial blood pressure, (3) Daytime saturation of oxygen in the arterial blood (SaO_2), (4) partial carbon dioxide pressure in arterial blood ($PaCO_2$), (5) partial oxygen pressure in arterial blood (PaO_2), (6) apnea–hypopnea index (AHI), (7) periodic limb movement index (PLMS), (8) supine AIH, and (9) nonsupine AHI.

POSA is the most frequent.

As we know, in our practice, many patients modify snoring and witnessed apneas changing positions from supine to lateral decubitus.

The prevalence of OSA and PLM is not high, but strongly correlate with arousals index and snoring and contributes to lower sleep quality. In this situation, OSA treatment is a good solution for both problems.

The phenotypes vary significantly when comparing specific anthropometric, clinical, and polysomnographic findings. However, these differences cannot be

identified only by measuring only the AHI index. The phenotype classification is completed classification with the AHI [3].

This is crucial for a complete diagnosis and treatment of OSA.

3.4 Obstructive Sleep Apnea Adult

The criteria diagnosis is in Table 3.2.

OSA is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction, during sleep and can occur in any age group.

It often results in a reduction of blood oxygen saturation and are in general terminated by brief arousals from sleep. These events last a minimum 10 s.

The partners report snoring, breathing interruptions, as well episodes of gasping or choking.

Patients awaken in the morning feeling tired and unrefreshed.

This phenomenon may be exacerbated by the ingestion of alcohol or sedation medication.

During the day, excessive sleepiness during activities as conversing, eating, walking, or driving.

There is a direct relationship between frequency of AHI, and daytime symptoms, and its impact on life quality, but is not well correlated with the degree of oxygen desaturation.

A common finding in OSA is refractory hypertension, a risk factor, independent of obesity or smoking.

Patients with OSA have coronary artery disease, atrial fibrillation, and stroke.

In severe forms, it can develop pulmonary hypertension and cor pulmonale.

Also, it is associated with common gastroesophageal reflux symptoms, nocturia, mood disturbance, and erectile dysfunction.

Table 3.2 Diagnosis criteria of adult sleep apnea syndrome

Obstructive sleep apnea adult
Diagnostic criteria
A + B or C
A—One or more of following:
1—Patient complaints of sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms
2—Patient wakes with breath holding, gasping or choking
3—Bed partner testimonies snoring or breathing interruptions
4—Patient with hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus
+
B—Polysomnography (PSG) or Out of Center Sleep Testing (ambulatory) (OCST) demonstrates:
Five or more predominantly obstructive respiratory events
OR
C—Polysomnography or OCST demonstrates:
Fifteen or more predominantly obstructive respiratory events (apneas, hypopneas, or Respiratory-Effort Related Arousals (RERAs)) per hour

Some questionnaires, as Epworth Sleepiness Scale, can measure daytime sleepiness and quality of life. From a clinical perspective, there is no difference between patients that have predominantly apnea or hypopnea.

Patients with UARS (upper airway resistance syndrome) is a variant of OSA, where there are obstructive events, which results in arousals, but minimal arterial oxygen desaturation. In general, they snore and report daytime sleepiness [4].

Estimates of prevalence are dependent of how sleep-related respiratory events are defined.

General population-based studies indicate that OSA associated with daytime sleepiness occurs in 3–7% of adult men and 2–5% of adult women. However, because many individuals with OSA do not endorse daytime sleepiness, the incidence must be much higher. Some studies refer prevalence of AHI index >5/h as 24% in men and 9% in women, and the prevalence of OSA increases with age [5].

The ratio of men/women is approximately two to one.

Occurs in all racial and ethnic groups.

The major predisposing factor is obesity. About 60% of moderate or severe OSA is attributed to obesity. The risk increases as the degree of weight gain increases, with a high prevalence of morbid obesity. The BMI is vital. As weight increases, OSA will become worse. Weight loss will improve the severity of OSA.

If the patient has normal weight and forms OSA, there is a need to check for maxilla-mandibular malformation or adenotonsillar (mainly in children) enlargement, as well as neck enlargement (♂ >43 cm; ♀ >39 cm).

In women, menopause is a risk factor, and replacement therapy may be protective.

Anatomic characteristics of the head and neck either, either hereditary or acquired, may influence OSA (mandibular size, mandibular position, palatal height, enlarged adenoids or tonsils, etc.).

Endocrine disorders such as acromegaly or hypothyroidism are also risk factors.

Children with Down syndrome have a high prevalence of OSA as well as patients with neurologic disorders such as myotonic dystrophy.

Alcohol consumption and use of sedating drugs may worsen OSA.

However, there are no clear data if smoking is a risk factor for OSA.

Also, nasal obstruction due to rhinitis or anatomical anomalies (such as hypertrophic rhinitis or deviated septum or valve collapse) predispose to OSA.

As demonstrated by familial clusters, OSA can be a heritable condition.

First-degree relatives of OSA patients are twice as likely to have OSA, compared to not familial affected. In addition, about one-third have hereditability obesity in OSA.

Genetics is essential in craniofacial morphology and ventilatory control.

However, a unique gene responsible for OSA heritability has not been demonstrated.

Studies show that the severity of OSA measured by the AHI tends to progress slowly time. Being more evident in men than women.

In middle-aged individuals, OSA is a significant risk factor for refractory hypertension, coronary artery disease, congestive heart failure, stroke, atrial fibrillation bradyarrhythmia or tachyarrhythmia, and premature mortality [6].

It is an essential factor for developing type 2 diabetes mellitus, independent of obesity? [7].

OSA increases the severity of depression, reduces job performance, causes impaired familial relationships, reduces overall quality of life, and may accelerate de onset of Alzheimer disease.

Also, the risk of vehicle accidents is significantly augmented in drivers with OSA.

OSA can occur in any age or group and increases between young adulthood and middle age, and the plateau is about age 65.

In PSG, OSA is documented by cessation of airflow with ongoing respiratory efforts. Oxygen saturation lowers from 1% or 2 to 40%.

Some events associated with the increased respiratory effort, and arousal, and normal oxygen saturation, is an event defined as RERAs.

In isolated snoring, there are no apneas, hypopneas, or RERAs.

Other causes of sleepiness then OSA, should be kept in mind, such as narcolepsy, idiopathic hypersomnia, and insufficient sleep [1].

3.5 Obstructive Sleep Apnea Pediatric

Above are the criteria for pediatric OSA (Table 3.3).

In children, upper airway obstruction occurs predominantly during REM sleep.

Even short obstructive apneas may be associated with severe hypoxemia because children have a lower functional residual capacity and a higher metabolic rate than adults.

Snoring is usually loud with pauses and gasps.

They may sleep in unusual positions such as seated or neck hyperextended.

Excessive daytime sleepiness may be present.

These children have developmental, behavioral, and learning issues, including attention deficit, hyperactivity, moodiness, irritability, and impaired academic performance.

The prevalence in children is estimated 1–4%. Predisposing and precipitating factors are, adenotonsillar hypertrophy and obesity.

Table 3.3 Diagnosis criteria of children obstructive apnea syndromes

Criteria A and B must be met:
A. The presence of one or more of the following:
1. Snoring
2. Labored, paradoxical, or obstructed breathing during the child's sleep
3. Sleepiness, hyperactivity, behavioral problems, or learning problems
B. PSG demonstrates one or more of the following:
1. One or more obstructive apneas, mixed apneas, or hypopneas, per hour of sleep
C. A pattern of obstructive hypoventilation, defined as at least 25% of total sleep time with hypercapnia ($PaCO_2$ >50 mmHg) in association with one or more of the following:
1. Snoring
2. Flattening of the inspiratory nasal pressure waveform
3. Paradoxical thoracoabdominal motion

Craniofacial anomalies and Down syndrome, neuromuscular disease, cerebral palsy, gastroesophageal reflux, mucopolysaccharidosis, cleft palate treated with pharyngeal flap, and environmental tobacco exposure, are predisposing factors to OSA.

There is evidence of an increased risk in children of families with OSA, but the genetic factors are unknown.

Symptoms begin within the first few years.

It is essential to treat early because of the behavioral and cognitive complications the may occur together with a deficit of the child's development.

PSG demonstrates obstructive and mixed apneas, hypopneas, and periods of obstructive hypoventilation, associated with desaturation and hypercapnia [1, 8].

3.6 Central Sleep Apnea Syndromes

These syndromes below described have the common criteria related in Table 3.4.

The criteria to be classified as CENTRAL SLEEP APNEA SYNDROMES are the ones in Table 3.5.

Table 3.4 Central sleep apnea syndromes

Central Sleep Apnea Syndromes
Central apnea syndrome with Cheyne–Stokes breathing
Central apnea due to a medical disorder without CSB
Central sleep apnea due to medication or substance
Central apnea due to high-altitude periodic breathing
Primary central sleep apnea
Primary sleep apnea of infancy
Primary sleep apnea of prematurity
Treatment-emergent central sleep apnea

Table 3.5 Diagnosis criteria of central sleep apnea syndromes

Criteria Central Sleep Apnea Syndromes
A
1—Sleepiness
2—Difficulty initiating or maintaining sleep, frequent awakenings or nonrestorative sleep
3—Awakening short of breath
4—Snoring
5—Witnessed apneas
B—PSG shows all the following:
1—5 or more central apneas or central hypopneas/hour of sleep
2—No. of central apneas >50% of total apneas or hypopneas

3.6.1 Central Apnea Syndrome with Cheyne–Stokes Breathing

This syndrome is characterized by a crescendo-decrescendo ventilation pattern associated to central apnea–hypopnea. Heart failure is the primary cause of CSA-CSB.

In association, patients have excessive daytime sleepiness, insomnia, or nocturnal dyspnea.

It is seen in subjects older than 60 years, males.

It is observed in N1 and N2, and attenuated in REM.

Predisposing factors are congestive heart failure, stroke, and renal failure.

In general, there is subtle oxyhemoglobin desaturation [9].

3.6.2 Central Apnea Due to a Medical Disorder

It is a consequence of a medical or neurological disorder.

Most patients have brainstem lesions of developmental, vascular, neoplastic, degenerative, demyelinating, or traumatic.

Patients present with sleep fragmentation, excessive daytime sleepiness, or insomnia.

The Chiari malformation appears during infancy. Older patients can suffer from stroke [1].

3.6.3 Central Sleep Apnea Due to a Medication or Substance

In this disorder, the patient is taking an opioid or another respiratory depressant, and there is an absence of CSB.

The use of potent long-action opioid drugs may carry central apneas during sleep, such as methadone, morphine, oxycodone, fentanyl, and suboxone.

If the patients are withdrawn from these drugs, the central apnea may resolve, but the abuse can lead to death.

This appears in the non-REM sleep, mainly in N3 [10].

3.6.4 Central Sleep Apnea Due to High-Altitude Periodic Breathing

It is characterized by the criteria of CSA with history of recent ascent to high altitudes [7].

The clinic is comprises alternating periods of central apnea and hypopnea associated with a recent ascent to high altitude, over 2500 m, accompanied by dyspnea [11].

3.6.5 Treatment-Emergent Central Sleep Apnea

This is a new entity. The diagnostic criteria are the same as CSA, but this pathology emerges in patients treated with CPAP.

In some patients, CPAP use shows a significant resolution of the obstructive events. It entails the emergence, or persistence of central apnea or hypopnea, with a number of central apneas or hypopneas above 50% of the total events.in a diagnostic sleep study. During treatment with CPAP, CSA persists or emerges, despite significant resolution of obstructive respiratory events, and any other CSA disorder [12].

Finally, three rare clinical identities in CSA children and adults:

Primary central sleep apnea

Primary central sleep apnea of infancy

Primary central sleep apnea of prematurity

3.7 Sleep-Related Hypoventilation Disorders

The primary feature of these disorders is insufficient sleep-related ventilation, resulting in abnormally high arterial partial pressure of carbon dioxide ($PaCO_2$) during sleep.

Awake hypoventilation is defined as an arterial partial pressure of carbon dioxide ($PaCO_2$) ≥45 mmHg.

The prevalence of these disorders is rare.

Hypoventilation generally results from impaired respiratory drive and CO_2 and O_2 chemosensitivity.

There might also be hypoventilation with hypercapnia and hypoxemia [13].

3.7.1 Obesity Hypoventilation Syndrome (OHS)

It is a well-known disease. The old designation was Pickwick syndrome.

OHS is characterized by obesity and daytime hypercapnia (arterial $PaCO_2$ >≥ 45 mmHg), that cannot be fully attributed to an underlying cardiopulmonary or neurologic disease.

Hypercapnia worsens during sleep and is often associated with severe arterial oxygen desaturation. Hypoventilation is usually worse during REM sleep (Table 3.6).

Table 3.6 Diagnosis criteria of obesity hypoventilation syndrome

Diagnostic criteria A–C must be met:
A—Presence of hypoventilation during wakefulness ($PaCO_2$ ≥45 mmHg) as measured by arterial PCO_2, end-tidal PCO_2, or transcutaneous PCO_2
B—Presence of obesity (BMI >30 kg/m^2 in adults; for children >95th percentile)
C—Hypoventilation is not primarily due to lung parenchymal or airway disease, pulmonary vascular pathology, chest wall disorder (other than mass loading from obesity), medication use, neurologic disorder, muscle weakness, or a known congenital or idiopathic central alveolar hypoventilation syndrome

Most OHS patients have comorbid OSA (80–90%).

Patients with OHS commonly complain of hypersomnolence, morning headaches, fatigue, mood disturbance, and impairments of memory or concentration.

Physical examination may reveal cor pulmonale or circulatory congestion, such as plethora, scleral injection, and peripheral edema.

Laboratory testing commonly shows polycythemia and elevated serum CO_2 on electrolyte testing (≈ serum bicarbonate), reduced forced vital capacity during pulmonary function testing, right heart strain, right ventricular hypertrophy and right atrial enlargement on electrocardiography and ventricular dysfunction on echocardiography.

Consequences of chronic hypercapnia and hypoxemia include pulmonary artery hypertension, cor pulmonale, and neurocognitive dysfunction.

The prevalence of OHS in populations of patients with OSA varies across studies but is often in the range of 10–15% of obese patients with OSA.

Although the prevalence of OHS is higher in men than women, the difference is not as prominent as in OSA. Obesity is believed to be the primary pathophysiologic factor.

Central nervous system depressants, such as alcohol, anxiolytics, and hypnotics, may further worsen respiratory impairment.

The serum bicarbonate level is usually elevated due to renal compensation for chronic respiratory acidosis (hypercapnia) [14].

3.7.2 Congenital Central Alveolar Hypoventilation Syndrome

It is a syndrome of autonomic dysfunction. Primarily, there is the failure of automatic central control of breathing, due to a mutation of the PHOX2B gene.

It appears at birth and is rare.

It is associated with autonomic abnormalities, including Hirschsprung disease (16% of patients), autonomic dysfunction (e.g., decreased heart rate variability or hypotension), neural tumors (e.g., ganglioneuromas, swallowing dysfunction during the early years, and ocular abnormalities (e.g., strabismus) [1].

3.7.3 Late-Onset Central Hypoventilation with Hypothalamic Dysfunction

Patients are usually healthy until early childhood (often 2–3 years of age); however, they develop dysphagia and severe obesity, followed by central hypoventilation, which often presents as respiratory failure.

There is hypothalamic dysfunction.

These patients often develop hypothalamic endocrine dysfunction: diabetes insipidus, inappropriate antidiuretic hormone hypersecretion, precocious puberty, hypogonadism, hyperprolactinemia, hypothyroidism, temperature dysregulation,

and decreased growth hormone secretion, mood and behavior abnormalities have been reported. Developmental delay or autism may be present [15].

3.7.4 Idiopathic Central Alveolar Ventilation

Is defined as the presence of decreased alveolar ventilation, resulting in sleep-related hypercapnia and hypoxemia, in individuals with presumed normal mechanical properties of the lung, and respiratory pump.

3.7.5 Sleep-Related Hypoventilation Due to a Medication or Substance

This disorder is characterized primarily by chronic hypoventilation and hypercapnia due to prolonged use of medications or substances, known to depress ventilatory drive and/or impair respiratory muscle mechanics.

These agents include long-acting narcotics, anesthetics, sedative compounds, and muscle relaxants. In addition, the risk of respiratory insufficiency is increased with the concomitant use of alcohol or with polypharmacy.

3.7.6 Sleep-Related Hypoventilation Due a Medical Disorder

In this disorder, there is a chronic obstructive pulmonary disease (COPD) and parenchymal lung disease. Polycythemia is accompanied by severe chronic hypoxemia.

This disease is usually most severe during REM sleep [16].

3.7.7 Sleep-Related Hypoxemia

The disease is related to a significant hypoxemia during sleep and is secondary to a medical or neurological disorder. Chronic hypoxemia can develop from airway or parenchymal pulmonary disease, chest wall disorders, pulmonary hypertension, or neurologic and neuromuscular disorders.

Hypoxemia due to underlying lower airway obstructive disease, pulmonary parenchymal disease, vascular pathology, and other causes of hypoventilation is generally prolonged (several minutes or longer). In contrast, sawtooth fluctuations of oxygen saturation (typically less than 1 min) characterize hypoxemia due to OSA or CSA.

Prevalence may be higher in patients with more significant perturbations of pulmonary function or neuromuscular weakness.

3.8 Isolated Symptoms and Normal Variants

3.8.1 Snoring and OSA

Snoring is a respiratory sound generated in the upper airway during sleep that typically occurs during inspiration but may also occur in expiration.

It occurs without episodes of apnea, hypopnea, RERAs, or hypoventilation. Does not cause symptoms of daytime sleepiness, insomnia in the patient, or reported by the partner witnessed breathing pauses.

The snoring intensity may vary and will often disturb the bed partner's sleep and even awaken the patient. Occasional snoring is almost universal [17].

So, this type of snoring, has variously been referred to as habitual, primary, or simple snoring.

But in general, snoring is a cardinal symptom of obstructive sleep apnea.

In addition, those individuals with snoring and comorbid cardiovascular disease (especially pulmonary or systemic hypertension, coronary artery disease, or atrial fibrillation) are at increased risk for the presence of OSA [18].

Therefore, PSG or OCST is required to rule out OSA in such populations effectively. It should also be noted that patients who initially have isolated snoring may be at risk for developing OSA with aging or weight gain.

Estimates of snoring vary widely, depending on its definition. The incidence of snoring in children is 10–12%. The Wisconsin cohort study reports habitual snoring in about 24% of adult women and 40% of adult men.

Prevalence of snoring increases with age in both sexes, except that the most reported snoring starts to decrease again in men after 70 years of age (this may be due to reduced hearing acuity in older individuals).

Snoring is most common in adult men and is also linked to obesity. Nasal obstruction increases the risk of snoring. Ingestion of alcohol, muscle relaxants, narcotics, or other substances that decrease upper airway muscle tone predisposes an individual to snore. Smoking, particularly in males, has also been shown to be a risk factor [19].

Snoring increases during pregnancy.

In children, an association has been reported between snoring and adenotonsillar hypertrophy.

There is a vibration of the uvula and soft palate during snoring, although it may also involve the faucial pillars, pharyngeal walls, and larynx.

If PSG is performed, snoring tends to be loudest during stage N3 or REM sleep.

Some studies have suggested that adult snorers may have a higher prevalence of cardiovascular disease, including hypertension, stroke, and ischemic heart disease.

Snoring tends to increase during pregnancy.

3.8.2 Catathrenia

Catathrenia, also known as sleep-related groaning, is included in the Sleep-Related Breathing Disorders (SRBD) section because it appears to be associated with prolonged expiration, usually during REM sleep.

Typically, a deep inspiration is followed by prolonged expiration and a monotonous vocalization resembling groaning. The pattern is sometimes called bradypnea.

The affected individual is usually unaware of the problem, but the clinical evaluation is sought, due to complaints of the bed partner or family members.

It is thought to be rare and more common in men.

Several episodes may occur nightly and often in clusters.

The long-term consequences of catathrenia are unknown, but the disorder is primarily a social problem for the affected individual.

3.9 Clinical Presentation of OSA

Sleep and wake symptoms of OSA	
Nocturnal symptoms	Daytime symptoms
Snoring	Excessive daytime sleepiness Fatigue
Witnessed apneas	Morning headaches
Dyspnea (choking/gasping) Night sweats Bedwetting	Neurocognitive impairment: Vigilance Executive functioning Motor coordination Memory or concentration issues
Drooling	Diminished quality of life
Dry mouth	Mood and personality changes: Depression Anxiety Irritability
Bruxism	Sexual dysfunction: Decreased libido Impotence Abnormal menses
Restless sleep/multiple arousals Fragmented sleep	
Gastroesophageal reflux	
Nocturia	

The golden standard for the diagnosis of OSA, is polysomnography.

However, the process is time consuming, labor intensive, and costly.

Moreover, the interpretation sometimes is difficult. Different sleep problems often coexist, potentially complicating the diagnosis and management.

The screening for OSA includes the sleep history, review of symptoms, and physical examination.

So, symptoms and signs and clinical history are essential, and necessary for evaluation of the clinical picture of SRD, and knowledge of other associated comorbidities.

Whenever possible, the patient should come with the bed partner. However, the clinical history is still necessary to elaborate on a questionnaire of suspicion and severity of OSA, such as the Epworth Sleepiness scale or STOP-BANG. No symptoms or signs by themselves are predictive of OSA or its severity. Therefore, they are important for the evaluation of the clinical picture of SRD and to knowledge of other associated comorbidities.

However, no symptoms or signs by itself are predictive of OSA or its severity.

Some authors propose that age, sex, BMI, and medical history are superior to the symptoms variables for predicting OSA [20].

Many patients with OSA remain undiagnosed (0.3–5%).

Many studies prove that adverse health outcomes are associated with OSA, regardless of daytime sleepiness.

We must refer that some comorbidities, can carry important information, such as resistant hypertension (the risk of OSA is 80%), diabetes, headache, and so on.

With this information, we can identify patients for OSA study.

Then a polysomnography can be done.

A study in Switzerland in 2015, reported 50% of men, and 25% of women had moderate OSA.

In 2002, Sleep Heart Health study revealed that 24% of men and 9% of women aged 30–49 had mild OSA.

In the United States, it is estimated that 82% of men and 93% of women have undiagnosed OSA.

Unmodifiable and modifiable factors influence the risk of OSA [21].

The first group includes male sex, age, race, genetic predisposition or family history, and cranial facial anatomy.

The second includes obesity, medications such as muscle relaxants or drugs (opiates, benzodiazepines, alcohol), endocrine disorders (hypothyroidism, hypothalamic disease, polycystic ovarian syndrome, smoking, and nasal obstruction.

3.10 Comorbidities

OSA is associated with several comorbidities, including stroke, myocardial infarction, hypertension, arrhythmias including atrial fibrillation, pulmonary hypertension, congestive heart failure, hyperlipidemia, glucose intolerance, type 2 diabetes, and depression.

Patients with cardiovascular disease have a great prevalence of OSA, moderate or severe OSA hypertension (30–83%), heart failure (55–20%), arrhythmias (50–20%), stroke (75–57%) and coronary heart disease (38–65%) [19, 20].

3.10.1 Sleep History

The sleep history starts with patients, total sleep time based on bedtime, time to fall asleep and wake up, difficulty falling asleep, staying asleep, or daytime naps.

In some patients, their insufficient sleep determinates attention deficit and memory.

There are some indirect data, as sometimes of caffeine abuse, which means, that the patient uses it to combat daytime sleepiness.

Sleep deprived or OSA patients suffer from drowsy diving that make them prone to accidents mainly in long distance trips [20].

3.11 Risk Factors

The morbidity rate of OSA in population is between 9 and 38% and is higher in male, obese, and older patients.

Recent studies have also shown OSA patients to have a higher prevalence of psoriasis compared to general population [22].

3.11.1 Sex

Men are at higher risk than women (two- or threefold risk in men). It is less severe in women than men, with the same BMI.

The exception is during pregnancy, which is of particular risk in women.

Snoring and witnessed apneas are more common in men. On the other hand, daytime excessive sleepiness, insomnia, and fatigue are more common in women.

OSA is prevalent in 60–70% of women with polycystic ovary [23].

3.11.2 Excessive Body Weight

Excessive body weight is a common clinical finding, in more than 60% of patients referred for a diagnosis for sleep evaluation.

A strong correlation between increased obesity and OSA. It correlates with abdominal and neck circumference.

An increase of 10% in BMI, increases by sixfold moderate OSA to severe and rises the Apnea/Hypopnea Index (AHI) index by 32%. A 10% decrease in BMI lowers AHI in 26%.

Excessive body weight affects breathing in numerous ways.

Weight loss is very effective to reduces the severity of OSA.

3.11.3 Age

Epidemiologic surveys reveal that more than 50% of adults over the age of 65 years have had some form of chronic sleep-related complaints.

The risk of OSA increases with age.

Prevalence in men older than 65–72 years is 23%, and 30% in older than 80.

On the other hand, despite the high prevalence of OSA with age, the partner's witnessed snoring decrease, may be due to deafness [21].

3.11.4 Race

The sleep heart study reveals the risk of severe OSA in blacks is 20% and whites 17%.

Another study shows the prevalence of OSA is 30% in whites, 32% in blacks, 38% in Hispanics, and 39% in Chinese.

While Asians are generally, less obese than whites, disease prevalence is similar to in the west. Moreover, for a given age, sex, and BMI, Asians have more significant disease severity than whites.

Snoring, a cardinal sign of obstructive sleep apnea, has been reported in 27.8% of Hispanic men and 15.3% of women [24].

3.11.5 Familial and Genetic Predisposition

Family susceptibility to OSAS increases directly with the number of affected relatives.

Craniofacial and cephalometric abnormalities, volume of lateral parapharyngeal, tongue, and genetic determinants of obesity and fat distribution are predisposing factors [25].

3.11.6 Alcohol

Alcohol intake can induce apneic activity and apnea duration and worsen the severity of hypoxemia.

Long-term alcohol abuse on OSA is not well known.

3.11.7 Smoking

Sleep instability occurs due to the reduction of night nicotine and the inflammatory process of the airway.

Smokers are three times more likely to have OSA than no smokers.

3.11.8 Other Causes

OSA is related to menopause, not due to hormonal changes, fat deposition, and weight gain, and can be controlled by Hormone Replacement Therapy.

Also, patients with hypothyroidism have increased susceptibility to OSA [5].

3.12 OSA Sleep-Related Nocturnal Symptoms

The most frequent night symptom is **snoring**.

It can be simple, habitual without apnea, or associated with apnea, a cardinal symptom. It is exacerbated by alcohol intake, weight gain, sedatives or opioids, sleep deprivation, or supine position. It is aggravated by nasal obstruction.

It leads to difficulty with bed partner.

Snoring is very common in the general population (35–45% in men and 15–28% in women). However, only 6% of patients with OSA do not snore. The description by the partner is essential for the medical history. The patient doesn't recognize that they snore (about 75%).

Those who snore and have cardiovascular changes, are at risk of having OSA. The prevalence of snoring increases with age till 70 years.

In patients without OSA, and with a BMI less than 30, increasing snoring correlates with a significant increase in cause mortality.

Non palatal snoring is associated with increased in observed all-cause mortality controlling for age, sex, BMI, and AHI.

There is a relation between snoring and carotid artery atherosclerosis, especially in sound frequencies of snoring.

The odds of high-risk features are four to eight times higher in snorers than non-snorers in the same conditions.

The snoring increases during pregnancy [18, 19, 26].

3.12.1 Witnessed Apneas

They are the second most important symptom in OSA, observed by bed partners (up 75%). It is associated with loud effort for breathing, gasps, moans, body movements, and brief wakening. Patients have no conscious of the situation.

Nocturnal dyspnea is sometimes described by patients, as a choking sensation or suffocation. These episodes occur with arousals and may be associated with feelings of panic, and anxiety.

It must be distinguished from causes of paroxysmal nocturnal dyspnea, such as Cheyne–Stokes breathing, left heart failure, nocturnal asthma, and laryngeal stridor.

Other common symptoms are drooling (30%) and dry mouth (75%) caused by mouth breathing due to nasal obstruction.

In OSA, about 40–54% suffer from it.

3.12.2 Bruxism

Bruxism may be caused by micro-arousals, occurring during sleep, and are considered the primary causal factor of night jaw closing muscle activation.

It is characterized by clenching and grinding the teeth, or by breathing and thrusting the mandible. The causes are multifactorial and mostly of central origin.

Sleep bruxism occurs mainly in non-REM sleep, N1, and N2, when there is a fluctuation of sympathetic/parasympathetic activity. It can be a defense mechanism against obstruction of the upper airway [27, 28].

3.12.3 Restless Sleep

When this occurs, patients wake up tired in the morning, maybe accompanied by nocturnal sweat (>65%), due to respiratory effort and autonomic instability during sleep. However, diaphoresis may appear in many other diseases [29].

3.12.4 Gastroesophageal Reflux

It occurs in 64–73% of patients. Some authors say that in OSA upper airway obstruction leads to increased intra-abdominal pressure, combined with more negative intrathoracic pressure, which results in increased intradiaphragmatic pressure gradient, which leads gastric contents to the esophagus.

Some studies shows that when the patient is treated with CPAP, the reflux decreases around 48% [30].

3.12.5 Nocturia

It is present in 28% of patients and is related to the severity of OSA. The pathophysiological mechanism includes the increased secretion of natriuretic peptide with an increase in intra-abdominal pressure [31].

3.13 Sleep-Related Daytime Symptoms

3.13.1 Excessive Daytime Sleepiness

It is a cardinal feature of OSA syndrome and results from abnormal sleep.

The most common is daytime sleepiness. The reason is sleep fragmentation with arousals, and insufficient sleep [32].

During the day, the patient has a tendency to fall asleep during diverse situations as after lunch, driving, working, etc.

It can be registered through questionnaires like the Epworth Sleep Scale [33, 34].

If severe, it can cause vehicle and machinery accidents, poor school and job performance, and relationship problems.

Several studies have shown that patients with OSA tend to high motor vehicle crash rates [35].

In a study in Swedish patients, the authors found that baseline snoring and sleepiness were significantly related to occupational injuries. Patients with OSA, or heavy snoring, were two or threefold as likely to have occupational injury, in the past 10 years.

In patients with OSA without treatment, 41% manifested sleepiness at the wheel.

The Epworth Sleep Scale (ESS), depressive symptoms, and the risk of exposure (annual mileage) are predictors of sleepiness.

Other behavioral factors are sleep deprivation, shift work, and nonrestorative sleep.

In a recent survey, 17% of European drivers reported episodes of sleepiness at the wheel in the previous 2 years [36].

In a study, around 3% of Australian adults reported a diagnosed OSA with elevated ESS, having a significant tendency to doze off, during the daytime, including while driving.

Car crashes accident rate has been estimated to be fatal in 11% of sleepy drivers, in contrast to a 5% of the general population [37].

Near miss accidents in sleepy drivers is 10%.

We must distinguish between fatigue or lethargy, or depression. Also, other reasons for chronic insomnia, are depression, fibromyalgia, medication or substance abuse, or other organic diseases such as cardiac disease.

A direct relationship between snoring and daytime sleepiness is independent of AHI [36, 37].

ESS questionnaire may measure this situation especially when accompanied by the STOP-BANG questionnaire.

3.13.2 Morning Headaches

These are frequent in half of OSA patients. When the patient wakes up, it is dull, scattered, and lasts 1 or 2 h. However, it is not specific and can be associated with other situations, like hypertension, sinusitis, depression, and other medical conditions.

It is related to hypoxemia and hypercapnia during sleep, with vasodilation. Treating OSA solves the problem [38].

3.13.3 Neurocognitive Impairment

It is due to sleep fragmentation. The resulting hypoxemia can lead to anoxic brain damage, and affects the executive, vigilance and motor coordination, and short and long-term memory.

Some recent studies mention the relationship between OSA and Alzheimer's disease, in relation to the β amyloid and tau in CSF. OSA can accelerate the process of Alzheimer's disease [39, 40].

3.13.4 Mood Alterations

These are frequent and lead to a decreased quality of life the most common symptom is depression.

Other behavioral manifestations are irritability, anxiety, aggression, and emotional liability.

Treatment with CPAP alleviates the symptoms of depression and improves the quality of life [41].

3.13.5 Sexual Dysfunction

Sexual dysfunction, erectile dysfunction (ED), and decreased libido are associated with OSA. The sleep-related erection is a natural involuntary phenomenon in REM in healthy males, regulated by the hypothalamus. In a Korean study, ED is associated with OSA accompanied by low-oxygen saturation, vascular endothelial dysfunction, and a pudendal neuropathy [42].

CPAP or surgical sleep treatment improves sexual quality of life [37].

Severe OSA may cause **vertigo** due to hypoxia of the posterior labyrinth and can damage the brainstem [43].

3.14 Clinical Signs

3.14.1 OSA Common Physical Findings

During physical examination, it is important to observe the **body mass** of the patient as obesity is frequently associated with OSA. Obesity (BMI >30 kg/m^2) has high sensitivity (93%) and specificity (73%) for OSA.

In the ENT examination, we must check the **neck circumference** in men >43 cm, and women ≥39 cm. It is a high predictor of OSA, with a sensitivity 61% and a specificity 93% [21].

In OSA, airway obstruction occurs between the nares and the trachea.

We must begin our observation in the **nose**, the first structure on superior airway anatomy.

It is an important in OSA and should not be forgotten.

The nares should be observed, asking the patient to breath, paying attention to the movement of lateral cartilage during inspiration, and the function of the internal valve. There is a need to watch the septum if it is deviated and obstructive. Inferior turbinate hypertrophy may block the nasal cavity and produce difficulty breathing.

The correction of nose disorders, should be performed to improve OSA tolerance to CPAP.

Some authors refer that daytime nasal obstruction is an independent risk factor for OSA [44].

Because increasing nasal resistance, results in increased of negative oropharyngeal pressure during inspiration, leading to upper airway collapse.

The craniofacial morphology, the neck diameter and length, the tongue, the pharynx, and the larynx must be observed.

Features such as retrognathia, tonsillar hypertrophy, enlarged tongue or soft palate, inferiorly positioned hyoid bone, maxillary and mandibular retroposition and decreased posterior airway space can narrow upper airway dimensions, narrow upper airway dimensions and promote the occurrence of apneas and hypopneas during sleep.

The most common craniofacial abnormalities associated with OSA are retrognathia and a high palate arch.

Retrognathia pushes the base of the tongue backward, producing a diminished retroglossal space. In many patients ,that are mouth breathers, since childood,the palate wil be high.

There is a need to check the temporomandibular joint (TMJ), where a typical click or jam can be felt on movement which might result from bruxism. I might worsens the airway collapse.

During **mouth** examination, many patients present macroglossia or retroposition of the tongue. This may influence sleep even more in the supine position.

Malocclusion, mainly in Angle 2, leads to retroposition of the tongue.

A flexible fiberscope is used to evaluate the nose, the nasopharynx, pharynx walls, epiglottis, and larynx.

The obstruction is more severe, if there is a voluminous tongue.

Mallampati score or Friedman tongue position the score is done to classify the relation of the tongue and is scored from 1 to 4.

The palatine tonsils' size is also important, and we can score from 0 to 4, a major factor for obstruction [16].

The enlarged or elongated uvula and palate contribute to snoring and OSA by vibration or reduction of the retro-palatine space. Enlarged tonsils can accompany these features.

The golden standard for pharyngeal evaluation is nose–pharynx–larynx endoscopy.

Examination can be performed to see the anatomy, the obstruction zone and the patient breathing pattern.

The examination should be completed in some situations with drug-induced sleep endoscopy (DISE). Although it may increase cost and time, it allows an accurate airway examination.

OSA patients also may have dental problems, like dental caries, and teeth grinding from bruxism. This can be observed in sleep by the partner.

During the clinical examination, we must pay attention to the cranial anatomy, the neck diameter, nose, palate, teeth, tongue, pharynx, and larynx.

All findings should be recorded in the clinical history or examination protocol, for clinical evaluation and for treatment of the patient.

Finally, the clinical history and examination must be complemented with other exams to get the precision diagnosis, for a correct treatment [20, 45].

Take-Home Message

- OSA is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep and can occur in any age group. It often results in a reduction of blood oxygen saturation and is generally terminated by brief arousals from sleep. These events last a minimum of 10 seconds.
- Central Sleep apnea is characterized by a crescendo-decrescendo ventilation pattern- associated with central apnea–hypopnea. Heart failure is the primary cause of CSA-CSB.
- Sleep-related hypoventilation disorder is characterized by insufficient sleep-related ventilation, resulting in abnormally high arterial partial pressure of carbon dioxide (PaCO2) during sleep. There are diverse types.
- Sleep-related hypoxemia is related to significant hypoxemia during sleep and is secondary to a medical or neurological disorder.
- Risk factors for OSA include being male, excessive body weight, age, race, familial and genetic predisposition, alcohol, smoking, and hormonal changes.

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Diagnosis: How Is Diagnosis Performed

4

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4.1 Clinical History

The diagnostic approach of any disease presupposes an investigation initiated by a detailed anamnesis, pertinent physical examination, and the elaboration of differential diagnoses. The request for complementary tests aims to confirm the diagnosis, establish the criteria of severity, and assist in clinical considerations for the therapeutic approach.

Anamnesis in sleep medicine also has its usefulness in identifying risk factors, conducting clinical research, and differential diagnoses of sleep diseases. It is well known that, in adults, the main symptom of sleep disease is excessive daytime sleepiness. However, it is also seen for clinical psychiatric and drug disorders [1]. To differentiate

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if the excessive daytime sleepiness is caused by Obstructive Sleep Apnea (OSA), it is crucial to carry out a complete clinical history and a complete sleep history, addressing various issues, such as sleep habits and the number of hours spent per night.

To make an adequate history considering a patient's sleep, it is essential to know of the variability of normal sleep. If health professionals who work with sleep do not look at this peculiarity of sleep physiology, the clinical history will become inadequate. Sleep considered as "normal" must be interpreted through variables that include age group, culture, ethnicity, gender, genetics, and individual [2]. Roughly speaking, normal sleep occurs when an individual wakes up with a refreshing sleep sensation, without excessive daytime sleepiness, on the following day. However, this analysis is relatively superficial to a health professional who proposes to assist individuals with sleep complaints.

It is known that there are several risk factors for the development of snoring and OSA, so it is crucial to question them in the anamnesis of a patient with suspected obstructive sleep [3]. The following questions should always be present in a sleep anamnesis for these patients:

- When did the symptoms start?
- Do symptoms correlate with weight gain?
- Did symptoms start after starting new medications or alcohol use?
- Have day and night symptoms worsened with increased frequency and intensity of snoring?
- Is there a relationship between symptoms and menopause?
- Is there a relationship with symptoms of gastroesophageal or pharyngeal–laryngeal reflux?
- Is there a family history of nocturnal snoring or OSA?

These questions are important because obesity, alcohol consumption, menopause, medications that cause muscle relaxation, and pharyngeal–laryngeal reflux are risk factors for obstructive sleep breathing [3, 4]. In addition, some studies show a correlation between OSA and gastroesophageal reflux (GERD) [5].

Excessive daytime sleepiness (EDS), as the main symptom of sleep disorders in adults, can be evaluated objectively and subjectively. The objective instruments for assessing EDS are the wakefulness maintenance tests (MWT) and multiple sleep latencies (MSLT), which are tests that are difficult to logistic, and little used in clinical practice [1, 6]. The subjective instruments for evaluating EDS are sleep questionnaires. In addition to the questionnaires to assess EDS, there are others specific to each sleep disease and assess patient's quality of life with symptoms or after treatment [7]. These questionnaires will be covered below.

4.1.1 Sleep Questionnaires in the Approach to the OSA

Sleep questionnaires are essential for triaging severe cases, to measuring the impacts of sleep on individual life quality, deciding the best complementary sleep examination method to be requested, monitoring the response to the proposed treatments, for epidemiological studies and [3].

4.1.1.1 Epworth Sleepiness Scale (ESS)

ESS is currently the subjective test for evaluating drowsiness most used in clinical practice. It is relatively simple and self-administered, which quantifies the risk of the individual falling asleep in 8 specific daily life situations [7]. Most studies consider that a score lower than 10 points means the absence of excessive daytime sleepiness. A score greater than or equal to 10 points is classified as excessive daytime sleepiness [8] (Fig. 4.1).

Although widely used, its real value for patients with OSA is not yet fully established; often, even a patient with severe OSA may not present the symptom of ESS [9]. In a study to screen professional drivers for the diagnosis of OSA, low sensitivity (53.2%) and low specificity (58.8%) were found for the diagnosis of moderate and severe OSA [9].

The ESS is reproducible when applied at different times; a study showed no changes in the values answered by the volunteers after 71 days of the application [10].

When the correlation between ESS and polysomnography values is checked, a study demonstrated that the higher the AHI value, the higher the ESS [8]. Another

THE EPWORTH SLEEPINESS SCALE

Name: _____

Today's date: _____ Your age (years): _____

Your sex (male = M; female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* change of dozing
3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____

Fig. 4.1 The Epworth Sleepiness Scale. (Taken from article [8])

study found that the ESS values were significantly higher in severe OSA carriers when compared with mild and moderate apneas ($p < 0.001$). However, no statistical difference was found in the ESS values between mild and moderate forms [11].

4.1.1.2 Berlin Questionnaire

The Berlin questionnaire is a tool used to verify the probability of an individual having OSA. Unlike sleepiness scales, such as ESS, the evaluation by this questionnaire is directly related to the OSA entity. Therefore, it is recommended to be used in primary health units by family physicians to screen individuals who need to perform polysomnography [3].

This questionnaire uses symptom and physical examination data to achieve the final score. It consists of 10 questions divided into three categories, including: (1) The severity of snoring, including a question about OSA (items 1–5 of the questionnaire); (2) Excessive daytime sleepiness and fatigue (items 6–9); (3) Presence of systemic arterial hypertension or obesity (item 10). In addition, the questionnaire also includes information about age, gender, height, and weight [12].

If the individual responds positively to at least one item in two of the three categories, it is classified as high risk for OSA. The Berlin questionnaire has a sensitivity between 69 and 86%, and a specificity of 56–95%, with a positive predictive value ranging from 77 to 96% for OSA diagnosis in patients with such suspected disease [3]. In addition, a Korean study demonstrated a strong correlation between positive Berlin questionnaire results and AHI [12].

In clinical practice, the Berlin questionnaire has another practical utility in consultations performed by anesthesiologists before surgical procedures. Knowing the increased risk for anesthetic and surgical complications in patients with OSA, it is used in preanesthetic consultations to verify the need to perform a sleep monitoring test or prevent possible surgical and anesthetic complications in individuals with suspected OSA.

4.1.2 STOP-BANG Questionnaire

The STOP questionnaire was developed by Chung et al. [13] to be applied by anesthesiologists in preanesthetic consultations to assess the suspected diagnosis of OSA. It consists of four YES/NO questions about snoring, physical fatigue, witnessed sleep breathing pauses, and systemic blood pressure. It presents a sensitivity of 79.5% and specificity of 48.6% to detect individuals with an AHI greater than 30 events per hour [13]. STOP is a mnemonic rule for the 4 English terms: *Snoring, Tiredness, Observed apneas, and blood Pressure*.

To increase the sensitivity and specificity of this questionnaire, it was proposed the addition of four factors to the STOP questionnaire: body mass index (BMI), age, cervical circumference, and gender. Thus, the STOP-BANG questionnaire was created, which increased sensitivity to almost 100%, although specificity decreased to 37% [14]. STOP-BANG obeys the mnemonic rule of English terms, namely:

Snoring, Tiredness, Observed apneas and blood Pressure (STOP), *BMI, Age, Neck circumference, and Gender* (BANG).

This questionnaire has the advantage of being very direct and applied quickly (usually takes about 1–2 min). A score of at least three affirmative answers is used as a cutoff point to separate individuals with a low and high risk of having OSA [9].

4.2 Physical Examination in the Diagnosis of OSA

The recognition of characteristics on physical examination, which are associated with the presence and/or severity of OSA clinical suspicion, allows early and individualized intervention for the patient. Despite having been the target of studies for more than 40 years, there is no finding of high-specificity physical examination for the diagnosis of sleep apnea [15]. However, the heterogeneity of pathophysiological and clinical phenotypes may reason the absence of a characteristic sign. Still, several populations and case-control studies had shown anthropomorphic characteristics associated with the prevalence and severity of OSA and therapeutic success rates. In addition, a higher prevalence of OSA in middle age and male gender are highlighted [16].

Body mass index (BMI) is, admittedly, a measure of overweight and obesity is strongly correlated with OSA diagnosis [3].

A BMI greater than 25 kg/m^2 increases the risk of apnea by 2 times, and BMI greater than 30 kg/m^2 increases the risk four times [17]. Other measures related to body adiposity, such as neck circumference (NC) and the ratio between waist and hip, correlate with moderate OSA. Still, after correction with a model including BMI, NC, and waist-hip ratio, only BMI and NC are risk factors [16]. A NC of at least 40 cm has a sensitivity of 61% and a specificity of 93% for OSA regardless of gender. Several diagnostic screening questionnaires containing age, gender, BMI, and NC showed high predictive diagnostic power [3, 12, 13, 18].

The specific physical examination of the upper airways has some relationships with the therapy to be indicated [19–21]. Nasal alterations with associated septal deviation and of inferior turbinate hypertrophy have a higher prevalence among apneic rather than controlled-group individuals [19], without an association with the severity of OSA [22]. Nasal breathing difficulties are related to poor adaptation to continuous pressure equipment (CPAP) [23] (Fig. 4.2).

The oropharynx examination of the is subjectively standardized by the position of the structures within the cavity. We classified the palatine tonsils in 5°: 0 tonsils removed; 1 occupies less than 25% of the space between the sidewall and the midline; 2 occupies between 25 and 50% of the area between the lateral wall and the midline; 3 occupies more than 50% and less than 75% of the space between sidewall and midline; 4 occupies more than 75% up to 100% of the distance between the side walls and the midline. The actual volume of tonsils is agreed with subjective classification, with a correlation between tonsillar hypertrophy and the presence of sleep apnea, but not with severity [24]. The position of the relaxed tongue inside the

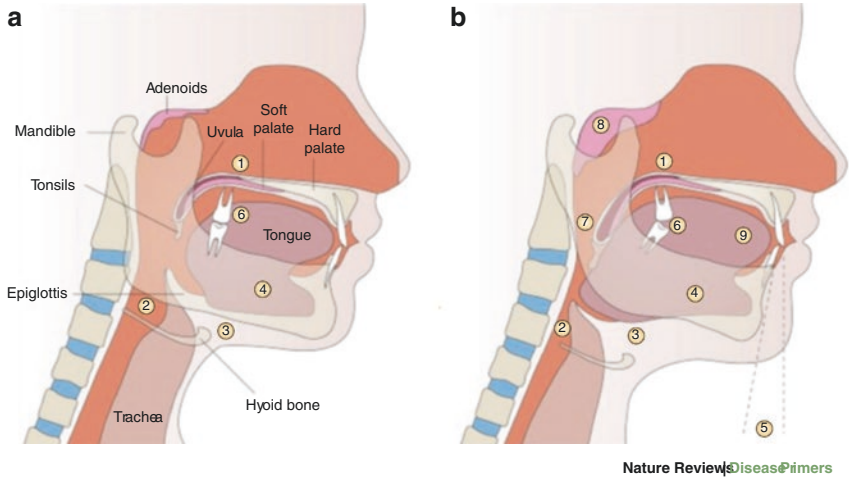

Fig. 4.2 (**a**) Normal anatomy. (**b**) Typical anatomical changes in obstructive sleep apnoea syndrome (OSAS): a long soft palate and enlarged uvula (1); a reduced retroglossal pharyngeal airway space (2); an increased distance between the hyoid bone and the mandible(3); a shorter and more vertical mandible (4); a retro-position of the mandible, which is measured by the angle (retrognathia) (5); dental overbite or loss of normal dental occlusion (6); tonsillar hypertrophy (7); adenoid hypertrophy (8);and macroglossia (unusual large tongue) (9). [Lévy, P. et al. (2015) Obstructive sleep apnoea syndrome. Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.15]

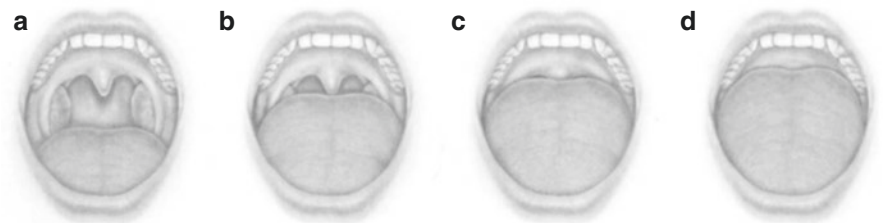

Fig. 4.3 Mallampati classification, Friedman adaptation et al. 1999. (**a**) Mallampati 1. (**b**) Mallampati 2. (**c**) Mallampati 3. (**d**) Mallampati 4

mouth concerning the palate is classified as the Mallampati index (Fig. 4.3). Alterations of the oropharynx (such as positioned retro palate, thick palate, and uvula, medialized tonsillar pillars, and tonsillar hypertrophy, grade 3 or 4) are associated with the presence of OSA [19, 21, 25]. The association of BMI, Mallampati classification and tonsils grade was organized into a model that predicts the OSA risk and the success of pharyngeal surgery. In adults, uvulopalatopharyngoplasty

surgery shows a success rate when Friedman's classification is grade 1 or 2, which corresponds to the nonobese subject, with low Mallampati, and hypertrophic tonsils [26]. The shape of the ogival palate and modified Mallampati 3 or 4 were shown to be associated with AHI [26].

Skeletal craniofacial alterations can be evaluated by physical examination and confirmed by cephalometry. Related to the diagnosis of sleep apnea are maxillary and mandibular hypoplasia. In addition, a narrow and ogival hard palate may predispose to OSA [3]. Recently standardized facial photographs have been added to identify facial phenotypes that correlate to skeletal craniofacial alterations and presence of OSA [27].

4.3 Complementary Exam in the Diagnosis of OSA

4.3.1 Nasofibrolaryngoscopy

This exam is critical to evaluate the upper airway and locate possible obstructive sites involved in the origin of respiratory disorders. Usually used in the ENT office, it allows visualization of tumors and anatomical anomalies [3, 19]. It is fundamental to mention that the exams are performed during wakefulness and usually in seated patients.

A complete evaluation of the nasal cavities in detail, the nasopharynx, oropharynx, the soft palate up to the larynx. There is observation of the size of the tonsils, uvula, lingual tonsils, the base of the tongue and the epiglottis. The Muller Maneuver research—forced inspiration—allows to simulate the tendency of airway collapse, but the subjectivity of research and interpretation make its standardization difficult. Also, aspects suggestive of laryngopharyngeal reflux could be investigated.

4.3.2 Drug-Induced Sleep Endoscopy

Drug-induced sleep endoscopy (DISE) has been used for the diagnostic evaluation of the site of airway obstruction [28] allowing exploration of anatomical sites for a possible therapeutic intervention. May it be for upper airway surgery (UAS) [29, 30], or mandibular advancement device (MAD) [31]. In addition, sleep endoscopy is part of the protocols for hypoglossal nerve stimulation implant surgery [32]. It is also proposed to explore the upper airways for patients who do not tolerate CPAP, due to the possible identification of structural changes during the use of positive pressure equipment, for example, patients with an epiglottis that closes the laryngeal inlet while using positive pressure machines [33]. This exam provides a dynamic assessment of the upper airway [34].

There is a discussion about the best drug to induce sleep, or sedation. Studies have shown differences between drugs. Comparatively to propofol, midazolam produces greater collapse in the velopharynx and base of the tongue than propofol. The comparison between propofol and dexmedetomidine showed that propofol increases

collapse in the entire airway compared to the last one. The disadvantages of using dexmedetomidine would be the longer onset of action, half-life, and cardiovascular effects such as bradycardia [34].

On the other hand, when sleep architecture was evaluated, only the use of midazolam for more than 90 min of examination allowed an architecture similar to natural sleep, with non-REM and REM sleep [35]. Propofol showed an increase in N3, a reduction in N1, and the absence of REM sleep [36]. Thus, the evaluation of sleep endoscopy lasting between 15 and 30 min makes it possible to reliably assess obstructions occurring in N1 and N2 [34]. Still, there is no clarity about the use of sleep endoscopy in patients with REM-related OSA.

Given the risks caused by respiratory and cardiological changes, DISE must be performed under monitoring. It is widely performed in the operating room. Ideally, monitoring the level of sedation through the bispectral index (BIS) [30]. The interobserver agreement is linked to the experience in performing DISE, requiring a learning curve to obtain reliable observations [37].

While evaluating DISE findings related to the severity of OSA, the lateral collapse of the oropharyngeal region and the anteroposterior region of the base of the tongue and the BMI were considered predictors of the severity of apnea [38]. A meta-analysis [39] describes findings when evaluating the sites of obstruction in 2 points, 92% present obstruction in the soft palate and 58% obstruction at the base of the tongue. When 4 different levels are evaluated: 84% have obstruction in the soft palate, 32.8% in the palatine tonsils, 52% for the base of the tongue, and 34.3%; in the epiglottis. In this study, obstruction at the tongue base correlates with the mean AHI (Fig. 4.4).

4.3.3 Biomarkers

A polysomnography exam confirms the final diagnosis and severity degree of OSA. However, this laboratory exam is costly, is not readily available, and is time-consuming. Therefore, there are other tools that expand the diagnosis providing screening, diagnosis, severity, evolution, and prognosis. Biomarkers could be an alternative tool. However, OSA is correlated to several metabolic dysfunctions and comorbidities, making it challenging to identify a high specificity biomarker. Strong evidence is based on small studies performed in sleep centers or participants with complaints of snoring and tiredness. There isn't a population cohort where this association could be tested.

Meta-analysis have shown that some inflammatory biomarkers such as C-reactive protein, tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), interleukin 8 (IL-8), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and Selectins. On this M-A, it is possible to highlight that IL-6 is two times higher in apneic patients than in controls, ICAM 3 times, and IL-8 4 times higher [40]. Another M-A [41] appointed that plasma IL-6 and IL-10 are suitable biomarkers to identify adults with or without OSA; this conclusion is influenced by the high sensitivity and specificity reported by Li et al. respectively, 100% and

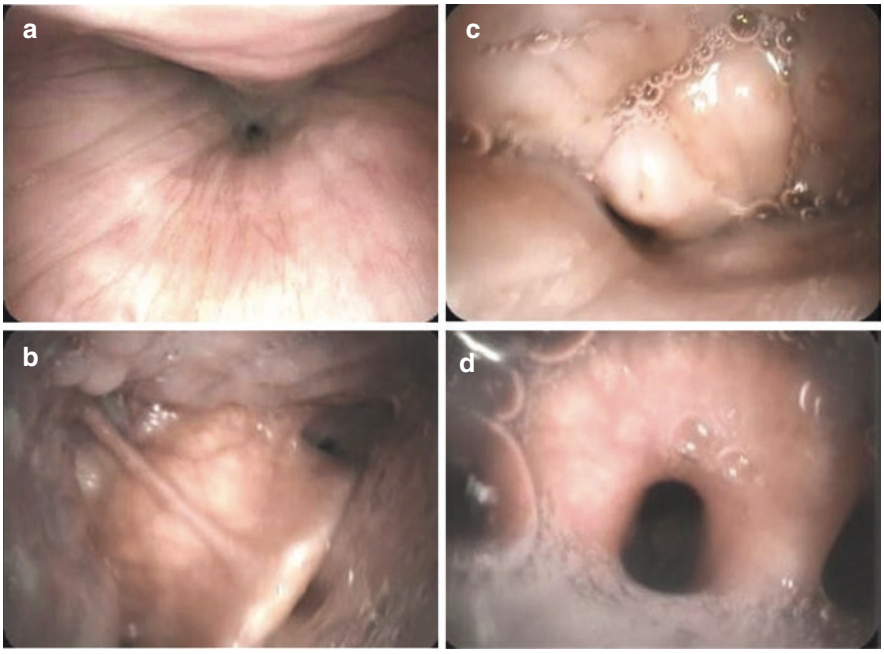

Fig. 4.4 (**a**) Sleep endoscopy showing retropalatal area obstruction. (**b**) Sleep endoscopy showing hypopharynx obstruction. (**c**) Sleep endoscopy showing larynx collapse (type closing door). (**d**) Sleep endoscopy showing larynx collapse (type closing book). [Salzano G, Maglitto F, Bisogno A, et al. Obstructive sleep apnoea/hypopnoea syndrome: relationship with obesity and management in obese patient. Acta Otorhinolaryngol Ital 2021;41:120–130. https://doi.org/10.14639/0392-100X-N1100]

100% for IL-6 and 100% and 97% for IL-10. Other possible biomarkers that could be cited are acid uric, PTH, and vitamin D, but the level of evidence does not support clinical use [40, 41].

4.4 Polysomnography and Sleep Monitoring

In Sleep Medicine, the patient's report on objective data about his night of sleep is often impaired. With polysomnography (sleep monitoring)—perhaps still the only complementary examination available—it is important to highlight the frequent complaint of patients submitted to in laboratory polysomnography, and the subjective impression of the evaluated night of sleep does not correspond to the nights at home.

Understanding the different monitoring modalities and characteristics of each patient and the pathology may allow a better understanding of the disease. Therefore, the quality of polysomnography is fundamental for the follow-up of any patient.

4.4.1 Polysomnography—Sleep Monitoring

Polysomnography is still the "gold standard" for the diagnosing Sleep Breathing Disorders and other sleep-related disorders [1]. It should be performed at night in the sleep laboratory for at least 6 h under the supervision of a trained technician. The quality of the test is fundamental for the diagnosis and therapeutic planning, and post treatment control. Therefore, it is essential to emphasize the need for a new polysomnography study after the implementation of treatment to measure the real impact of the proposed treatment.

Sleep monitoring techniques have been systematically updated over the years, with the incorporation of new technologies [42]. Since the first standardization for sleep interpretation in 1968 [43], almost 30 years have passed for a significant review of these criteria [44]. The American Academy of Sleep Medicine published in 2007, and updated in October 2020 (version 2.6) the technical criteria for sleep monitoring, updating the rules for sleep and respiratory parameters analysis [45].

The minimum parameters to be used in polysomnography are
- Electroencephalogram: electrodes F4–M1, C4–M1, and 02-M1
- Electrooculogram: bilateral
- Electromyogram: chin, tibial anterior bilateral
- Nasal and oral airflow recorded by thermistor or thermocouple sensors
- Recording of nasal pressure obtained by a pressure transducer
- Record of thoracic and abdominal movement
- Electrocardiogram
- Oximetry digital
- Hoarse record
- Body position record

Data captured on a polysomnography night should be interpreted by a physician with a specialization in Sleep Medicine following American Academy of Sleep Medicine criteria. Reading and interpretation training requires specific training. The polysomnographic tracing is read in periods of 30 s for sleep staging with differentiation of Stages REM and N1, N2, N3, and marking of respiratory and limbs events. The entire night study is checked by the polysomnographic tracing [44].

The final report of the polysomnography must provide the following data
- Parameters used for monitoring
- Sleep architecture:
  - Total record time—TRT
  - Total sleep time—TST
  - Efficiency: >85% (TST/TRT)
  - Latencies: NREM and REM
  - Total time awake after sleep onset
  - Time at each stage
  - Percentage of TST at each stage

- Arousal:
  - Total number
  - Index

It is important to have a differentiation between those associated with respiratory events and those associated with limbs movements: total number and index.

- Cardiac events:
  - Frequencies
  - Arrhythmias
- Lower limbs movements
  - Periodic movements of members
  - Awakenings associated with movements
- Respiratory events:
  - Hypopnea–apnea index (AHI)
  - Oxyhemoglobin desaturations: average, minimum, and desaturation index per hour
  - Predominant decubitus during sleep and in the presence of respiratory events
  - Presence of snoring
- Conclusion:
  - Description of exam findings
  - EEG abnormalities
  - Non-ECG abnormalities
  - Behaviors observed during sleep (somniloquism, sleepwalking, etc.)
  - Hypnogram (optional)

4.4.2 Portable Sleep Monitoring—OCST (Out of Center Sleep Testing)

In 1994, the Practical Parameters of the American Association of Sleep Disorders—the current American Academy of Sleep Medicine [46]—were published for the evaluation of OSAS with Portable Monitoring, defining the types of Sleep Study—Table 4.1—and discussing the technical criteria and limitations for its application.

A rational protocol for the indication of home studies, detailing their indications and limitations, has been delineated over the years. The points listed are for diagnostic suspicion, that entail groups of patients and criteria of use. Undoubtedly, patients with Sleep Breathing Disorders are the main beneficiaries. Collop et al. [47] describe a flowchart rationalizing the indication of Home Monitoring, concluding that this tool should be integrated into a broad program of evaluation and follow-up of the patient and conducted by a sleep specialist physician.

This monitoring can be assisted or not by a polysomnography technician and allows the examination to be recorded in the patient's home. Its limitation is the loss of monitoring channels due to failure or loosened channel issues, which has been estimated between 4 and 33%, and the significant variability of equipment and

Table 4.1 Studies for sleep apnea assessment (minimum 06-h monitoring)

	Level I Standard polysomnography	Level II Comprehensive portable polysomnography	Level III Modified portable sleep apnea testing	Level IV Continuous single- or dual-bioparameter recording
Parameters	Minimum of seven, including EEG (C4-A1 or C3-A2), EOG, chin EMG, ECG, airflow, respiratory effort, oxygen saturation	Minimum of seven, including EEG (C4-A1 or C3-A2), EOG, chin EMG, ECG or heart rate, airflow, respiratory effort, oxygen saturation	Minimum of four, including ventilation (at least two channels of respiratory movement, or respiratory movement and airflow), heart rate or ECG, oxygen saturation	Minimum of one
Body position	Documented or objectively measured	May be objectively measured	May be positively measured	Not measured
Leg movement	EMG or motion sensor desirable but optional	EMG or motion sensor desirable but optional	May be recorded	Not recorded
Personnel	In constant attendance	Not in attendance	Not in attendance	Not in attendance
Interventions	Possible	Not possible	Not possible	Not possible

EEG electroencephalogram, *EOG* electrooculogram, *EMG* electromyogram, *ECG* electrocardiogram

technologies involved. Studies discuss the diagnostic failure of sleep monitoring, both in the gold standard and in-home monitoring, observing rates of 20% of AHI failure below 15/h and variations between 15 and 25% in consecutive night studies. With an interval of 30 days, only 45% of the cases presented night-to-night differences less than or equal to 5 events/h.

Type II monitoring allows the identification of different sleep phases with a demonstration of statistics and calculations of AHI/h of sleep. It has the limitation of the technician going to the patient's residence to fit and remove the equipment the next day. There is no relocation of registration channels if they are disconnected during the exam.

Type III monitoring does not assess sleep phases nor differentiate whether the events occur at wakefulness or during sleep. It gives information and determines only respiratory events, not allowing the diagnosis of other events such as limb movement. Some equipment allow the patient to assemble it at home without the need for the technician to move.

Type IV monitoring captures 1–2 channels, and one of them is mandatorily oximetry. It does not evaluate the sleep phases and does not differentiate the types of apneas but evidences the desaturations. However, it does not allow for the evaluation of any sleep-related data.

Peripheral Arterial Tonometry (PAT) [48] is a new method proposed to diagnose OSA. This technology uses a sensor (modified digital plethysmography) that eliminates the venous pulse and continuously measures changes in arterial volume in the finger. Changes in the arterial volume are regulated by α-adrenergic innervation and reflect the sympathetic activity. Events of apneas or hypopneas lead to arousals and therefore increased sympathetic activity and peripheral vasoconstriction, resulting in attenuation of the PAT signal. Watch-PAT® is a portable device that detects obstructive events by noticing changes in sympathetic activity associated with the end of events. This equipment also aims to analyze, in addition to AHI and RDI, total sleep time and sleep phases [49].

All portable sleep monitoring should also issue a report showing the type of monitoring. The parameters used to obtain the data, and a report of the possible records performed. Version 2.6 of the American Academy of Sleep Medicine Manual defines the items to report. The clarification of these data will allow the evidence of objective respiratory data per hour of sleep or monitoring time.

4.5 Obstructive Sleep Apnea Syndrome

The initial description of Obstructive Sleep Apnea Syndrome was made by Guilleminault in 1976. The definition of clinical parameters of normality with the "cutoff" in 5 events/h was described in 1985.

Obstructive sleep apnea is characterized by repetitive episodes of upper airway obstruction (respiratory events) resulting in oxygen desaturation and awakenings. The respiratory events are described as:

- Apnea Respiratory pauses of at least 10 s, baseline decrease in at least 90% with respiratory effort in chest brace or abdomen.
- Hypopnea is characterized by partial airway obstruction. They have the same consequences as apneas. They consist of a decrease in nasal pressure baseline by 30%, minimum duration of 10 s and desaturation of 3% or arousal.
- Increased airway resistance is characterized by the same symptomatology of OSAS but without apnea or hypopnea in polysomnography, with *the presence of RERA*: awakening associated with respiratory effort. It consists of an event lasting at least 10 s with increased respiratory effort leading to an awakening. It can be evaluated on the flow sensor by a flattening on the flow curve extending the inspiratory period.

The publication of the International Classification of Sleep Disorders—3rd. Edition 2014—Table 4.2—seeks to highlight, in addition to complaints or symptoms, the presence of comorbidities and adds the possibility of sleep monitoring being

Table 4.2 Sleep apnea diagnostic criteria

Diagnostic criteria
((A and B) or C) + D must be met
A. The presence of one or more of the following:
1. The patient complains of sleepiness, fatigue, insomnia, or other symptoms leading to impaired sleep-related quality of life.
2. The patient wakes with breath-holding, gasping, or choking
3. The bed partner or other observer reports habitual snoring or breathing interruptions during the patient's sleep
B. Polysomnography (PSG) or home sleep apnea test (HSAT) demonstrates:
1. Five or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals) *per* hour of sleep during a PSG or per hour of monitoring (HSAT).
C. PSG or HSAP demonstrates:
1. Fifteen or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals) per hour of sleep during a PSG or per hour of monitoring (HSAT).
D. The symptoms are not better explained by another current sleep disorder, medical disorder, medication or substance use.

American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed, text revision. Darien: IL: American Academy of Sleep Medicine; 2023

performed outside the *laboratory (OCST)*. It includes the possibility of the respiratory event index being described "by monitoring time," in addition to "per hour of sleep" as traditionally described validating monitoring without recording sleep data.

4.5.1 Criteria for Severity of OSA

The OSA severity criteria were empirically created in 1999 with a publication by the American Academy of Sleep Medicine (AASM) [50]. This publication created severity categories based on the apnea-hypopnea index (AHI) of polysomnographic examination. The rationale for this classification derived from data from the Wisconsin sleep cohort [51], a large cross-sectional study that correlated The AHI with the isolated measurement of blood pressure made on the night of polysomnographic examination. This study concluded a linear increase in blood pressure with increased AHI and highlighted that the risk of hypertension became substantial with an AHI of around 30 or more. Therefore, the AASM created the categories of mild, moderate, and severe OSA, noting that there were no data to differentiate the mild and moderate categories. However, despite this recognized lack of evidence, this classification remains in vigor and is widely used in research and clinical practice [52].

According to AHI, OSA in adults is classified as

1. Normal: AHI from 0 to 4.9/h of sleep.
2. Mild: AHI from 5 to 14.9/h of sleep.
3. Moderate: AHI from 15 to 30/h of sleep.
4. Accentuated: AHI above 30/h sleep.

Note that in this classification, the moderate category includes the AHI limit values of 15 and 30.

Despite the evolution of the sensors used in polysomnography, and several changes that occurred in the interpretation of the tracings—particularly in the way of marking a hypopnea [53, 54]—this classification remains unchanged. In addition, this same classification is used for all types of examinations that record respiratory events during sleep, that is, polysomnography (examination with objective sleep quantification) and polygraphs (examination without objective quantification of sleep). Some sleep laboratories record, in addition to apneas and hypopneas, a third respiratory event known as "RERA" (respiratory effort related arousal: awakening associated with respiratory effort). The index that sums apneas, hypopneas and RERAs is known as respiratory disorder index (RDI). The numerical criterion of severity used for the RDI is the same used for the AHI above.

For the population under 18 years of age, the most used OSA severity classification involves obstructive AHI (AHIo) [53]. In obstructive AHI, obstructive and mixed apnea events and obstructive hypopneas are added, excluding apneas and hypopneas of a central nature. It should be emphasized that this classification of severity for children has even less scientific evidence than that used in adults and reflects little on the overall well-being of the child. According to AHIo, OSA in children is classified as:

1. Normal: AHIo from 0 to 1/h of sleep.
2. Mild: AHIo from 1.1 to 5/h of sleep.
3. Moderate: AHIo from 5.1 to 10/h of sleep.
4. Accented: AHIo above 10/h of sleep.

Although widely used, a simple numerical criterion is not sufficient to categorize, nor reflect, the various clinical presentations of patients with OSA. The oximetry values, although they point to the intensity of OSA, have not yet been effectively incorporated into any classification of the severity of this disease. It is believed that the spectrum of OSA is better understood when considering, in addition to polysomnography, the symptomatic aspects (such as daytime sleepiness and sleep quality) and the comorbidities present in each individual. However, incorporating this information into a new classification of severity of OSA has not yet occurred.

The evaluation of snoring remains without objective parameters for its measurement during sleep monitoring.

Take-Home Message

- Diagnosis of OSA is performed with a complete clinical history, sleep questionnaires, and a complete physical examination.
- Complementary physical examination includes a Nasofiberolaryngoscopy, Drug-induced sleep endoscopy (DISE), and Biomarkers.
- There is a need to perform a Sleep test. There are diverse types of sleep tests, with Polysomnography being the "Gold Standard". However, the limitation of

possibilities to perform this test has made it necessary to perform more simplified sleep tests.

- According to AHI, OSA in adults is classified as:
- Normal: AHI from 0 to 4.9/hour of sleep.
- Mild: AHI from 5 to 14.9/hour of sleep.
- Moderate: AHI from 15 to 30 /hour of sleep.
- Severe: AHI above 30/hour sleep.

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Treatment

5

"Whatever It Takes"

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5.1 Introduction: OSA as a Chronic and Difficult to Treat Disease

Obstructive sleep apnea (OSA) treatment is one of the most difficult challenges of the modern medicine for many and not related reasons.

1. First of all, OSA is by its nature a worsening disease with a natural trend to became more severe along the time. Basically, to treat OSA is like to swim against the current. Any possible treatment must face this natural trend of OSA to become more severe along the time, even if treated.
2. The detailed pathophysiology of OSA seems to be very complex and different in different subjects and probably not yet really well understood into detail. In the last decade, a set of most prominent pathophysiological components were described and introduced into the practice mainly for treatment selection.
3. From the surgeon perspective, the number of possible treatments (conservatives and surgical ones) is relatively high, and the selection rules for each of them are not completely clear-cut. There is a real risk that any different specialist overestimates the role of his own option among the many available.
4. From the patients' perspective, very frequently, the real impact of the disease into the patient's health is not completely understood, and this underestimation may produce a low level of motivation and more difficult treatment acceptation.
5. Moreover, a personal preference or not acceptance may compel the surgeon to shift to a treatment option different: from the most effective one to the best accepted by the patient. It implies that even along the time a therapy must be discontinued because it not anymore accepted by the patient, seeking for a different modality.
6. The different levels of efficacy of many treatments, frequently inferior to 100%, may require in a significant number of cases a combination of more than one single treatment, that's the complex problem of multimodal therapy.
7. Last but not least, all the conservative treatments (e.g., ventilation, MAD, etc.) must face the problem of long-term treatment adherence, and on the other hand,

treatments like surgery may pay the toll of a real efficacy only in a short or middle time span.

For all the above-mentioned reasons, OSA treatment for the single patients may be difficult to properly select, requires a high level of cooperation by the patient and an open and honest discussion among different specialists, and must be checked for persistent efficacy along the time. Many of these concepts are summarized in the so-called P4 medicine. "The four Ps offer a means to: Predict who will develop disease and co-morbidities and prevent rather than react to disease (see below); Personalize diagnosis and treatment; have patients Participate in their own care. P4 medicine is very applicable to obstructive sleep apnoea (OSA) because each OSA patient has a different pathway to disease and its consequences."

5.2 Treatment Goals

The common goals of all the proposed treatment for OSA may be summarized as:

(a) Relief of diurnal and nocturnal symptoms
(b) Prevention of possible complications
(c) Improvement of Quality of Life (QOL)

5.3 Primary, Secondary and Tertiary Prevention in OSA

- Obesity and increasing median age of patients play significant roles in the significant prevalence of OSA. The rise in body mass index (BMI) and medical comorbidities are shown to be directly associated with both the prevalence and the severity of OSA. A healthier lifestyle with regular exercise associated with weight loss has been shown to improve OSA in selected patients. Since the 1980s, it is known that alcohol ingestion increases the incidence of arterial oxygen desaturation and disordered breathing during sleep, and its consumption should be avoided. Other lifestyle interventions like sleep hygiene and tobacco cessation are recommended in OSA's prevention, although their real effectiveness has not been proved yet. As sleep quality is related to daily functioning and mood, which have an impact on overall quality of life, lifestyle interventions may entail not only reductions of cognitive impairments and depressive symptoms but also an increase of the patients' overall well-being.
- Secondary prevention emphasizes early disease detection, and its target is healthy-appearing individuals with subclinical forms of the disease. The subclinical disease consists of pathologic changes, but no overt symptoms that are detectable by physician's evaluation. Secondary prevention often occurs in the form of screenings, which aim to offer an early treatment or intervention and thereby reduce the incidence and mortality of the health problem within the population. Thus, it is crucial to identify as accurately as possible specific

demographic-clinical patterns in order to select high-risk populations who should undergo screening for OSA. It needs to be noted that a screening program would focus in particular on asymptomatic patients, because this group has a particularly high risk in developing neurological, pulmonary and cardiovascular complications, given the low motivation of this type of patients. However, evidence is still not sufficient to determine whether treatment of screen-detected asymptomatic OSA improves outcomes, in particular mortality or cardiovascular events. Several different morbidity biomarkers have been proposed for OSA. Data in literature show impaired levels of inflammatory markers related to oxidative stress in the exhaled breath of OSA patients in the form of an increase in proinflammatory cytokines and a decrease in anti-inflammatory cytokines. A perturbation of lipid metabolism, with an elevation of both fasting and postprandial lipid levels in blood or urines, is also described.

- Tertiary prevention is enforced in symptomatic patients and aims to reduce the severity of the disease as well as of any associated sequelae. While secondary prevention seeks to prevent the onset of illness, tertiary prevention focuses on reducing the effects of the disease once established in an individual. It is established that severe OSA is associated independently with higher incidence of stroke and with the presence of hypertension (OR = 1.60), diabetes (OR = 2.00), metabolic syndrome (OR = 2.80) and depression (OR = 1.92). From this perspective, the patient, in addition to the specific OSA treatment, should always be referred to cardiological, neurological, endocrinological evaluations and follow-up.

Endotypes and Phenotypes-Guided Treatment is the modern way to describe, classify and select in a unitary way the different interventions for addressing OSA. In Table 1, treatments are listed according to the target endotype.

1. Anatomic: Upper Airways (UARWs) increased collapsibility
   - CPAP
   - Surgery
   - Mandibular advancement devices
   - Weight loss
2. Functional: Reduced muscle responsiveness
   - Myofunctional therapy
   - Hypoglossus nerve stimulation
3. Functional: Increased loop gain
   - O_2
   - CO_2
   - Drugs (e.g., Acetazolamide)
4. Functional: Low respiratory arousal threshold
   - Drugs (e.g., Trazodone, etc.)

In all OSA patients, some degree of collapse is observed and treated with one or more than one so-called anatomical interventions (CPAP, surgery, MAD and weight

loss). In about one-third of all the OSA patients, an additional functional endotype may be demonstrated, possibly requiring an additional modality of treatment.

5.4 Continuous Positive Airway Pressure Therapy

The application of a continuous positive pressure in the airways (CPAP), through a nasal or oronasal mask, or nasal pillow, is the first therapeutic option that is found to prevent narrowing of the pharynx, the cause of snoring and apneas and hypopneas. The CPAP normalizes the respiratory activity during sleep and restores a correct sleep architecture. The CPAP titration consists in finding the therapeutic value of the PAP, i.e., the minimal positive pressure that prevents the occurrence of apneas and hypopneas. There are two main ways of titrating CPAP, manually in sleep laboratory and with autoadjusting PAP (APAP) at home. The second one, less time consuming and expensive, is currently the most widely used in daily clinical practice. A meta-analysis showed that in adults with OSA, positive airway pressure (PAP) compared to no treatment results in a clinically significant reduction in disease severity, sleepiness, blood pressure and motor vehicle accidents, and improvement in sleep-related quality of life. In addition, the initiation of PAP in the home demonstrated equivalent effects on patient outcomes when compared to an in-laboratory titration approach. It has been also demonstrated that the use of APAP or the noninvasive ventilation with a double level of pressure support (bilevel PAP) did not result in clinically significant differences in patient outcomes compared with standard continuous PAP. The APAP has a role in finding the therapeutic value of the PAP rather than in OSA therapy. When apnea and hypopnea events are associated with other and/or predominant respiratory disorders like hypoventilation or Cheyne–Stokes breathing, the treatment of choice is bilevel-PAP. It has shown a clinically significant improvement in PAP adherence with the use of educational, behavioral, troubleshooting and telemonitoring interventions. Systematic reviews for specific PAP delivery method showed that nasal mask compared to oronasal mask has improved adherence and slightly greater reductions in OSA severity; heated humidification compared to no humidification reduces some continuous PAP-related side effects; and pressure profile PAP did not result in clinically significant differences in patient outcomes compared with standard continuous PAP. CPAP is safe, effective and well-tolerated treatment in adults and even in children with severe OSA, especially in those with craniofacial abnormalities, neurological disorders or obese. Adherence to the treatment is considered valid if carried out for at least 4 h per night for at least 70% of the nights. It has no absolute contraindications. Relative contraindications are the presence of bubbles in the lung and infectious pathology of the upper airways and ear. The most common adverse effects of CPAP are the onset of rhinitis symptoms, dryness of the nasal and oropharyngeal mucous membranes, conjunctivitis, injuries and ulcers of the nasal bridge, feeling of suffocation and claustrophobia. Any functional (nasal valve collapse or floppy epiglottis) or anatomic (nasal septum deviation, tonsillar-adenoid hypertrophy, sinonasal polyposis) cause of significant upper airway occlusion can result in CPAP fails. All patients

that fail CPAP therapy would benefit from upper airway evaluation by the otolaryngologist to consider site-specific surgical therapies. In pandemic era, CPAP treatment should not be interrupted. Indeed, adopting mandatory government guidelines and local healthcare facilities to minimize the spread of viral infection ensured workplace safety and safety measures for patients and for health workers.

Among the various therapeutic options available today, the CPAP is the one for which there is evidence of a positive effect on cardiovascular and cerebrovascular morbidity, decrease in motor vehicle accidents and reduced mortality. Although it was proposed 40 years ago, the CPAP still represents the only effective therapy regardless of OSAS severity, as well as the treatment with the greatest evidence in terms of long-term benefits.

5.5 Oral Appliances (MAD)

A valuable conservative therapy for OSA, alternative to CPAP, is represented by the mandible protrusion by means of an oral appliance (OA). This device covers both the upper and lower dental arches and is configured so that the lower jaw is held forward in a more protruded position, thus allowing to widen the size of the pharynx, stretch tongue muscles counteracting tongue's collapse during sleep, stabilize the hyoid bone and the soft palate, and prevent the posterior rotation of the jaw. OA is indicated for patients with mild to moderate OSA or primary snoring and is also an accepted therapy for patients with severe OSA who are unresponsive or unable/unwilling to tolerate CPAP. An adequate number of healthy teeth (at least 6–10 teeth in each dental arch) should be present to anchor the OAs, and patients should be able to protrude the mandible forward and open the jaw without significant limitations in order to be suitable for OA treatment. The American Academy of Sleep Medicine (AASM) and the American Academy of Dental Sleep Medicine (AADSM) guidelines suggest the use of custom-made OAs (i.e., fabricated with patient-specific design features obtained from impressions) and titratable (i.e., a mechanism allows the mandible to be moved gradually in a forward position). Currently, there is no well-defined protocol that indicates the mandibular protrusion in which to build the device since there is no dose-dependent effect of mandibular advancement on treatment success. It is advisable to provide an individualized therapy for each single patient, start with a slight mandibular advancement and gradually increase the mandibular protrusion through the use of titratable OAs until the highest reduction in AHI is achieved. It is necessary to identify the minimum amount of mandibular advancement required for an individual patient while getting the highest reduction in AHI in order to optimize treatment efficiency while reducing the risk of side effects and, also, improving treatment adherence. Early recognition and adequate control of possible unwanted effects are crucial for the success of therapy with OA, as the effectiveness of therapy depends not only on the efficiency of the device in reducing AHI, but also on patient compliance. Uncontrolled side effects could in fact lead to a reduction in compliance up to the interruption of therapy with serious effects on the patient's health. Equally crucial for adherence to therapy is therefore

to inform the patient with specific informed consent about the possible onset of undesirable effects before undertaking therapy with OA, also underlining how such undesirable effects should not be considered as a factor limiting therapy in the light of the more serious risk to health of not treating a patient affected by OSA.

Most side effects of treatment with OAs are temporary and gradually disappear during the first few months of treatment. These minor side effects include mucosal dryness, tooth discomfort and hypersalivation. In the long term, the main side effects are represented by dento-skeletal changes and temporomandibular disorders (TMD), often of muscular origin. The dental effects are related to the muscle reaction to OA insertion. The protrusion of the mandible induced by OAs generates reciprocal forces on the soft tissues and the muscles that attempt to move the mandible backward to restore its normal position. These forces are transmitted to the teeth and to the bone to which the OA is anchored and thus can produce dento-skeletal changes. A significant correlation between the duration of the therapy and the change of these parameters is well documented in the literature. In conclusion, it is important to spread the idea that a transdisciplinary approach to OSA is essential for the diagnosis, the decision-making process and the monitoring of treatment response. As dentists, we must be aware that not all the problems related to OSA can be solved only by means of mandibular protrusion. Clinicians should be kept well-informed on the most up-to-date scientific evidence in order to provide an evidence-based clinical decision-making process for the treatment of OSA, from which a greater amount of patients would reliably benefit.

5.6 Drugs

However, the one-size-fits-all approach is not the best one in such complex and multifactorial pathology. For this reason, four phenotypes have been recognized, combined with an ideal target medical therapy as described below.

Impaired upper airway anatomy: Obesity is the major cause of narrow pharyngeal airway. Weight loss drugs in OSA have been tested with good results. The incretin mimic, liraglutide—a glucagon-like peptide-1 receptor agonist—reduced body weight by approximately 6%, BMI by approximately 10% and apnea/hypopnea index (AHI). Even fluid redistribution can accumulate to the neck. Diuretics or sodium-restricted diets which reduce fluid retention have been investigated as a potential treatment option to prevent nocturnal rostral fluid shift in OSA.

Low respiratory arousal threshold: Hypnotics are the target therapy for this phenotype, with the aim of inducing sleep. In the past, hypnotic use was not recommended due to perceived risk of reduced pharyngeal muscle activity combined with delayed arousal responses, which may cause prolonged respiratory events and worse hypoxemia. Nevertheless, new trials detected a different outcome with benzodiazepine receptor agonist zopiclone and the tetracyclic antidepressant trazodone. In any case, new studies are required to better understand the safety profile.

High loop gain: Drugs with carbonic anhydrase inhibitor properties such as zonisamide and acetazolamide have been shown to reduce OSA severity, potentially

via reductions in loop gain. Furthermore, these molecules have weak diuretic properties. Oxygen therapy has been used to reduce loop gain and, in an earlier study, to reduce the AHI by approximately 50% in people with a high loop gain phenotype.

Upper airway muscle responsiveness: Cannabinoids have been proposed to improve respiratory stability through attenuation of vagal feedback to the medulla to help stabilize breathing and activate pharyngeal muscles via serotonergic processes.

5.7 Nasal Surgery

Nasal surgery for sleep breathing disorders includes all corrective operations on the nose, united by an identical respiratory purpose, performed anatomically in the axis between the external valve and the choana (Fig. 5.1). The common purpose of all the nasal procedures on the stenotic nose is to reduce the resistance values to the passage of air and therefore to increase the nasal respiratory flow. In reality, not all the mechanisms that link nasal pathology and Disturbed Respiration during Sleep (DRS) are clarified with absolute certainty, and these uncertainties also reverberate on the therapeutic side. The nasal procedures reviewed and used can be summarized as follows:

1. Valvuloplasty
2. Septoplasty
3. Rhinoseptoplasty
4. Lower and middle turbinoplasty
5. Polypectomies and ethmoidectomies
6. Ablation of obstructing masses
7. Combinations

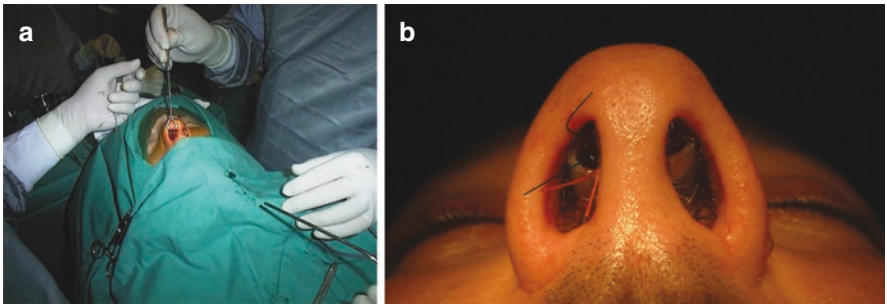

Fig. 5.1 (**a**) Intraoperative view of nasal surgery, (**b**) nostrils' view with nasal splints at the end of the surgery

5.8 Palate Surgery

The first therapeutic attempts of OSAS date back to the beginning of the 1980 s of the last century and were CPAP treatment and the palate surgery. CPAP immediately proved to be an effective therapy as opposed to surgical therapy, which was initially characterized by the high frequency of undesirable side effects (open rhinolalia and leakage of liquids and solids from the nose during swallowing) and by the low percentage of positive results. Initial failures were primarily due to the use of extensive resective-demolition techniques, in which surgery was directed only at the medial region of the palatine pillars and uvula. At the end of the 1990s, the limitation of a resective surgery of the soft palate with the unnecessary sacrifice of the uvula, whose resection involved the loss of the constant humidification of the pharyngeal mucosa, with great disappointment of the patients, began to be understood. It was only at the beginning of the 2000s that the international scientific community began to understand the importance of the pharyngopalatal muscles in maintaining the patency of the upper airway. The rationale for the use of more conservative surgical techniques was consolidated because of the advantages of putting them under tension by anchoring them—through sutures—to rigid structures, such as the pterygoid raphe, so as to better expand the airway lumen in a minimally invasive, more physiological way and without having to demolish the muscles. The growing knowledge of the pathophysiology underlying obstructive sleep apnea has led to the development of new surgical procedures, increasingly conservative, but all aimed at combating both anteroposterior and lateral collapse. These include Anterior Pharyngoplasty-CAPSO modified; Lateral Pharyngoplasty; Expansion Sphincter Pharyngoplasty; Functional Expansion Sphincter Pharyngoplasty; Barbed Roman Blinds Technique; Barbed Anterior Pharyngoplasty-BAPh; Barbed Reposition Pharyngoplasty (BRP). The goal of all these techniques was to increase the respiratory space of the airway lumen without sacrifice of the muscles, but only by pulling them anteriorly or laterally in order to stabilize the walls of the oropharyngeal sphincter. Since the early 2000s, the DISE (drug-induced sleep endoscopy), a dynamic endoscopic examination of the first airways that simulates the nocturnal condition as it is performed during a pharmacologically induced sleep and in supine position, has become widespread. This examination has allowed a better understanding of OSA pathophysiology, since it has allowed to identify the structures directly involved in snoring and apneic obstructions, to be treated surgically. As a result of DISE, the selection of patients who are candidates for surgical therapy has been improved because it is possible to characterize the collapse of the oropharyngeal walls responsible for airway lumen closure (latero-lateral, antero-posterior, circular). An important conceptual and technological innovation in palatal surgery for OSAS was born in 2011 from the idea of Prof. Mario Mantovani to use the "Barbed Sutures." These are surgical sutures, resorbable, self-locking, that do not require knots to approximate the anatomical structures involved. Another great advantage of the barbed sutures is to ensure a homogeneous distribution of the tensile-modulative forces over the entire extension of the suture thread and not concentrated only in correspondence of the knots and therefore in a few points as with

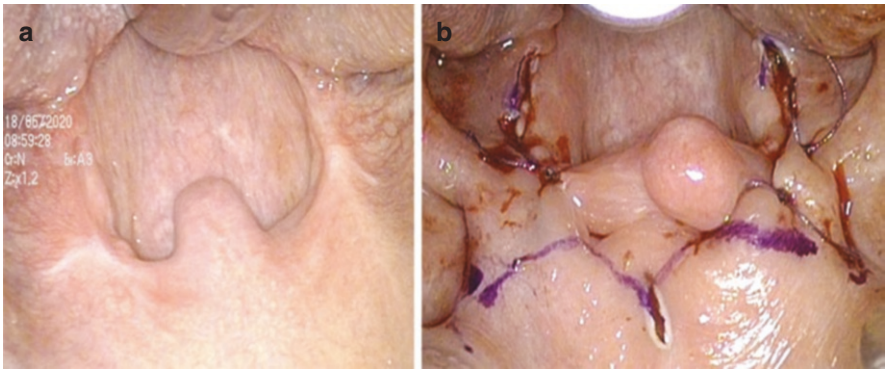

Fig. 5.2 Barbed reposition pharyngoplasty. (**a**) Palate image in previous tonsillectomized patient. (**b**) Intraoperative image of BRP

traditional sutures. In chronological order, the last surgical technique proposed is the BRP (barbed reposition pharyngoplasty) whose philosophy summarizes the history of the evolution of palatal surgery (Fig. 5.2). Among the various characteristics of the method, there is the peculiarity of being a repeatable technique in cases of partial therapeutic success as well as being reversible in the immediate postoperative period in case of complications or inaccuracies of technique. This opportunity has contributed together with the effectiveness and consistency of the functional results obtained in the long term to the favorable acceptance by surgeons, as demonstrated by its wide diffusion.

Currently, throughout the world but particularly in Italy, several variants of BRP have been proposed, all aimed at stretching the palate-pharyngeal muscles, without any demolition, with different vectors of lumen opening in order to counteract the vectors of closure highlighted during DISE.

5.9 Tongue Surgery

Tongue suspension has been firstly proposed by De Rowe et al. This is a transoral technique in which suspension of the base of the tongue to the mandible is performed using a nonabsorbable suture loop anchored to a titanium self-tapping screw inserted, with the aid of a disposable drill, in correspondence to the geni apophysis of the mandible; this loop aims to prevent the tongue, during sleep, from falling backward, being aided by gravity and hypotonicity of the genioglossus muscle. In the experience of several centers, this technique has proved to be effective, over time, in cases with high back-tongue narrowing, in which the loop exerts its action on the lingual body stabilization in supine decubitus. Patient compliance is variable, and postoperative pain and dysphagia are possible.

Genioglossus advancement (GA) consists of an anterior translation of the portion of the mandible that includes the genial tubercles with the relative insertion of

the genioglossus muscle. Riley et al. first described the GA technique for the treatment of OSA in 1984. It is performed by making a rectangular incision in the para symphyseal mandible with a drill; a bone rectangle is extracted anteriorly and locked in an advanced position with microscrews. When performed correctly, the patient enjoys distinct improvement in retrolingual airway patency. Advancement of the genial tubercles is believed to tighten the genioglossus muscle, thereby mitigating relaxation and posterior positioning of the base of the tongue and obstruction of the hypopharynx. Even for the expert surgeon, this is not a simple operation, and well-controlled complications (abscess, hematoma and mandible fracture) could occur. The key to ensuring the success of this surgical treatment requires accurate assessment and localization of the attachment of the belly of the genioglossus muscle to the mandible to ensure maximal advancement of the genioglossus muscle.

Transoral robotic surgery is a minimally invasive technique for the OSA treatment that is performed entirely transoral through the da Vinci surgical robot proposed by Vicini et al. Through a three-dimensional endoscope and two operating robotic arms, it is possible to perform a resection of hypertrophic base of tongue tissue and the resection or remodeling of the suprahyoid epiglottis (Fig. 5.3). In a time not exceeding 40 min, the procedure allows a possible resection of a significant volume of lymphatic and/or muscle tissue in the region of the base of the tongue. Resection could range, according to different authors, from 10 to 30 cc. According

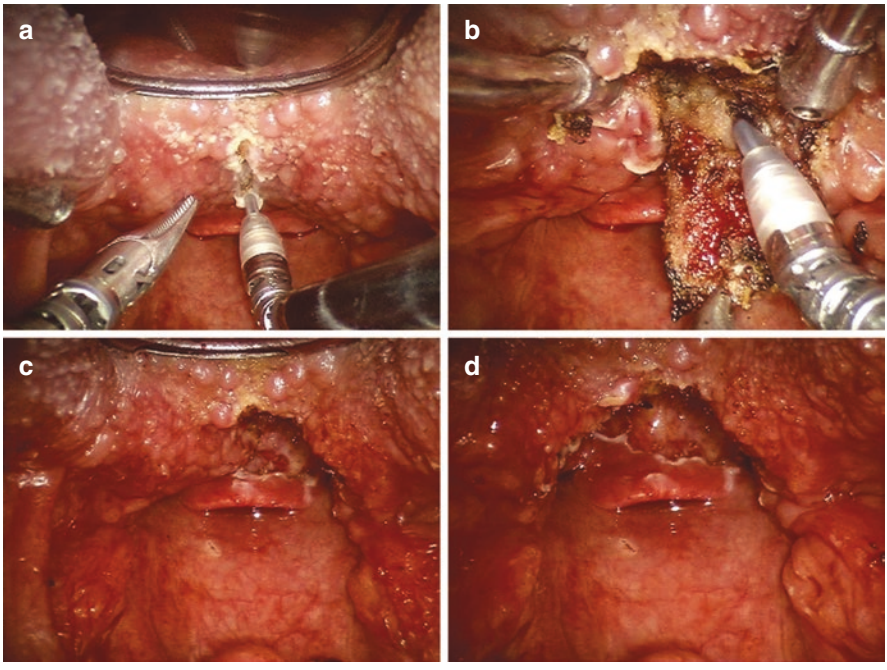

Fig. 5.3 Transoral base of tongue resection. (**a**) initial midline incision, (**b**) right side base of tongue resection, (**c**) right side resection completed, (**d**) Total base of tongue resection

to the literature, TORS is reserved to treat selected OSA patients with hypertrophic primary tongue (muscular or lymphatic) with an estimated reduction of apnea–hypopnea index in around 70%–80% of cases. Also, different recent meta-analysis studies confirm the effectiveness of this innovative approach for patients with severe OSA. Major intraoperative and postoperative complications (bleeding, stenosis) are rare, and postoperative taste disturbances and dysphagia are often temporary. Long-term regrowth of the lymphatics is very low.

Transoral endoscopic coblation tongue surgery is another transoral surgical option available for the tongue base is the CELL technique (Coblation endoscopic lingual lightening), as described by Prof. Li HN. The surgeon adapts a cephalic approach (tonsillectomy position) to expose the base of the tongue, and using an endoscope (30° up), the base of the tongue is visualized. A mechanical holder can be used to allow bimanual manipulation. Using coblation technology, an ablating of the hypertrophic lingual tonsils is performed until the vallecular exposure is obtained (Fig. 5.4). This technique does not allow the measurement of the removed tissue as they are ablated. Alternatively, a resection of the base of tongue tissue is also possible, according to the modified CELL technique proposed by Prof. Bahgat et al. A midline glossectomy is also possible with this approach in cases of an enlarged body of the tongue. Moreover, coblation tongue channeling can induce rigidity of tongue muscles and volume reduction of about 1 cm^3 by making 10 tongue body channels. There was no increase in significant complications associated with CELL, and long-term taste disturbances and dysphagia are reported in a minority of cases.

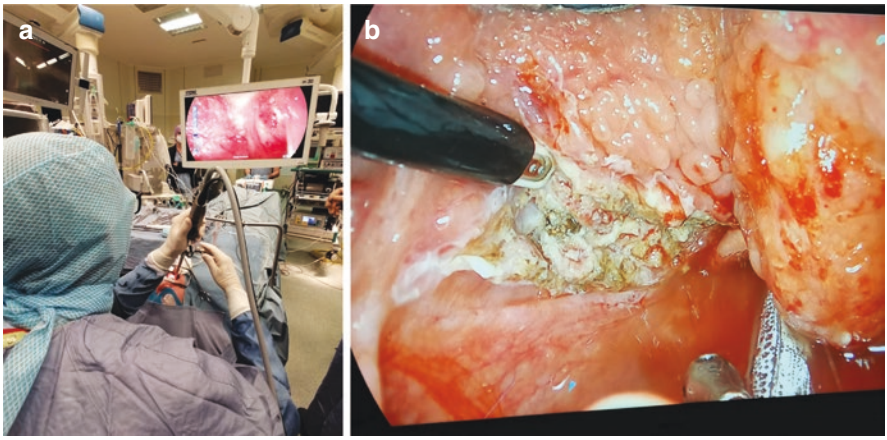

Fig. 5.4 Transoral endoscopic coblation tongue surgery. (**a**) Operation room setting and (**b**) endoscopic surgery intraoperative view

5.10 Hypoglossal Nerve Stimulation

The development of alternative treatments for OSA is strictly related to a deeper comprehension of the mechanisms causing obstructive events during sleep. Although anatomic factors might play a significant role in the genesis of OSA, several authors indicate that dysfunctional neuromuscular control of breathing during sleep must also be considered an important cause. In fact, a reduced activity of motor nerves and upper airway dilators muscles, in particular the hypoglossal nerve and the genioglossus muscle, has been observed in OSA patients when compared with healthy controls. Electrical stimulation of the upper airway dilator muscles directly or via the hypoglossal nerve has therefore emerged as a potential therapeutic target for OSA management. Today, there are three systems for hypoglossal nerve stimulation available in the market. The Inspire II Upper Airway Stimulation (UAS) system (Inspire Medical Systems, Maple Grove, MN) is the most widespread device, and it consists of a respiration sensor, a programmable implanted pulse generator (IPG) and stimulating electrodes. The stimulation electrode is placed on the hypoglossal nerve distally in order to recruit tongue-protrusion function; the sensing lead is placed between the internal and external intercostal muscles to detect ventilatory effort; the neurostimulator is implanted in the right/left ipsilateral mid-infraclavicular region. This system is contraindicated in case of hypoventilation syndromes or congestive heart failure, chronic obstructive pulmonary disease and assumption of opioid medication. Moreover, significant sleep comorbidities (e.g., severe insomnia), physical limitations (e.g., head and neck cancer, breast cancer reconstruction or chest wall deformity) or imaging requirements (e.g., MRI) may be considered as relative contraindications to implantation [4]. Inspire II UAS is indicated in moderate to severe OSA patients who have failed a trial of PAP therapy. A percentage of central and mixed apnea events below 25% and the absence of a complete concentric pattern of palatal collapse on DISE are two essential requirements for implantation. Finally, significant obesity is a relative contraindication with a BMI limit ranging from 32 kg/m^2 to 35 kg/m^2. The ADHERE registry (Adherence and Outcome of Upper Airway Stimulation for OSA International Registry) was introduced in 2016 to allow data collection regarding patients implanted with Inspire devices in the United States and Europe. Data about the effectiveness and the safety of this system have been published by several authors supporting it as a valid alternative to ventilatory treatment [5, 6]. ImThera Medical (ImThera Medical Inc., San Diego, CA) system consists of multiple stimulating electrodes that have to be placed around the most proximal part of the hypoglossal nerve [7]. This system sequentially stimulates different sectors of the hypoglossal nerve trunk. The cuff electrode remains continuously activated, and therefore, a respiratory sensor is not needed. Mwenge and colleagues demonstrated the effectiveness and low incidence of side effects of this system [8]. Another device developed by Nyxoah (Gilde Healthcare, Mon-Saint-Guibert, Belgium) allows bilateral stimulation of the most distal branches of hypoglossal nerve [9]. The implanted stimulator is placed submentally and is controlled and activated by an external device that is positioned by the patients every night. Preliminary studies show promising results.

5.11 Multilevel Surgery Concept

In a significant number of OSA patients selected for surgery, more than one site must be treated in order to restore a functional airway. The most common combination is nose and palate, but sometimes also tongue base and or epiglottis are included. When more than one site is operated on, the overall procedure must be considered a multilevel procedure.

5.12 Multimodal Treatment Concept and Evidence-Based Medicine

The combination of contemporary sleep surgery with advances in modulation of arousal threshold, loop gain and muscle tone will truly define precision in OSA care. The most pressing need is its integration with physiologic phenotyping. Considering a broad spectrum of surgical techniques and conservative methods, a decision algorithm is necessary to effectively modulate the therapeutic strategy. Definitively, it is emerging that the success of any surgical therapy may not be sustainable in the long term. For these reasons, therapeutic measures can be combined into a bimodal or multimodal treatment.

Take-Home Message: For any single OSA patient, do consider all the available treatment options, as stand alone or in combination. Conservative options first, multimodal if required. An interdisciplinary discussion may be useful for defining the best choice/s. Try to balance the most suitable (according to endotype and phenotype) and effective (according to literature and your own expertise) with the best accepted by the patient, who is the final judge. No one of the so far described therapies may register a 100% of long-term efficacy. Along the time, don't forget to check the real compliance for CPAP, MADs, positional and weight loss, and to check persistent efficacy for surgery. Nothing is forever: do consider to offer different successive options along the time. OSA is a chronic condition, possibly requiring more than one treatment along its long story. The basic goal is to increase QOL of your patient and to prevent OSA complications. Whatever it takes.

Take-Home Message

- OSA treatment is one of the most difficult challenges of modern medicine
- Continuous positive pressure in the airways (CPAP) through a nasal or oronasal mask, or nasal pillow, is the first therapeutic option that has been found to prevent narrowing of the pharynx, the cause of snoring and apneas and hypopneas.
- Oral appliances (MAD) are valuable conservative therapy for OSA, and an alternative to CPAP.
- Nasal procedures allow to reduce the resistance values to the passage of air and increase the nasal respiratory flow.

- **DISE** allows a identification of the structures directly and to characterize the collapse of the oropharyngeal walls responsible for airway lumen closure (latero-lateral, antero-posterior, circular).
- There are many types of palatal procedures that can be performed according to the needs and experience of the surgeon that modify the palatal area without resecting the muscles.
- Tongue base surgery is used to reduce tongue size, but especially at the base of the tongue if there is a hyperplasic lingual tonsil.
- Hypoglossal nerve stimulation has emerged in the past years as an excellent treatment for opening the airway by stimulation of the hypoglossal nerve that has an action of opening the airway.

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Orofacial Myofunctional Therapy

6

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Abbreviations

AHI	Apnea–hypopnea index
CP	Control pause
DISE	Drug-induced sleep endoscopy
ENT	Ear, nose, throat specialist
ESS	Epworth sleepiness scale
g/cm^2	Grams per square centimeter
IOPI	Iowa oral performance instrument
kps	Kilopascals
OMD	Orofacial muscle disorder
OMT	Orofacial myofunctional therapy
OSA	Obstructive sleep apnea
Pcrit	Upper airway collapsibility
RCT	Randomized controlled trial
SDB	Sleep-disordered breathing
TDS	Tongue digital spoon.
UA	Upper airway

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6.1 Concept

Orofacial myofunctional therapy (OMT) is used for the diagnosis and treatment of orofacial muscular disorders (OMDs) [1]. OMDs are one or a combination of the following:

- Abnormal sucking habit of the thumb, finger, lip, or tongue.
- Resting posture and inappropriate opening of the mouth and lips (lip seal incompetence).
- Interdental protrusion of the tongue at rest.
- Resting protrusion of the tongue against the maxillary incisors.
- Position of the tongue in posterior lateral or interdental rest.

6.2 Inadequate Tongue Thrust When Speaking or Swallowing (Atypical Swallowing)

Patient with atypical swallowing (Video 1).

The orofacial muscle complex must be balanced, and proper development will ensure well-formed craniofacial structures.

An imbalance in the orofacial muscle complex in childhood will probably result in an imbalance in the pharynx muscles, promoting sleep-disordered breathing (SDB) in adulthood. Swallowing involves accurate muscle coordination, and all Ear Nose, and Throat specialists (ENT) should be aware of this process.

Normal swallowing proceeds in the following way:

- The tongue tip is placed just posterior to the maxillary incisors.
- The midpoint of the tongue is raised to the roof of the mouth.
- The tongue moves against the hard palate in a posterior direction, tipping at a 45° angle so that the rear part of the tongue is against the pharyngeal wall.
- Simultaneously, with the tongue's action in the swallowing position, the buccinator and the master muscles exert lateral force against the dentition.

6.3 The Orbicularis Oris Muscle Exerts a Posterior Force Against the Upper Anterior Teeth

The swallowing act is repeated approximately 2000 times a day, and if it is not done correctly, functional issues will be converted into anatomical issues problems that will have pathological consequences.

The three major muscle groups affecting occlusion during the swallowing act are:

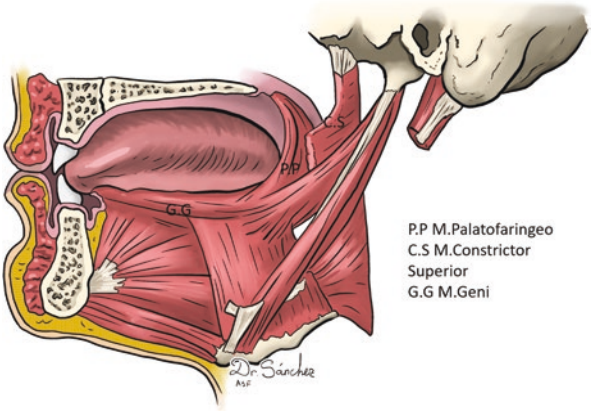

Fig. 6.1 Sagittal view from tongue and pharynx muscles

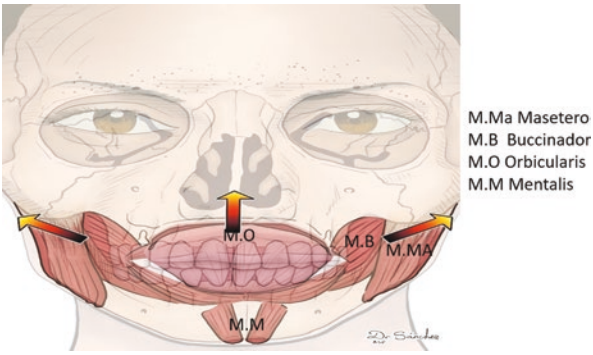

Fig. 6.2 Balance between orbicular oris, masseter, and mentalis muscles

- The tongue is the only muscle in the body attached to only one end. The tongue muscle functions during the act of swallowing as a moving force, as an impeding force, or as both a moving force and an impeding force.
- The masseter and buccinator muscles are activated each time the patient swallows. Failure to activate these muscles is caused either by the placement of the tongue between the teeth during deglutition or by poor posterior occlusion.
- The orbicularis oris muscle, acts as a stabilizing influence on the dentition. The lips are the natural anterior retainers for the teeth. Patients who exhibit weak orbicularis oris muscles due to functional or organic problems inevitably exhibit a poor occlusal relationship [2] (Figs. 6.1, 6.2, and 6.3).

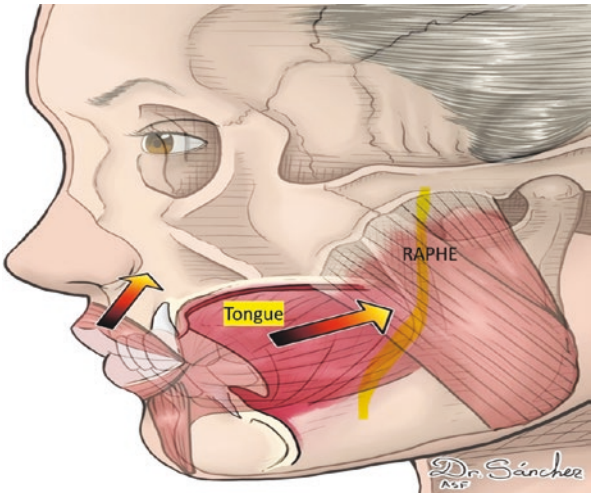

Fig. 6.3 Forces from tongue and orofacial muscles pulling backward and upward starting the deglutition process. See a connection with hamulus with pharynx muscles

6.4 Background

The treatment of SDB by OMT is a relatively recent discovery (2005) of accidental origin. Participants in a randomized controlled trial (RCT) who practiced the didgeridoo for an average of 20 min per day, 5 days a week for 4 months, demonstrated a reduction in their apnea–hypopnea index (AHI) of 6.2 events/h [3]. Interestingly, in this study, there was no reference to any OMT. Instead, the study focused on training or electrostimulation of the upper airway muscles (UA) with the expectation that the intervention would reduce UA collapsibility during sleep.

There are very few publications with enough credible scientific evidence that can be presented. A critical study is a recent meta-analysis by Megphara [4], in which OMT's effectiveness and usefulness in treating obstructive sleep apnea (OSA) are demonstrated. This study, carried out in 237 patients with OSA, showed that oropharyngeal exercises caused a reduction in the AHI from 28.0 ± 16.2/h to 18.6 ± 13.1/h, an increase in the minimum oxygen saturation by 2.5%, with an improvement in the subjective parameters of sleepiness as shown by a decrease in the Epworth Sleepiness Scale (ESS) from 12.71 ± 5.73 to 8.78 ± 5.80. These results demonstrate the benefit of performing the OMT exercise regimen.

Our group published an RCT [5] following the intervention in 18 patients with severe OSA; the AHI decreased by 53.4% from 44.7 (range 33.8–55.6) to 20.88 (14.02–27.7) events/hour ($P < 0.001$). The oxygen desaturation index decreased by 46.5% from 36.31 (27.19–43.43) to 19.4 (12.9–25.98) events/hour ($P = 0.003$). The ESS score decreased from 10.33 (8.71–12.24) to 5.37 (3.45–7.28) in the treated group ($P < 0.001$), but the Pittsburgh Sleep Quality Index did not change significantly (Fig. 6.4). AHI results in control and study groups after using OMT in severe OSA.

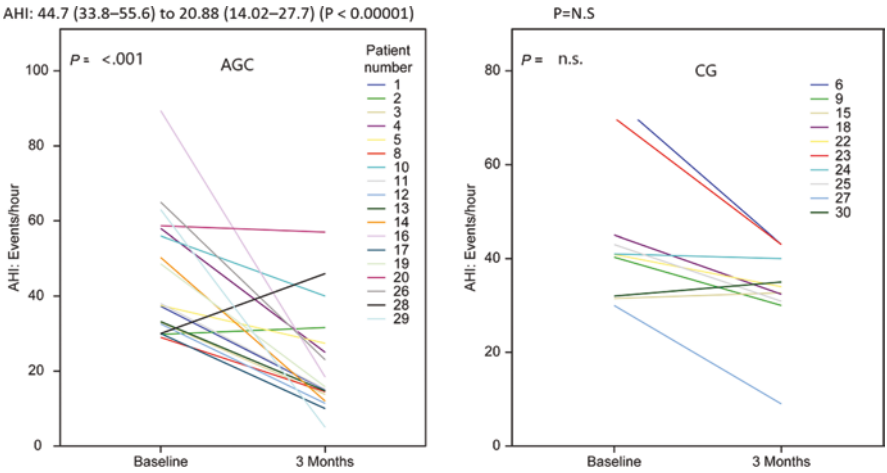

Fig. 6.4 AHI results in control and study groups after using OMT in severe OSA

Carrasco et al. [6] reported that the available evidence demonstrates a positive effect of OMT in reducing OSA in adults as assessed using polysomnography and clinical variables. The available evidence is solid for the impact of OMT on snoring reduction in adults. However, there is no evidence to support the use of OMT to treat UA resistance syndrome, including how long the effects last or which OMT protocol is better in children or adults. Despite these knowledge gaps, the available evidence indicates that OMT is safe. Therefore, the available evidence for the use and safety of OMT suggests that it should initially be offered as a noninvasive therapy for patients with SDB.

6.5 The Pathophysiological Basis of OSA and Muscle Control

The reason patients with OSA are less able to contract their muscles is unknown [7].

Poor neural coordination during sleep, inefficient muscle contraction due to excess fat or muscle hypertrophy, changes in fiber type, and a greater propensity to fatigue have all been observed [8].

Patients with OSA have less muscular effectiveness than healthy patients [9].

Patients with OSA suffer from lingual apraxia. Apraxia is the inability to perform specific movements with the tongue. They also suffer from stereognosis, or the failure to identify specific geometrical shapes inside the mouth with the tongue [10].

Patients with OSA have lower muscle tone than healthy individuals [11]. Muscle tone measured with certain instruments showed lower strength than in healthy controls.

6.6 Myofunctional Examination

What should an ENT specialist know about an OMD? First, as explained in other chapters of this book, a correct anatomical examination of the patient must be performed.

As in all therapies, it is paramount to know how to identify whether the patient is suitable for the treatment and to refer them to a speech therapist. This can only be achieved through systematic examination and a functional approach.

An examination of OSA patients must focus on two main questions, what is the location of their tongue, and how are they breathing. Simultaneously we must observe their posture both, standing, and sitting.

6.6.1 Breathing

How does our patient breathe? First, we must pay attention to how our patient breathes and whether they breathe primarily through their nose or mouth. Once any obstacles in the UA have been removed through surgery (e.g., septoplasty), the ENT doctor must ensure that the patient is using the organ that has just been unblocked. Studies carried out with Rhesus monkeys [12], and anatomical models [13] based on orthodontic changes show that persistent oral breathing leads to long-term orofacial malformations. It has also been shown that sustained oral breathing is associated with SDB [14]. Correct breathing implies that it should be done mainly through the nostrils, and should always be silent, with inspiration and expiration cycles happening through the nose no more than 15 times per minute. We can ask our patients to hold their breath and measure the time they stay without breathing or their control pause (CP). Patients with a low CP probably suffer from a loop gain phenotype of OSA, and surgical treatment will not be effective [15].

ENTs must recognize hyperventilation syndrome in OSA patients. This manifests in patients with clear nostrils who complain of unsatisfactory nasal breathing. They exhibit a high number of breaths per minute, which cause respiratory alkalosis, hindering the release of oxygen in tissues by red blood cells and causing a false sensation of breathlessness in the patient [16]. It is related to empty nose syndrome; therefore, the use of the validated Nijmegen questionnaire is recommended for diagnosis [17]. Cases in which the patient does not breathe in such a way indicate a disorder that requires specialized re-education, such as the Buteyko method with a specialized therapist.

6.6.2 Tongue Position

Close attention must be paid to the tongue position when the mouth is closed. A tongue at rest must always be positioned above the upper incisors, on the incisive papilla, and swallowing must start from this point. Anything that involves another tongue position is abnormal. Nasal breathing is certain if the tongue remains in an

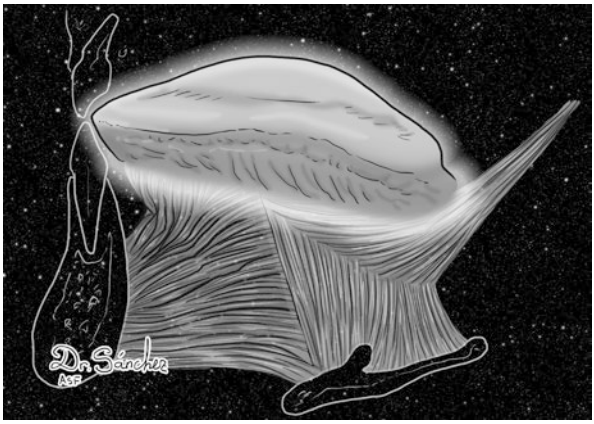

Fig. 6.5 Tongue as center of solar system (upper airway muscles)

upright position, even when the mouth is open. The tongue should be considered the main objective of the myofunctional evaluation, just as the sun is the center of the solar system (Fig. 6.5). Tongue as the center of the solar system (UA muscles).

6.6.3 Bite Classification

The position of the teeth or type of bite is very important for the patient's optimal health. A common cause of bad bite "malocclusion" is childhood habits such as thumb sucking, tongue thrusting, pacifier use beyond age 3, and prolonged bottle use.

Most common bite problems:

- Primary canine relationship. According to the Angle classification: Class I: normocclusion, this is the correct position where the first molar should fit above and slightly in front of the lower first molar. Class II; the upper first molar occludes far in front of the lower first molar. Class III: the upper first molar is wedged behind the lower first molar. The lower first molar.
- Crossbite: crossbite when the position of the upper teeth is slightly in front of the lower teeth; on the contrary, with the lower teeth forward when closing the mouth, causing the chin to protrude.
- Open bite: does not allow the teeth to come together at some point in the dental arches. It usually occurs in the front, although it can also affect the back teeth. It is due to genetic reasons or the constant repetition of a habit, making the chewing and speaking process difficult.
- Overbite (OVB): overbite is the overlapping of the upper front teeth concerning the position of the lower teeth. It is recorded as normal, reduced (<2 mm), or increased (>4 mm).

The study of malocclusion should be considered since there is an association between snoring and crossbite. The presence of a posterior crossbite is related to the

altered balance between the tongue and cheeks. On the other hand, mouth breathing is associated with a decrease in the prominence and width of the nose. These facial features could reduce upper airway space resulting in obstructive apnea events [18].

6.6.4 Tongue Tie

Pathological tongue tie, or ankyloglossia, is a limiting factor for the success of OMT. For some authors, its relationship with OSA is controversial [19]. There are two types of tongue tie described in the literature:

The anterior tongue tie is a vertical fold of mucous membrane that joins the anterior part of the tongue to the floor of the tongue at its center.

The posterior tongue tie, which is not recognized by some authors [19] consists of abnormal collagen fibers located in the submucosa that form membranous structures that follow from the anterior frenulum, deep into the tongue stratus. For some authors, it is known as a submucosal frenulum.

Approximately 2%–12% of the world's population has a tongue tie [20]. It is a hereditary disorder. The presence of a tongue tie in childhood is a suggestive factor for possible SDB [21]. The reasons why a tongue tie can cause SDB are as follows.

OSA is related to the abnormal collapse of the UA during sleep. This anomaly occurs in children and adults when sleeping, where a change in the tone of the pharyngeal muscles and the reflex response also occurs. Position and intrinsic factors such as critical oxygen level (Pcrit) and other extrinsic factors cause an increase in nocturnal collapse that occurs while lying on one's back.

The three extrinsic factors that affect the retropalatal and retroglossal spaces are fat deposits, lymphoid tissues subject to chronic inflammation (tonsils and adenoids), and craniofacial structures that influence the size of the UA. Craniofacial structures are also subject to environmental influences and the genetic context. Genetic abnormalities at birth cannot affect the UA until a certain growth stage. Environmental factors produce their effect in a more latent way and influence the appearance of OSA after many years of acting silently and inadvertently. On the other hand, environmental anomalies interact with genetic expression, revealing genetic traits [22]. Just as nasal breathing is essential for the growth of orofacial structures, so is the tongue's. At birth, the tongue is located high on the palate and through activities such as swallowing, chewing, and sucking. It causes stimulation of the intermaxillary synchondrosis, that is active until 13–15 years of age, causing a normal orofacial growth that should be associated with nasal breathing. A short tongue frenulum is associated with swallowing difficulties during infancy and speech problems in older children. It is also associated with oral breathing, which causes bite abnormalities that require orthodontic treatment. These alterations modify the airway size, increasing the risk of OSA [23, 24].

The anterior tongue frenulum can be examined by the following several different protocols. One of these is the Marchesani protocol [25], in which the patient is asked to place the tongue behind the maxillary incisors and open the mouth without taking it off. A measurement of the mouth opening is performed, then asking the

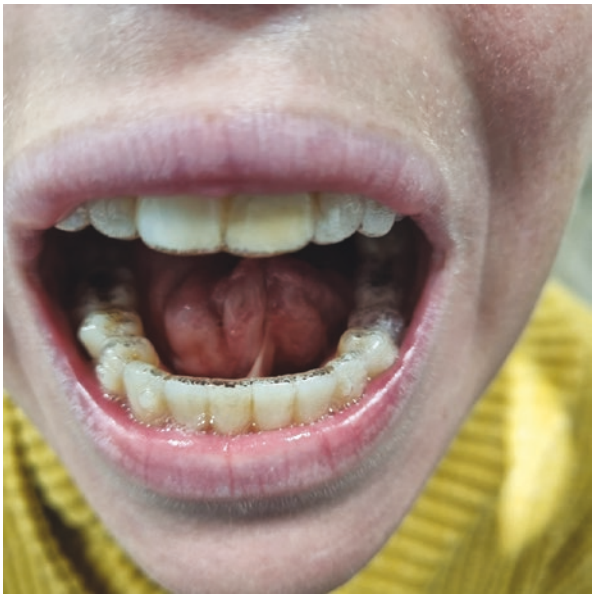

Fig. 6.6 Adult tongue tie in a patient with severe OSA

patient to open their mouth as wide as possible with their tongue down position. If the difference is more significant than 50% between the two measurements, that patient is considered to have a pathological tongue tie or ankyloglossia (Fig. 6.6).

From experience, whenever one is faced with a prominent anterior frenulum, one should consider the possibility of a posterior or submucosal frenulum. Sometimes it is possible to feel this structure behind the first one, but usually the diagnosis is made by following a functional examination protocol.

We recommend following the Hazelbaker protocol [26].

6.6.4.1 Tongue Tie Anatomical Evaluation

Appearance of the tongue when lifted: 2 points (round or square shaped), 1 point (small indentation), 0 points (heart or V shaped).

Frenulum elasticity: 2 points (very elastic), 1 point (moderately elastic), 0 points (no elasticity).

Length of the frenulum when the tongue is raised: 2 points (more than 1 cm or included on the tongue); 1 point, 1 cm; 0 points (less than 1 cm).

Insertion of the tongue frenulum into the tongue: 2 points (posterior to the tip), 1 point (at the tip), 0 points (notched or notched tip).

Insertion of the frenulum on the alveolar crest: 2 points (on the floor of the mouth or below the crest), 1 point (just below the crest), 0 points (on the alveolar crest).

6.6.4.2 Tongue Tie Function Evaluation

Lateralization: 2 points (complete); 1 point (body of the tongue, but not the tip); 0 points (none).

Tongue elevation: 2 points (tip to half-open mouth), 1 point (only the edges to half-open mouth), 0 points (tip remains on the alveolar ridge or only rises when the mouth is closed).

Stick out the tongue: 2 points (point on the lower lip), 1 point (tip only on the gum), 0 points (none of the above).

Tongue extension: 2 points (complete), 1 point (moderate or partial), 0 points (little or none).

Tongue concavity: 2 points (completely concave edges), 1 point (concave edges); 0 point (no concavity).

Peristalsis: 2 points (complete anterior to posterior from the tip), 1 point (partial originating posterior to the tip), 0 points (none).

Snapping during lactation: 2 points (none), 1 point (periodic), 0 points (with each suck).

Perfect score, 14 points; 11 points, acceptable if anatomical evaluation is 10.

If <8, requires surgery.

6.6.4.3 Tongue Tie Surgery [27]

When talking about tongue tie surgery, we must establish different concepts. Frenectomy consists of removing the frenulum tissue, (although it is sometimes also used for lip frenulum surgery). Frenuloplasty consists of dissection of the frenulum with a subsequent suture in zetaplasty of the defective tissue. Finally, frenectomy is the most frequent treatment and only consists of carrying out a cut without a suture. A laser (diode, CO_2) or a conventional surgical technique can be used to perform the procedure. No significant differences have been demonstrated in these procedures [27]. The therapeutic objective of surgery must be twofold on the one hand, to eliminate an anatomical barrier and, on the other, to develop a recovery of function. It is essential to consider the possible treatment of restrictive frenulum with OMT before and after surgery to recover any lost functionality. Cases have been described where the apnea worsened after the surgical procedure. In our experience, this is because the patient has not been treated with OMT beforehand [28]. We try to identify the medial tongue septum (the fascia between the two heads of the upper branch of the genioglossus muscle) and proceed with its dissection. Surgery should be performed in a blunt and classical manner. The main objective of surgery is to eliminate restrictive fibrotic tissue, so the surgical technique must avoid the use of instruments that may contribute to increasing fibrosis (electrocautery). Performing the surgery, while the patient is awake is recommended in adults so that they can move their tongue during surgery. During the intervention, the patient is asked to move the tongue forward and up and to the sides to highlight the restrictions to be eliminated. In cases where the surgery cannot be performed while the patient is awake (in the case of children), we recommend using 2.0 silk points at the tip that would allow one to move the tongue at all times. We recommend dissection with cold instruments (120 mm Metzenbaum scissors or curved or straight-tipped iris scissors), a sterile swab, and a corrugated probe. If hemostasis is performed; it should be done with a bipolar scalpel with low power output (10 W). The tissue to be cut first is pressed with hemostatic forceps and, when it is found to be ischemic, is cut with scissors.

The dissection is complete when the patient can place the tip of the tongue in the area of the incisal papilla. At the same time, while the mouth is open, as wide as possible and they can suck against the anterior palate without restriction. Subsequently, the mucosal defect is sutured with vicryl rapide 30 (coated vicryl Ethicon US LLC) (Video 2).

6.6.5 Muscular Strength

It is advantageous to assess the muscle strength of the lingual muscles and the perioral muscles. We recommend using of Iowa *Oral Performance Instrument* (IOPI, Northwest Co., LLC, Carnation WA, USA) to identify the hypotonic patient most likely to improve with this treatment [11]. The main measurements of the IOPI focus on evaluating the strength of the lingual muscles and the strength of the perioral muscles. It is performed by compressing a balloon connected to the device that the patient inserts into their mouth. To measure the maximum anterior lingual force, the patient is asked to perform a peak compression of the balloon while resting on the papilla. This value corresponds to the tone of the genioglossus muscle. Three measurements are made with a 1-min rest between each. The highest value obtained is taken as a reference. For the buccinator muscles, the balloon is placed between the gingival mucosa and the cheek, then the patient is asked to make a contraction with the balloon. The value obtained corresponds to the tone of the buccinator muscle. Measurements are obtained in kilopascals (Fig. 6.7). Using reference tables obtained from the normal population allows the patient to know the state of their musculature during the test and provides a reference of where their muscle tone should be, based on their age and gender [29]. Finally, it has been shown that patients with SDB have lower than average values on this test and that an increase in values translates into improved [5] sleep quality of sleep [30].

Fig. 6.7 Example of the use of IOPI in consulting buccinator muscle measurement

Fig. 6.8 Tongue digital spoon

Figure 6.7 shows a patient who gives permission to use scientifically his image elsewhere; however, you can shade the eyes in order not to be recognized.

Another instrument recommended for measuring tongue strength is the Tongue Digital Spoon (TDS) (Fig. 6.8). We have carried out 20 tongue strength measurements using the TDS in a healthy adult population, with the IOPI as the gold standard. To validate the procedure, we performed replicate measurements on 20 individuals aged 20–70. We found a mean TDS measurement of 115.99 g/cm^2 in young subjects, 98.47 g/cm^2 in middle-aged subjects, and 84.23 g/cm^2 in older people. There was a significant difference in the measurements between younger and older participants. There was also a significant correlation between TDS and IOPI measurements (Pearson correlation coefficient, $r = 0.69$, $P < 0.001$). We found the TDS to be a valuable tool in daily clinical practice for measuring of the strength of the tongue in a healthy population. It has potential application in oropharyngeal monitoring and rehabilitation [31].

6.7 Exercises

Two types of exercises are highlighted isometric exercises that are aimed at correcting a motor tone deficiency (hypotonia) with which repetitions can be performed, and those exercises that are beyond a functional problem and require the introduction of more complex isotonic exercises, including evaluation by a speech therapist. Therefore, it is essential to perform them with a certain rhythm (Video 3).

There are no strict regulations these exercises or how they should be performed [32]. Therefore, it is recommended to group them into batches of 9, with a maximum duration of 20 min before going to bed. Examples of these exercises are shown in our

video in books [33] or Apps [34, 35] (Video 4). The ideal is to have the advice of a specialist speech therapist with regular weekly visits to evaluate the correct execution of the exercises, quantifying the anatomical changes through questionnaires [33]. However, when there is no access to a speech therapist, using the values obtained through the IOPI is recommended. An increase in these values implies the correct performance of the exercises. In our practice, we organize monthly appointments with our patients; this measurement does not require a consultation longer than 5 min.

Based on our experience, we consider adapting the exercises to the anatomical location of the collapse diagnosed with sleep-induced endoscopy [5]. In other words, if the presence of a tongue collapse is confirmed through drug-induced sleep endoscopy (DISE), we would inform our speech therapist of this diagnosis to tailor the exercises appropriately [11].

The main drawback of this, a priori attractive therapy, is a lack of adherence, which is less than 10% [36]. According to our experience, this is because the patient does not understand why some exercises are to be performed. There is a lack of feedback when evaluating the results, and there is a lack of communication with the therapist in situations where regular visits are not possible.

We suggest improving this adherence by:

- Providing the patient with as much information as possible about the anatomical causes of their SDB, offering to explain their DISE and IOPI.
- Repeating the sleep studies as needed at the end of a series of exercises and, if it is not possible, use the information of diagnostic applications on the market. Repeating IOPI monthly, we are aware of the need for accuracy in the performance of the exercises.

6.8 Providing All the Possible Means of Contact (i.e., Telemedicine) Between the Therapist and the Patient [20]

We have recently published our protocol where OMT is included as routine therapy in all patients treated in our institution [37].

Our group has published a study with nonadherent patients to any therapy. The main factors to adhere to OMT were proper tongue function without tongue restriction and low IOPI scores on the tongue strength measures [38]. We hypothesize that the ideal patients for this therapy are those with these characteristics.

6.9 Conclusions

OMT for treating SDB is a valuable therapy with promising satisfactory results. However, more well-designed, science-based studies are needed to confirm this point.

Like any therapy, proper selection of the patient is essential. A patient who would benefit the most from this therapy manifests a hypotonic phenotype of the oral cavity with the absence of anatomical abnormalities that limit the performance of exercises.

Beforehand, because this therapy has the lowest adherence, the therapist must be provided with enough diagnostic and therapeutic tools to treat this problem.

Take-Home Message

- Orofacial myofunctional therapy (OMT) uses a combination of physical therapy exercises to improve the bite, breathing, and facial posture of those with orofacial myofunctional disorders (OMDs). It is a valuable therapy with promising, satisfactory results.

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OSA in Children

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7.1 Introduction

Unlike in adults, obstructive sleep apnea (OSA) in children often presents without witnessed apneas, and the signs and symptoms may be more subtle than those in adults. This can make identification hard since children are not likely to complain about sleep problems; thus, a sibling or parent/guardian will often be the first to express concerns about a child's sleep. Concerns often include restless sleep, fatigue or sleepiness (hypersomnia), difficulty falling or staying asleep (insomnia), sleeping in strange positions, or other abnormal behaviors during sleep (parasomnias). Because of this, a complete history and physical are essential when considering sleep disorders in children.

7.2 Epidemiology

Epidemiologic studies of sleep-disordered breathing (SDB) and OSA in children in the United States report OSA rates of 1%–4% in the United States [1].

Parental reports of snoring (scaled often to always) range from 3.2% to 34.5% in one summary [1], while another summary noted snoring in 10% to 25% of preschool and elementary school children [2]. Unlike adults, the incidence of OSA seems to be similar between girls and boys but becomes more prevalent in boys in adolescence [1].

SDB is also strongly associated with high body mass index (BMI) and low socioeconomic status, Black and Asian race, but the relationship between these factors is not yet well understood [3–10]. OSA severity is also associated with Black race,

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Table 7.1 Conditions associated with OSA and snoring in children

Achondroplasia
Apert syndrome
Beckwith–Wiedemann syndrome
Cleft palate
Crouzon syndrome
Down syndrome (Trisomy 21)
Klippel–Feil syndrome
Mucopolysaccharidosis
Obesity
Pierre–Robin sequence
Pfeiffer syndrome
Prader–Willi syndrome
Treacher–Collins syndrome

even after controlling for obesity, family income, and maternal education [11]. However, neighborhood-level socioeconomic status, including poverty level, may explain a significant portion of the Black race effect. Parents and caregivers of children with craniofacial anomalies may mistakenly assume that SDB and OSA are "normal" for their child, and thus, screening is critical for these children [18]. See Table 7.1 for a list of conditions associated with a high risk of pediatric OSA. In addition to these listed genetic conditions, children with choanal atresia, cerebral palsy, head and neck lymphangiomas, and those who have undergone pharyngeal flap repair are at risk for OSA and snoring.

7.3 Consequences of OSA

Consequences of OSA include poor school performance and learning difficulties which include lower scores in memory, learning, and problem-solving skills than in nonsnoring children [2, 12]. In the 2000s, observational studies reported that children with OSA are at risk for decreased quality of life (QOL), and neurocognitive, behavioral, and emotional difficulties. Difficulties related to neurocognition, behavior and QOL tended to normalize after the resolution of SDB, but recent evidence has shown that executive function and attention may not improve [13–16]. A 2020 randomized, controlled trial of preschool children who underwent either early adenotonsillectomy (T&A) or observation reported no benefit in neurocognitive measures for those who underwent surgery [17].

Pulmonary and cardiovascular complications have also been reported including, elevated systemic blood pressure in children with OSA [18–22]. Further, a dose–response relationship has been reported to exist between SDB and blood pressure severity in children [23]. It has also been reported that children with elevated blood pressure are more likely to experience hypertension and metabolic syndrome as adults [24]. In addition, children with hypertension have been shown to improve their blood pressure after T&A compared to nonhypertensive controls [25, 26].

There is also data reporting positive associations between OSA and sympathetic tone, and endothelial dysfunction, both of which have been shown to improve after T&A [27–31].

7.4 Diagnosis

7.4.1 History

Universal screening for snoring was first recommended by the American Academy of Pediatrics (AAP) in 2002 [32]. In addition to assessing for snoring, a comprehensive sleep history is essential to evaluate these children Table 7.2. This evaluation typically includes parental or caregiver input and should consist of information about overall nighttime sleep duration (as well as daytime napping), bedtime routines, and time to fall asleep. Additionally, signs of OSA should be assessed including positions associated with and duration of snoring, restless sleep, gasping or choking, night sweats, witnessed apneas, nocturnal enuresis (especially if secondary, i.e., recurrent after at least 6 months of being dry at night) and abnormal sleep behaviors, including night terrors, sleep walking, sleep talking and confusional arousals.

A description of daytime symptoms should be solicited, including hyperactivity, attention/focus issues, aggression, frequent mouth-breathing, nasal obstruction, poor school performance, and excessive sleepiness (Table 7.2). While excessive sleepiness is common in adults with OSA, it is less common in children with OSA and is often not the primary complaint of children or their caregivers. Feeding difficulty may also be reported for children with large tonsils, especially for bulky foods such as meat.

Sleep questionnaires can be used to screen children at risk for OSA and assess for symptoms commonly associated with SDB and OSA [33–35]. However, they have not been validated to diagnose OSA as a solo method. A 2020 meta-analysis of 27 articles found poor diagnostic accuracy for clinical scoring tools when compared to polysomnography (PSG) outcome measures [36].

Table 7.2 Frequent signs and symptoms of obstructive sleep apnea in children

Daytime symptoms	Nighttime symptoms
Open mouth breathing	Frequent snoring
Frequent nasal obstruction	Gasping or choking
Hyperactivity	Nighttime sweating
Aggressive behavior	Witnessed apneas
Attention-deficit disorder	Paradoxical breathing
Poor school performance	Restless sleep
Daytime sleepiness	Hyperextension of the neck
	Secondary nocturnal enuresis

7.4.2 Physical Exam

A combination of upper airway narrowing, and neuromuscular factors contribute to the development of pediatric SDB and OSA. Assessment of anatomic abnormalities requires a complete head and neck exam (Table 7.3). The general examination should include vitals with the body mass index and, ideally, a blood pressure measurement, an assessment of overall appearance, general head and neck appearance with particular attention to any craniofacial abnormalities, and the presence or absence of mouth breathing suggesting nasal obstruction. Voice should also be assessed as large tonsils may cause a muffled voice, while large adenoids may result in a hyponasal voice. Genetic consultation may be warranted for children with findings suggestive of conditions that increase the risk of SDB and OSA (Table 7.1).

Table 7.3 Physical examination in a child with obstructive sleep apnea

General
General overall evaluation
Vital signs including body mass index (BMI) and ideally blood pressure
Head and face including any craniofacial abnormalities
Presence or absence of mouth breathing
Voice—Assess for muffled or hyponasal voice
Nasal
External deformity
Nasal valve function
Inferior turbinates
Nasal septum
Hypertrophy of the nasal swell body
Polyps and masses
Signs of chronic inflammation including rhinorrhea, erythema
Oral cavity
Dentition
Tongue size, position, and protrusion
Hard and soft palate
Uvula and posterior pharyngeal wall
Tonsil size
Modified Mallampati score
Neck
Neck size
Hyoid position, including submental-to-hyoid distance
Tracheal position
Systemic
Heart and lung examination
Chest wall evaluation

Neck assessment should also include relative hyoid and tracheal positions and may include circumference in teenagers.

Nasal evaluation should include an assessment of the external nose, the nasal valve, the nasal septum, inferior turbinates, and an evaluation for polyps or masses and signs of chronic inflammation. In newborns, patency may be assessed by passing an 8 or 6 French catheter through each nare and into the oropharynx. Signs of chronic inflammation include erythema, rhinorrhea, duskiness of the nasal mucosa and polyposis. However, polyposis is rare in children except for those with cystic fibrosis. Anterior rhinoscopy is useful to identify septal deviation, turbinate hypertrophy, and nasal swell body hypertrophy contributing to nasal obstruction. Chronic rhinorrhea may also be seen in children with obstruction secondary to nasal masses, chronic sinusitis, or adenoid hypertrophy. Assessment of the nasal valve also includes evaluation for functional nasal valve collapse while the child undergoes deep inspiration. Nasal endoscopy can also be used to evaluate the nasal cavity for nasal polyps or masses, choanal atresia or stenosis, pyriform aperture stenosis, or adenoid hypertrophy.

Initial oral cavity and oropharynx evaluation should assess the mandible size and position as well as dental occlusion. Tongue size and position should also be evaluated for macroglossia and glossoptosis. The palate evaluation should include uvular evaluation for bifidity, inspection for an overt or submucosal cleft of the hard or soft palate, and documentation of palatal masses or a narrowed or high arched palate. The tonsils are then graded based on the four-point Brodsky scale: 0 for surgically absent tonsils, 1 for tonsils within pillars, 2 for tonsils just beyond the pillars, 3 for tonsils more than 50% beyond the midline, and 4 for tonsils that approximate the midline. The modified Mallampati score [37–39] is also useful for characterizing the oropharynx with the mouth open while the tongue is in a resting position. Grade I is scored when the entire uvula is visible, grade II when part of the uvula is visible, grade III when none of the uvula but some of the soft palate is visible, and grade IV when only the hard palate is visible.

Flexible laryngoscopy is recommended for infants and older children who require further evaluation. This procedure allows assessment of the nasal cavity, adenoidal tissue, velar closure, pharyngeal wall closure, the base of tongue, vallecula, epiglottis, hypopharynx, vocal folds, and frequently, a portion of the subglottis. It is important to evaluate adenoidal hypertrophy, laryngomalacia, and lingual tonsil hypertrophy, as well as vocal cord mobility and to evaluate for pharyngeal or hypopharyngeal masses.

7.5 Additional Studies

Lateral neck films can also be used to identify adenoidal size, nasal structural abnormalities, as and lingual tonsil hypertrophy [40]. Alternatively, cine magnetic resonance imaging (MRI) has been used to assess children with persistent sleep apnea [41]. Drug-induced sleep endoscopy (DISE) is a valuable diagnostic tool to evaluate

children with persistent OSA following T&A. Workup should include electrocardiograms and echocardiograms in children with underlying congenital cardiac anomalies.

7.6 Polysomnography

The gold standard diagnostic method for OSA is a nocturnal in-laboratory PSG [42]. A typical PSG includes 16 simultaneously recorded channels during sleep as noted in Table 7.4 [43]. This test's output includes objective measurements that characterize airway obstruction severity during sleep. These include sleep staging, such as rapid eye movement (REM), and non-REM staging (stages 1, 2 and 3). The apnea–hypopnea index (AHI) is also routinely reported to describe OSA severity; calculated as the mean number of apneas and hypopneas per hour of sleep. Hypopneas are considered a reduction in airflow of at least 30% for ≥2 breaths associated with either an oxygen desaturation of 3% or greater or an arousal [44]. Apneas are characterized by a complete cessation of airflow for at least 2 respiratory cycles. The obstructive AHI includes all apneas and hypopneas, including respiratory effort events. Unlike in adults, where an event must last at least 10 s, flow limitation in children only needs to last for two or more consecutive breathing cycles due to the differences in respiratory rates seen as children age [44]. Multiple studies have reported good test–retest reliability when comparing multiple nights of overnight pediatric PSG in the same child [45–48]. OSA severity in children is based on assessments of normal values. Currently, mild OSA is defined as an obstructive AHI between 1 and <5 events per hour, moderate OSA is 5 to <10, and severe OSA is 10 or greater events per hour.

Table 7.4 Parameters recorded during nocturnal polysomnography (PSG)

PSG measurement parameters	Electroencephalography (EEG)
	Electrooculography (EOG)
	Submental and leg electromyography (EMG)
	Electrocardiogram (EKG)
	Respiratory effort measurement
	  Respiratory inductance plethysmographic (RIP)
	Oxygen saturation
	End tidal carbon dioxide
	Airflow measurement (oronasal)
	  Pressure transducer
	  Thermistor
	Body position

PSG output	REM vs. non-REM sleep Apnea–hypopnea index (AHI) Obstructive AHI Peak-end tidal carbon dioxide Time with carbon dioxide >50 mm hg

Abbreviations: *REM* rapid eye movement, *Hg* mercury, *PSG* polysomnography, *mm* millimeters

PSG is nearly universally used by adult practitioners to diagnose OSA. However, children often undergo treatment for SDB without a formal diagnosis of OSA [49]. In addition, the 2012 AAP guidelines acknowledged that there are not enough sleep centers to accommodate all children with SDB and suggested that alternative testing, such as pulse oximetry, may be helpful in assessing children [42]. When a child does undergo a PSG in an adult sleep center, it is critical that pediatric scoring criteria are used to score the study.

Guideline recommendations regarding pediatric PSG indications vary. The American Academy of Sleep Medicine (AASM) recommends PSG whenever OSA is suspected based on clinical assessment, prior to decannulation, after T&A in children with symptoms of persistent OSA, and children at high risk for persistent disease after T&A [50]. Alternatively, 2019 practice guidelines from the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) recommend PSG for all children under 2 years old, for children in whom the need for surgery is uncertain and when there is a discordance between the physical exam and symptoms [51]. These guidelines also recommend PSG for children with obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses [51].

7.7 Treatment of OSA

7.7.1 Medical Treatment

While a trial of oral steroids was not shown to be an effective treatment for OSA, nasal steroids have been shown to reduce the number of respiratory events by up to 5 events/h [52, 53]. Leukotriene modifiers, specifically Montelukast, have been shown to reduce lymphoid tissue, decrease AHI, and improve hypercarbia [54]. In addition, combination therapy of montelukast and intranasal mometasone resulted in symptomatic improvement in 12 weeks with the highest effective rate in the group with combination therapy [55]. A 2019 meta-analysis included six studies and 668 children aged 2–5 years, which demonstrated that montelukast alone, or combined with intranasal steroids, is potentially beneficial for the management of mild OSA [56]. These medications may also be helpful for children with persistent OSA following T&A [57]. While montelukast is typically well-tolerated, the FDA issued a warning for children that this medication may results in serious neuropsychiatric adverse drug reactions, especially for children with pre-existing mood disorders [58].

Weight loss has also been reported to decrease OSA, especially in children with mild to moderate disease. In children with severe OSA, weight loss (whether through medical or surgical means) may reduce OSA severity but not necessarily a full resolution [59, 60]. However, adolescents are more likely to see complete resolution of their OSA when compared to adults undergoing bariatric surgery [61, 62]. Weight loss has also been reported to lower CPAP requirements [63].

Oral appliance therapy has been reported as first-line therapy for children with mild and moderate OSA over a 6-month treatment period [64, 65]. Rapid maxillary expansion has been shown effective for children with mild to moderate OSA [66]. A 2016 systematic review and meta-analysis of 17 studies with 314 children with OSA and transverse maxillary deficiency demonstrated improvements in AHI and lowest oxygen saturation. However, follow-up was less than 3 years in all these studies. Long-term (12-year) follow-up ($n = 23$) had demonstrated stable resolution of OSA on PSG [66].

7.8 Continuous Positive Airway Pressure

Positive airway pressure (PAP) is a first-line therapy in adults but is more commonly considered after surgery in children. Nasal continuous PAP (CPAP) has been approved for treatment of pediatric OSA since 2006 in the United States. CPAP is typically started during an overnight titration study in a sleep laboratory, although auto-titrating CPAP is also used in children before PSG evaluation. The range of CPAP pressures used in children typically starts at 4 cm of water, with a maximum of 15 cm for children under 12 years of age or 20 cm for those 12 years or older [67]. As with adults, the goal of CPAP use and titration PSG is to provide adequate positive airflow to overcome and eliminate obstructive events in order to maintain airway patency [68] . CPAP has been shown to be effective for OSA treatment in children aged 2–16 years; however, at least 30% to 50% stop using CPAP within 6 months of initiation [69]. In addition, there are concerns that long-term use of a CPAP mask in children may contribute to facial flattening and worsen long-term OSA as children develop and grow [70].

7.9 Surgical Treatment

7.9.1 Adenotonsillectomy

T&A is first-line management for children with OSA. As of 2010, outpatient adenotonsillectomies were performed in approximately 289,000 children in the United States under the age of 15 [71]. The Childhood Adenotonsillectomy Trial (CHAT), a randomized controlled trial of tonsillectomy versus observation, reported normalization of PSG findings in 79% of children who underwent T&A versus 46% who were observed [13]. Symptomatic improvement occurred in 80% of those who underwent T&A, but only 15% in the observation arm. The likelihood of persistent OSA after T&A depends on patient characteristics with increased rates reported in children with morbid obesity, craniofacial abnormalities, the genetic conditions including Down syndrome and achondroplasia.

Several methods are used to remove tonsils and adenoids; however, there is no universally recommended method. Common techniques include “cold steel,” electrocautery, and radiofrequency ablation although laser, microdebrider, and harmonic

scalpel have all been used [72]. Each of these techniques aims to minimize time under anesthesia as well as postoperative pain and bleeding.

The risk of bleeding after T&A is 1%–4%, depending on the technique. Other complications associated with T&A are quite low and include airway fires, anesthesia reactions, airway complications, nasopharyngeal stenosis, velopharyngeal insufficiency (VPI) or incompetence, and atlantoaxial subluxation [73]. After surgery, many children complain of pain and decreased oral intake. A return to the hospital may result from nausea, vomiting, and/or dehydration.

Tonsillotomy, also known as partial or intracapsular or subtotal tonsillectomy, has a lower risk of postoperative pain and hemorrhage than tonsillectomy although does have a risk of recurrence and regrowth of the tonsils. A 2017 meta-analysis of 32 studies reported that children undergoing tonsillotomy had less postoperative pain, quicker time to normal oral intake, and lower odds of hospital readmission, with similar patient satisfaction rates, quality-of-life improvements, and PSG improvements [74].

7.9.2 Adenoidectomy

Adenoidectomy alone may be performed to treat OSA when adenoid hypertrophy is identified in the absence of tonsillar hypertrophy or if there is a patient preference to attempt a lower morbidity surgery as first-line therapy. Adenoids can be assessed using either nasopharyngoscopy or lateral neck x-rays. A 2020 meta-analysis reported an adenoid regrowth rate of 8% (n = 4950 primary adenoidectomies) [75]. This same analysis reported that among 119,369 published primary adenoidectomies, there was a revision rate of 2%, with 26% of these revision surgeries performed for children with OSA [75]. Adenoid regrowth is reportedly more common in young children or when "blind" adenoidectomy techniques (like with a curette) as there is a higher likelihood of leaving residual adenoid tissue behind [76, 77]. A separate retrospective study of children who underwent adenoidectomy for SDB reported that 38% required subsequent revision adenoidectomy or tonsillectomy [78]. A 2016 study (n = 515) of children with moderate to severe OSA compared those who underwent adenoidectomy alone versus T&A and reported similar success rates for nonobese children with AHI <10 and small tonsils (<3); those with severe OSA or large tonsils were less likely to have resolution on a PSG with adenoidectomy alone when compared to the T&A group [79].

Adenoidectomy is also performed using several methods that include curette, electrocautery, microdebrider, and radiofrequency ablation with no single method recommended. Complications from adenoidectomy are rare, and recovery is typically quick. Postoperative bleeding is rare, and pain is significantly less than that seen with tonsillectomy. Much fewer common risks include VPI, nasopharyngeal stenosis, and soft palate injury. Many surgeons leave the inferior portion of the adenoids to reduce the risk of VPI, especially in children with submucous and overt cleft palates where this risk is high.

7.10 Pre-, Peri-, and Postoperative Management

Assessment of any child with OSA who is being considered for surgery should include questions regarding a personal or family history of bleeding or easy bruising, difficulty with anesthesia, history of cardiovascular issues or other medical comorbidities. When a bleeding risk is suspected, a hematologic workup should be considered. Of those children who present with bleeding after tonsillectomy, 19% had elevated prothrombin time, partial thromboplastin time, or platelet function assays, while only 4% were formally diagnosed with a coagulopathy [80]. For children with medical comorbidities, preoperative evaluation should be specifically tailored to the condition and the individual which may include specialty assessment, imaging, testing (e.g., electrocardiogram), or preoperative anesthesia consultation. For all children with OSA, the AAO-HNS recommends good communication between the surgeon and the anesthesia team regarding OSA severity and PSG findings as children with OSA are noted to be at increased risk for anesthetic complications [42, 81].

In the recovery room, close monitoring for hypoxemia and hypercarbia is essential as these children are at high risk for complications compared to children without OSA. For children 2 and younger, and those deemed high risk, overnight observation is recommended after surgery. The definitions of children at high risk by the AAP and AAO-HNS can be found in Table 7.5.

Children should also be sure to have adequate pain control. While opioids were commonly used in the past after T&A, many children are now treated with acetaminophen, ibuprofen, and steroids as first-line pain control. The use of opioids decreased significantly after the FDA issued a warning in 2013 that codeine use in children after tonsillectomy could result in respiratory depression and death [82]. Considering this, the 2019 AAO-HNS Tonsillectomy clinical practice guidelines

Table 7.5 High-risk conditions which warrant overnight observation after adenotonsillectomy per the American Academy of Pediatrics (AAP) and the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS)

AAP	AAO-HNS
Children <3 years	Children <3 years
Severe OSA (AHI > 24)	Severe OSA (AHI > 10, sat nadir<80%)
Cardiac complications of OSA	Cardiac complications of OSA
Failure to thrive	Failure to thrive
Obesity	Obesity with/without OSA
Current respiratory infections	Current/recent respiratory infections
Craniofacial anomalies	Craniofacial anomalies
Neuromuscular disorders	Neuromuscular disorders Down syndrome Behavioral factors that predispose to poor oral intake/difficult pain control

Abbreviations: *OSA* obstructive sleep apnea, *AHI* apnea–hypopnea index, *Sat* oxygen saturation

recommend against codeine use after surgery for children under 12 years old. The FDA also recommends against codeine use in children with obesity and OSA between 12 and 18 years of age, and some pediatricians have recommended against any codeine use for children in general [83].

7.11 Persistent OSA After T&A

A 2009 systematic review and meta-analysis of 1079 children demonstrated that PSG-assessed treatment success after T&A was 66.3% [84]. Risk factors associated with persistent OSA after T&A include craniofacial/mandibular anomalies, cerebral palsy, genetic disorders (e.g., Down syndrome), severe OSA, obesity, age over 7 years, and asthma in nonobese children [85–88]. The 2023 AAO-HNS expert consensus statement regarding Persistent OSA recommends that PSG be obtained for children with symptoms of OSA after T&A and children at high-risk for persistent disease [89]. These authors also recommended alternative testing, including oximetry, cardiorespiratory studies, and home sleep testing when PSG is unavailable. In addition, they noted that assessment of symptom burden and quality of life is useful at baseline and after treatment.

Assessment of the site of obstruction for children with persistent OSA should start with a physical examination, including the nasal airway, adenoid regrowth, oral cavity/oropharynx - including the palate and lateral pharyngeal walls hypopharynx and larynx. Drug-induced sleep endoscopy is also commonly used to assess these children using a flexible endoscope while the child is in a pharmacologically induced sleep-like state. This test is reported to have good interrater reliability as well as good test–retest reliability [90, 91]. A 2016 meta-analysis of DISE reported that the most common sites of obstruction were the tongue base, adenoids (based on regrowth), inferior turbinates, velum, and lateral oropharyngeal walls [92]. There is not yet a universally accepted grading system for pediatric DISE, although several have been proposed (VOTE, SERS, Chan, Bachar, Fishman, Boudewyns) [93–99]. Classification systems typically include the nose/nasopharynx, velum, oropharyngeal walls, tongue base, epiglottis and larynx/supraglottis [95, 96]. Table 7.5 summarizes the most commonly reported causes of persistent OSA as identified during DISE.

Imaging studies can also be helpful to assess for possible sites of obstruction. Lateral neck x-rays are useful for looking for adenoid regrowth and identifying enlarged lingual tonsils [100]. For those children with craniofacial abnormalities of the facial skeleton, CT scans can be help asses bony definition. Cine MRI is sometimes used to provide a high-resolution real-time dynamic assessment of the upper airway and identify sites obstruction [101]. Determining primary versus secondary sites of obstruction, such as lingual tonsil hypertrophy causing palatal narrowing/obstruction, is most helpful. It also is beneficial to differentiate between a large base of tongue with small overlying lingual tonsils versus true lingual tonsillar hypertrophy.

7.12 Treatment for Persistent OSA

A multidisciplinary approach is recommended for these children. It may include primary care providers, sleep medicine clinicians, dentists, pulmonologists, and otolaryngologists as well as additional providers as needed (genetics, Oro maxillofacial surgery, plastic surgery, behavioral nutritionists, and geneticists among others).

7.12.1 Nonsurgical Treatment

CPAP therapy is a primary treatment for persistent OSA after T&A and should be offered if no obvious anatomic target is identified. However, compliance is often low, and mask fitting can be problematic for very young children or those with craniofacial anomalies [102]. When used, ongoing reevaluation is necessary, given concerns about facial growth and the need to assess changes in the severity of persistent OSA with development and the impact of weight gain.

Oral appliances may be used for children and are likely most effective for those with permanent teeth in place, so regular replacement is less of an issue. While studies in children are limited, significant reductions in AHI and improvements in subjective outcomes have been reported [103–105].

Rapid maxillary expansion has also been used effectively to resolve mild to moderate OSA in children with high-arched palates and maxillary constriction [106]. A 2016 systematic review and meta-analysis of 17 studies, including 314 children, reported improvements in AHI and oxygen saturations after rapid maxillary expansion [66]. While numbers are minimal, a case series of 23 children followed for 12 years reported persistently normal PSG findings [66].

As with adults, weight loss has been shown to significantly improve the AHI in children [107]—whether medical or surgical. Medications such as Montelukast and nasal steroids (alone or in combination)have also been shown useful for treating mild OSA [108]. Positional therapy, including vibrational therapy, also appears to be effective for children, although data is limited [109–111].

7.12.2 Surgical Treatment—Nasal

Similar to adult studies, children with persistent OSA typically have an obstruction at multiple levels of the airway. Because oropharyngeal scarring and stenosis have been reported in 8.2% of children undergoing multilevel surgery including lingual tonsillectomy, many pediatric otolaryngologists consider staged surgery [112].

There is limited data regarding the impact of nasal surgery on OSA in children beyond adenoidectomy. Despite concerns regarding the impact of septoplasty on facial growth in children, long-term evidence (with 12.2 years of follow-up) found that endoscopic septoplasty did not interfere with nasal growth [113]. Studies of turbinate reduction in children with nasal obstruction and SDB

undergoing T&A have shown that those who undergo turbinate reduction at the same time as T&A have greater reductions in AHI than those undergoing T&A alone [114–116].

7.12.3 Surgical Treatment—Oropharyngeal/Tongue

While uvulopalatopharyngoplasty (UPPP) has been reported to be successful in 40% to 80% of adults, depending on their physical exam characteristics, there is limited information regarding the effectiveness of UPPP in children [117]. Expansion sphincter pharyngoplasty (ESP) with T&A has been studied in children with severe OSA and compared to ESP alone; they found that children who underwent both procedures had lower postoperative AHI and higher cure rates than those in the group who underwent ESP alone [118].

Lingual tonsil hypertrophy is a common finding in children with persistent OSA. A meta-analysis showed that removal of lingual tonsils resulted in a reduction of the AHI of 6.6 with an overall success rate of 52% [119, 120]. A review of the adverse effects of lingual tonsillectomy notes that these are similar to those for T&A and include bleeding, poor oral intake, and scarring [121]. This procedure may be performed independently or in association with tongue base procedures like tongue suspension or partial midline glossectomy.

Tongue suspension is intended to prevent the base of the tongue from falling back (glossoptosis) during sleep and involves a heavy suture that goes around the base of the tongue and is anchored anteriorly to the inside of the mandible. When performed in combination with radiofrequency to the base of tongue, it has been shown to have a 61% success rate in children [122]. Midline posterior glossectomy entails the removal of midline tongue tissue when the tongue is falling back and obstructing the airway or pushing the palate up and back into the nasal and upper pharyngeal airway. Small studies in children have reported improvements in AHI and symptoms when performed alone or in combination with lingual tonsillectomy [91, 123, 124]. Associated rare complications include dysphagia, minor bleeding, and taste disturbance as well as the possibility of bleeding from the lingual artery.

Tongue-lip adhesion is used to treat infants with glossoptosis who have micrognathia. It is intended to pull the tongue forward toward the lower lip and is typically used for children with Pierre–Robin sequence. A 2016 meta-analysis of children undergoing tongue-lip adhesion showed an improvement in AHI of 15.4 events/h (30.8–15.4) [125].

Genioglossal advancement is rarely considered in children as they need to have permanent teeth in order to safely perform the procedure. This procedure entails moving the genioglossal muscle attachment to the mandible and a surrounding portion of bone forward to open up the airway space behind the tongue. Because the tooth roots can be affected, it is not carried out in children until they have adult teeth.

Hypoglossal nerve stimulation therapy has been used to treat adolescents with Down syndrome and persistent OSA. The device stimulates the hypoglossal nerve during sleep, and this results in tongue contraction and anterior movement that may

or may not be coordinate with breathing, depending on the type of simulator implanted. Results for children with Down syndrome suggest that it is effective as salvage surgery for most children, and at 12 months, the mean decrease in AHI was 15.1 events/h, and 55% had an AHI < 5 while 75% had an AHI under 10 [126].

7.12.4 Surgical Treatment—Laryngeal

Epiglottopexy is considered for children with epiglottic prolapse causing airway obstruction. A 2020 summary of epiglottopexy reported a success rate of 53.6% [127]. Supraglottoplasty is performed for infants with OSA due to laryngomalacia as well as older children who develop sleep-state dependent laryngomalacia (i.e., laryngomalacia that is only seen during sleep). A meta-analysis found that supraglottoplasty was effective for both groups of patients, with significant improvements in both the AHI and the oxygen saturation nadir [128].

7.12.5 Surgical Treatment—Craniofacial and Tracheotomy

In children with craniofacial abnormalities, mandibular and maxillary surgery may be used to expand the skeletal structure and thus the pharyngeal airway. While benefits have been shown in adults, outcomes in children are limited and optimal timing for surgery is unknown [129–131]. Mandibular distraction osteogenesis is commonly used for young children with retrognathia and has been shown to be very effective in alleviating OSA, with a 73.4% success rate in the AHI in a 2018 systematic review [132].

Tracheotomy continues to be a useful procedure for children with severe OSA that is most commonly used for children with multilevel obstruction or infants without other obvious anatomic solutions. In a review of 29 children who underwent tracheotomy for severe OSA, the majority had associated neuromuscular comorbidity and craniofacial abnormalities [133].

7.13 Conclusion

The diagnosis and management of pediatric OSA continue to evolve as we work to find more accessible and broadly available assessment option. T&A remains the first-line therapy for children with OSA. Still, children with OSA after T&A should be assessed for the recurrence of tonsil tissue if partial tonsillectomy was performed or regrowth of adenoids. Additional assessments may include drug-induced sleep endoscopy and cine MRI to understand sites of obstruction. Both medical and surgical options should be considered for patients, and the impact of growth and development is crucial as you consider treatment for children.

Take-Home Message

- Adenotonsillectomy is first-line thereapy for children with OSA.
- For children with persistent OSA, drug-induced sleep endoscopy or cine MRI are used to assess for sites of collapse that may contribute to OSA. Medical and surgical options should be considered for children with persistent OSA and personalize therapy should be discussed.

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Obstructive Sleep Apnea and Systemic Autoimmune Diseases

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Philippe Chalem

Systemic inflammatory diseases of autoimmune origin constitute a heterogeneous group of diseases from the pathophysiological point of view. From a clinical perspective, they often present marked differences, determined by manifestations that are considered specific to each. However, they frequently share common clinical features that could make it difficult to establish a differential diagnosis.

This is the case of the pain and inflammation of the joints, a common denominator in many systemic autoimmune diseases. Constitutional symptoms such as fever, weight loss and chronic fatigue are frequent, nonspecific and often confusing manifestations.

Fatigue is one of the common denominators in many rheumatic conditions and is often considered a symptom that may indicate the inflammatory activity of the disease. This symptom is critical and is included in the evaluation scales of diseases such as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus and Sjögren's syndrome [1–4].

However, inflammatory activity in rheumatic diseases is not always documented when there is fatigue. When that happens, the presence of comorbidities, nutritional disorders, states of anxiety and depression or sleep disorders should be assessed. Obstructive sleep apnea is found within this last group [5].

Patients who suffer from systemic autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis and other seronegative spondyloarthritis, systemic lupus erythematosus, Sjögren's syndrome, progressive systemic sclerosis, inflammatory myopathies and vasculitides suffer from obstructive sleep apnea more frequently than the general population (Table 8.1) [5–12].

This raises the need to address the following questions: (1) Are there common pathophysiological pathways between obstructive sleep apnea and systemic

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Table 8.1 Systemic autoimmune disease and obstructive sleep apnea

Systemic autoimmune diseases related to obstructive sleep apnea
1. Rheumatoid arthritis
2. Ankylosing spondylitis
3. Systemic lupus erythematosus
4. Sjögren's syndrome
5. Systemic sclerosis
6. Inflammatory myopathies
7. Vasculitides

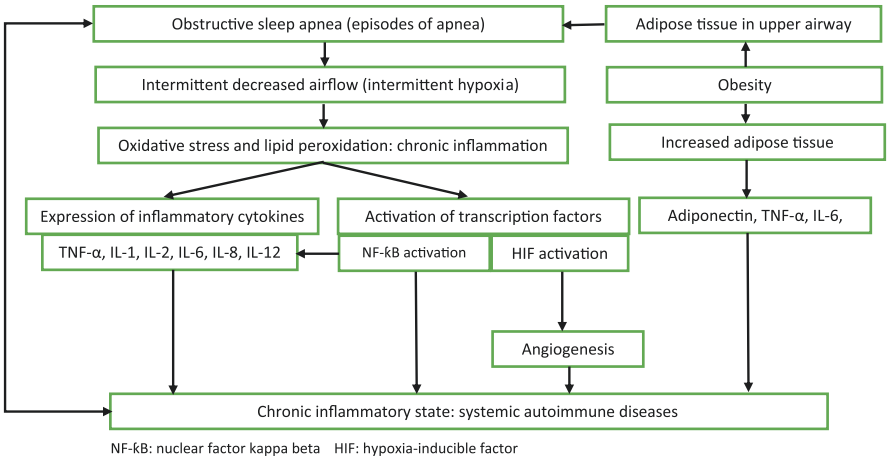

Fig. 8.1 Complex relationship between obstructive sleep apnea, autoimmunity and obesity

autoimmune diseases? (2) Are systemic autoimmune diseases a predisposing factor for developing obstructive sleep apnea? (3) Can obstructive sleep apnea predispose to systemic autoimmune diseases? Existing literature does not provide a satisfactory answer to these questions but sheds some light on the matter (Fig. 8.1).

8.1 Common Pathophysiological Pathways Between Obstructive Sleep Apnea and Systemic Autoimmune Diseases

Episodes of intermittent apnea result in decreased airflow (and therefore oxygen) through the airway, leading to tissue hypoxia. The consequence of this "intermittent hypoxia" is increased oxidative stress and lipid peroxidation. This leads to a state of chronic inflammation, which is characterized by the expression of cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6 and IL-8, among others [5, 13].

This inflammatory state is also characterized by the activation of transcription factors such as the hypoxia-inducible factor (HIF) and the nuclear factor kappa beta (NF-ƙB). HIF plays a role in angiogenesis processes that take place in inflammatory phenomena. In turn, NF-ƙB induces the transcription of genes related to proinflammatory cytokines (TNF-α, IL-1, IL-2, IL-6, IL-8, IL-12), promotes the proliferation of immune system cells and has an antiapoptotic effect on some of these cells [5, 13–16].

Additionally, alterations in sleep patterns that necessarily accompany obstructive apnea lead to changes in the immune system, such as a decrease in natural killer cells and an increase in proinflammatory cytokines such as IL-1 and IL-2 [5].

There is a complex interrelationship between obesity, obstructive sleep apnea and autoimmune diseases. The link between obesity and obstructive sleep apnea is well known, as it has been demonstrated that the accumulation of adipose tissue in the walls of the pharynx can cause a reduction in the caliber of the upper airway. Moreover, obesity is linked to proinflammatory states that may, in turn, favor inflammation and upper airway narrowing. Indeed, adipose tissue is responsible for producing adiponectin, TNF-α and IL-6, among other cytokines, which clearly further predispose to the onset of systemic autoimmune diseases. Therefore, this may lead to a multidirectional process whereby adipose tissue promotes the appearance of apnea and systemic autoimmune diseases, conditions that will reinforce each other (Fig. 8.1) [5, 17, 18].

8.2 Systemic Autoimmune Diseases as a Predisposing Factor for Obstructive Sleep Apnea

Several publications show that obstructive sleep apnea occurs more frequently in patients with systemic autoimmune diseases when prevalence figures are compared with the general population [7, 9, 10].

This raises the possibility of a causal relationship between systemic autoimmune diseases and obstructive sleep apnea. This could occur through several possible mechanisms, some of which were addressed in the paragraphs above. Inflammatory activity mediated by cytokines and transcription factors is common in several diseases. Moreover, factors specific to each disease may explain a greater predisposition to the onset of obstructive sleep apnea. Thus, alterations of the cervical spine (in rheumatoid arthritis and ankylosing spondylitis), retrognathia (in rheumatoid arthritis) or weakness of the pharyngeal muscles (in inflammatory myopathies) are local factors that can lead to upper airway obstruction and subsequent apnea (Figs. 8.2a–e). In other inflammatory diseases (such as Sjögren's syndrome, systemic sclerosis, vasculitides, systemic lupus erythematosus), the local mechanisms that may cause or worsen obstructive apnea are not very clear (Table 8.2) [5, 11, 14, 19–21].

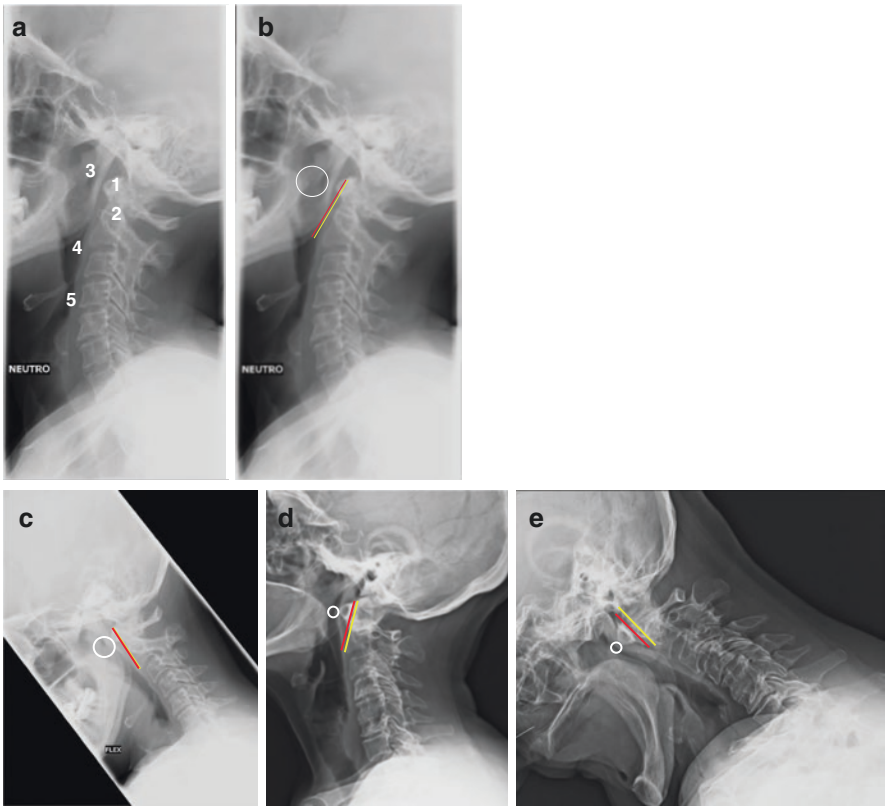

Fig. 8.2 (**a**) Lateral X-ray of the normal cervical spine (neutral position). Some anatomical structures are indicated: C1 vertebra (1), C2 vertebra (2), nasopharynx (3), oropharynx (4) and laryngopharynx (5). (**b** and **c**). In a normal cervical spine, both in the neutral position and in flexion, the anterior arch of C1 (red line) and the odontoid process of C2 (yellow line) are united and the nasopharynx retains its caliber (white circle). (**d** and **e**). When dislocation between C1 and C2 occurs in rheumatoid arthritis, the separation of the first two vertebrae (separation of the red and yellow lines) is accentuated by flexion of the cervical spine and may be accompanied by a decrease in the caliber of the nasopharynx (white circle)

Table 8.2 Local factors leading to upper airway obstruction in systemic autoimmune diseases

Disease	Local factor leading to upper airway obstruction
Rheumatoid arthritis	C1–C2 damage (dislocation, impaction, C2 erosion or fracture)
Rheumatoid arthritis	Subaxial luxation (below C2)
Rheumatoid arthritis	Temporomandibular damage (causing retrognathism)
Ankylosing spondylitis	Cervical spine involvement
Inflammatory myopathies	Involvement of respiratory and pharyngeal muscles
Sjögren's syndrome	Cytokine-mediated narrowing of the upper airway[a]
Sjögren's syndrome	Lymphoid infiltration of the upper airway[a]
Sjögren's syndrome	Increased viscosity of respiratory secretions[a]

[a] These mechanisms are less clear than in other diseases

8.3 Obstructive Sleep Apnea as a Predisposing Factor for Systemic Autoimmune Diseases

Existing studies in populations of patients with systemic autoimmune diseases have demonstrated the increased prevalence of obstructive sleep apnea in these groups. Furthermore, studies in cohorts of patients with obstructive sleep apnea have concluded they face a higher risk of developing systemic autoimmune diseases.

In 2016, Chen et al. published a retrospective study using nationwide databases in Taiwan. Data were obtained from 105,846 adults diagnosed with obstructive sleep apnea between 2002 and 2011. Patients with a previous history of autoimmune disease were excluded from this retrospective analysis. The study included a control group with 423,384 participants without obstructive sleep apnea. According to the results, patients with obstructive sleep apnea face an increased risk of suffering from autoimmune diseases, particularly rheumatoid arthritis (HR [95% CI]: 1.33), Sjögren's syndrome (HR: 3.45) and Behçet's disease (HR: 5.33). This study did not find an increased risk of developing systemic lupus erythematosus or systemic sclerosis among patients with obstructive sleep apnea [22].

In a smaller cohort, also from Taiwan, Kang and Lin report similar findings: the risk of developing rheumatoid arthritis was higher in patients with obstructive sleep apnea than in the control group (HR [95% CI]: 1.66) [23].

Even though a solid relationship between obstructive sleep apnea and the development of psoriatic arthritis or other spondyloarthritis has not been firmly established, a surprising link has been identified with the onset of cutaneous psoriasis. In Taiwan, Yang et al. found that a prospective cohort of patients with obstructive sleep apnea diagnosed by polysomnography faced an increased risk of developing psoriasis (HR [95% CI]: 2.30). Cohen et al. also established an association between obstructive sleep apnea and psoriasis in a cohort of nurses in the United States (RR [95% CI]: 2.19). However, this study does not specify the criteria (probably very heterogeneous) that enabled them to diagnose obstructive sleep apnea [24, 25].

8.4 Obstructive Sleep Apnea in Rheumatoid Arthritis

It is estimated that more than a third of patients with rheumatoid arthritis suffer from obstructive sleep apnea, a prevalence much higher than in the general population. The risk factors are the same as those described for individuals without arthritis: age, obesity and neck circumference. However, two circumstances specific to rheumatoid arthritis have been associated with obstructive sleep apnea: involvement of the cervical spine (Figs. 8.2a–e) and retrognathism associated with temporomandibular joint involvement [6, 26].

Rheumatoid arthritis frequently affects the cervical spine and causes lesions mainly at the level of the atlantoaxial joint (C1–C2 dislocation) and the odontoid apophysis of C2 (which can suffer erosions and even fractures). Additionally, atlantoaxial impaction or basilar impaction (due to damage to the atlantooccipital joints or the C1–C2 joints at the level of the lateral masses of the atlas) is also described.

Finally, subaxial subluxation can occur, a less frequent form in which the intervertebral joints at multiple levels below C2 are affected (Table 8.2) [27].

In a Japanese series, Shoda et al. describe 29 patients with cervical spine lesions without other factors that could increase the risk of obstructive apnea (such as obesity, adenoid hypertrophy, nasal obstruction, cricoarytenoid arthritis or temporomandibular involvement). Obstructive sleep apnea was found in 79% of cases. None of the patients had apnea of central origin, possibly because of the absence of significant spinal cord lesions. The authors suggest that obstructive apnea is determined by an interaction between the mechanical properties of the upper airway and neurological alterations in the regulation of muscle tone. Indeed, cervical spine lesions cause the spine to shorten, reducing the caliber of the upper airway and favoring its obstruction. In addition, the authors speculate that occipitocervical lesions could be associated with alterations of cranial nerves V, VII, IX, X and XII, responsible for controlling the muscles that dilate the airway, generating its collapse [28].

Surgical treatment of cervical spine deformities that corrects kyphosis associated with atlantooccipital and atlantoaxial joint disorders has been shown to increase airway patency, improving obstructive apnea [29].

The involvement of the temporomandibular joints is widely known in rheumatoid arthritis. Severe damage to these joints may cause retrognathism, leading to the reduction in the caliber of the upper airway and its obstruction. CPAP treatment has been proposed in these rare cases. Tracheostomy proved to be the solution in an extremely severe case. Surgical interventions on the temporomandibular joint have also been considered (Table 8.2) [30–33].

Regardless of the evident cause–effect relationship between the anatomical alterations described in patients with rheumatoid arthritis and obstructive sleep apnea, it should be noted that in most cases, apnea is related to systemic inflammatory phenomena. Therefore, systemic treatment with disease-modifying drugs that act on proinflammatory cytokines may be useful to improve respiratory alterations. Although there is not enough evidence in this regard, the impact of pharmacological treatment of arthritis on obstructive sleep apnea should be the subject of future research [34].

8.5 Obstructive Sleep Apnea in Ankylosing Spondylitis

A retrospective study was carried out in Taiwan with a cohort of 2210 patients diagnosed with ankylosing spondylitis between 2003 and 2013 and a control group of 8840 adults (Tsao et al. 2019). The study found an adjusted hazard ratio (aHR) of 2.826 (95% CI: 3.169–19.792) for developing obstructive sleep apnea. Indeed, during the 11-year follow-up period, 30 patients with ankylosing spondylitis (1.36%) developed obstructive sleep apnea compared to 40 controls (0.46%) [7].

Wiginder et al. found different results in Sweden. Using home sleep monitoring devices, the authors compared 46 ankylosing spondylitis patients with 179 controls.

Approximately half of the subjects in both groups (47.8% and 50.8%, respectively) had obstructive sleep apnea. It is possible that the sample size did not allow finding differences between the two groups [35].

It is well known that the inflammatory activity of certain systemic diseases can cause tiredness and produce sleep disturbances, further worsening the symptoms of fatigue. Obstructive apnea can also manifest itself in daytime tiredness, independent of the inflammation. Manifestations of the systemic inflammatory activity of ankylosing spondylitis may sometimes be confused with sleep disorders [36–38].

It has been proposed that cervical spine involvement in ankylosing spondylitis may cause upper airway stenosis, favoring the development of obstructive apnea. It is also important to consider the role of inflammation mechanisms on the mucosa and lymphoid tissue adjacent to the airway, which could contribute to obstructive phenomena (Table 8.2) [39, 40].

The treatment of obstructive sleep apnea in patients with ankylosing spondylitis does not differ from the usual treatment (sleep hygiene, avoiding certain medications, weight loss, postural measures, using a CPAP). Furthermore, it has been suggested that anti-TNF and other anti-inflammatory agents can reduce apnea symptoms and improve sleep quality, although there is no agreement in this regard [39–41].

8.6 Obstructive Sleep Apnea in Inflammatory Myopathies

As inflammatory myopathies (polymyositis, dermatomyositis and inclusion body myopathy) are low-prevalence diseases, there are fewer publications on the relationship with obstructive sleep apnea than other systemic autoimmune diseases.

Selva-O'Callaghan et al. published a case series of 16 patients with inflammatory myopathies (12 with dermatomyositis, 2 with polymyositis and 2 with inclusion body myopathy) who underwent polysomnography. The mean apnea–hypopnea index (AHI) was 28.7, and sleep apnea (defined as an AHI higher than 5) was documented in 14 of the 16 patients (87%). Episodes of apnea of central origin were detected only occasionally. Treatment with CPAP in four patients showed very good results [11].

Rodríguez Cruz et al. published their experience with 15 patients with inclusion body myopathy. Using home sleep monitoring devices, the authors diagnosed sleep apnea (AHI higher than or equal to 5) in 100% of the patients. The mean AHI was 23.4; five patients had mild apnea (AHI: 5–15), six had moderate apnea (AHI: 15–30) and four had severe apnea (AHI higher than 30) [42].

Based on the available literature, no specific guidelines can be established regarding the treatment of obstructive sleep apnea in inflammatory myopathies. In addition to the treatments currently described (including positive pressure devices), pharmacological treatment—immunosuppressants and glucocorticoids—is essential to achieve recovery of the respiratory and pharyngeal muscles (Table 8.2).

8.7 Obstructive Sleep Apnea in Sjögren's Syndrome

A retrospective study in Taiwan included 12,926 patients diagnosed with Sjögren's syndrome between January 1, 2002, and December 31, 2011. The control group consisted of 51,704 individuals without autoimmune diseases. The diagnosis of sleep apnea was made by polysomnography. After adjusting for age, sex and comorbidities, obstructive sleep apnea incidence was significantly higher in patients with Sjögren's syndrome than in controls (0.61% and 0.33%, respectively). The risk of developing obstructive sleep apnea was found to be increased, with an aHR of 2.48 (95% CI: 1.89–3.24) [12].

Karabul et al. published a prospective study on 44 patients with Sjögren's syndrome, consecutively recruited between April 1, 2019, and December 31, 2020. All patients underwent a polysomnography study and 84% (37 of 44) were diagnosed with obstructive sleep apnea, reflecting a higher prevalence than the general population. Of the patients diagnosed with obstructive sleep apnea, 12 (27%) suffered a mild form, 19 (43%) a moderate form and 6 (14%) a severe form. Comparing Sjögren's syndrome patients with and without obstructive sleep apnea revealed a statistically significant association between apnea and age, higher body mass index, overweight and obesity. There was no relationship between apnea and lung involvement associated with Sjögren's syndrome [9].

The mechanisms by which Sjögren's syndrome is associated with obstructive sleep apnea are unclear. There are several possibilities, which could contribute simultaneously. As mentioned above, cytokine-mediated proinflammatory states can promote inflammation and narrowing of the upper airway. Additionally, lymphoid infiltration of the upper airway contributes to a decrease in airway caliber. The increased viscosity of respiratory secretions associated with the sicca syndrome may also contribute to airflow obstruction. Simultaneously with airway dryness, an increase in the surface tension of the liquid layer lining the mucosa has been described. This increase in surface tension favors airway collapse, requiring a significant increase in intraluminal pressure to achieve reopening. However, it has not been corroborated that the upper airway in Sjögren's syndrome patients is systematically more prone to collapse (Table 8.2) [43].

8.8 Obstructive Sleep Apnea in Systemic Lupus Erythematosus

Chronic fatigue is undoubtedly one of the common nonspecific symptoms in patients with systemic lupus erythematosus. It could reflect the inflammatory activity of the disease, its sequelae, the presence of depression, the side effects of medications or alterations in sleep patterns [44, 45].

Valencia-Flores et al. compared 14 systemic lupus erythematosus patients with 11 healthy controls of similar age but with a lower body mass index (26.78 kg/m^2 on average in the lupus patients versus 20.85 kg/m^2 in the controls). The number of respiratory events per hour (apneas and hypopneas) was quantified, determining the

respiratory disturbance index (RDI). The mean RDI in the patients with lupus erythematosus was 8.84 and 1.89 in controls. Half of the patients had mild or moderate apnea: moderate apnea (RDI >10 and <30) was diagnosed in 3 of the 14 patients with lupus (21.5%), and mild apnea (RDI >5 and <10) was diagnosed in 4 patients (28.6%). Additionally, a significant increase in abnormal limb movements was found in lupus patients with and without respiratory disorders [8].

Iaboni et al. also reported sleep disturbances in a group of 35 patients with lupus. The AHI was higher than 5 in 20 of the 35 patients (57%). Nine patients (25.7%) with obstructive sleep apnea were found to have an AHI higher than 10; the average AHI in this group was 19.3. Even though this article does not specify the AHI of the control group of 17 healthy individuals, it compares other parameters (sleep efficiency, awakening/hours of sleep), finding sleep disturbances in patients with lupus that could partly explain the frequently reported fatigue [45].

As in other systemic autoimmune diseases, obstructive sleep apnea is frequently found in patients with systemic lupus erythematosus. It has been postulated that chronic use of glucocorticoids may partially explain sleep disturbances, but this has not been sustained. No mechanisms specific to lupus have been described to explain the higher frequency of obstructive sleep apnea, but the previously mentioned inflammatory mediators probably play a role [8, 18, 19, 45–47].

8.9 Obstructive Sleep Apnea in Systemic Sclerosis

Medical literature describes two main types of systemic sclerosis (scleroderma): the limited and diffuse cutaneous forms. The former usually presents itself without pulmonary parenchymal involvement, but pulmonary hypertension is a frequent manifestation. In the latter, both pulmonary hypertension and interstitial involvement are frequent manifestations. The increase in pulmonary artery diameter allows for estimating pulmonary hypertension. Yakut et al. used home sleep monitoring devices to evaluate 62 patients (58 women). Obstructive sleep apnea was diagnosed when AHI ≥15/h. Interstitial involvement and pulmonary artery diameter were assessed using computed axial tomography. Obstructive sleep apnea was documented in 20 patients (32%): 17/42 (40%) with the limited form and 3/20 (15%) with the diffuse form. There were no differences in lung parenchyma involvement between patients with and without apnea. An increased pulmonary artery diameter was found in 10/20 patients (50%) with obstructive sleep apnea. This finding was evident in only 6/17 (14%) patients without apnea. The authors concluded that in patients with systemic sclerosis, obstructive sleep apnea is associated with an increased risk of pulmonary hypertension, regardless of lung parenchymal involvement, with an odds ratio (OR) of 4.7 (95% CI: 1.06–20.88) [48].

Two additional studies found that the prevalence of obstructive sleep apnea (defined as AHI ≥5/h) in patients with systemic sclerosis is approximately 50%. One of these studies included 38 patients with interstitial lung disease. The other study included 39 patients, finding no relationship between interstitial lung disease and obstructive sleep apnea [10, 49].

Obstructive sleep apnea is a frequent manifestation in patients with systemic sclerosis, both in the diffuse and the limited variants. It most likely contributes to pulmonary hypertension and does not seem to correlate with interstitial lung disease. The diagnosis and treatment of obstructive sleep apnea should be part of the comprehensive management of patients with systemic sclerosis.

8.10 Obstructive Sleep Apnea in Systemic Vasculitides

The vasculitides are a highly heterogeneous group of low-prevalence diseases characterized by the inflammation of the blood vessel wall and occlusion of the vascular lumen with subsequent tissue ischemia. The clinical manifestations of vasculitides are highly diverse. Except for Behçet's disease, no studies were found on obstructive sleep apnea.

A retrospective study in Taiwan included 1221 patients diagnosed with Behçet's disease and followed up between January 1, 2002, and December 31, 2011. The control group consisted of 4884 individuals without autoimmune diseases. Polysomnography was used to diagnose sleep apnea. After adjusting for age, sex and comorbidities, the incidence of obstructive sleep apnea was significantly higher in patients with Behçet's disease than in controls (1.23% and 0.33%, respectively). The risk of developing obstructive sleep apnea was found to be increased, with an aHR of 1.99 (95% CI: 1.06–3.72) [12].

Tascilar et al. studied 51 patients with Behçet's disease without neurological involvement and compared them with 21 healthy controls. Polysomnography was performed on 40 Behçet patients and all controls. The AHI was significantly higher in Behçet patients than in the control group. However, when patients with active and inactive Behçet's disease were compared, no difference was found in the frequency of sleep alterations [50].

Obstructive sleep apnea is more frequent in patients with Behçet's disease than in the general population, although it does not seem to worsen disease activity or be caused by it. Likewise, it seems evident that obstructive sleep apnea contributes to Behçet patients' fatigue and impaired quality of life. The correct diagnosis and treatment of obstructive sleep apnea should be part of the comprehensive management of patients with Behçet's disease.

8.11 Conclusions and Future Perspectives

Obstructive sleep apnea is more frequent in patients with systemic autoimmune diseases than in the general population. Sleep disorders may be partially responsible for fatigue and impaired quality of life in patients with autoimmune diseases, highlighting the need to actively assess the presence of these disorders. Current treatment does not differ from that used in patients without autoimmune diseases (sleep

hygiene, avoiding certain medications, losing weight, postural measures and positive pressure devices). An adequate understanding of the complex pathophysiological mechanisms (still to be determined) will allow for better treatment of autoimmune diseases and sleep disorders.

Take-Home Message

- Patients with systemic autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, inflammatory myopathies, Sjogren's syndrome, systemic lupus erythematosus, systemic sclerosis, and vasculitides suffer from obstructive sleep apnea more frequently than the general population.
- There are common pathophysiological pathways between obstructive sleep apnea and systemic autoimmune diseases (activation of transcription factors and induction of the transcription of genes related to the production of proinflammatory cytokines).
- Early diagnosis and timely treatment of sleep disorders in patients with autoimmune diseases will improve their quality of life and long-term prognosis.

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OSA and Cardio vascular Disease

9

Caroline M. Van De Heyning, Lobke L. Pype, and Hielko Miljoen

9.1 Introduction

Obstructive sleep apnea (OSA) is associated with a broad spectrum of cardiovascular diseases, comprising arterial hypertension (AHT), heart failure, and heart rhythm disturbances. Moreover, OSA is an independent risk factor for cardiovascular mortality [1], and it has been shown that treatment with continuous positive airway pressure (CPAP) improves survival in patients with severe OSA [2]. In this chapter, we will discuss the epidemiology, pathophysiology, diagnosis, and treatment of the most prevalent and important cardiovascular diseases in the context of OSA (see Fig. 9.1).

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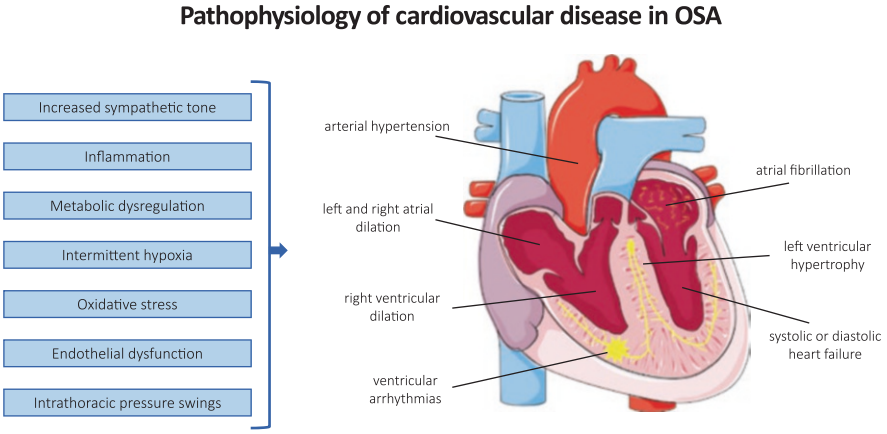

Fig. 9.1 Depiction of the different pathophysiological mechanisms by which obstructive sleep apnea affects the cardiovascular system including autonomic dysfunction with increased sympathetic nerve activity, inflammation, metabolic dysregulation, hypoxia, oxidative stress, endothelial dysfunction, and intrathoracic pressure swings. These mechanistic pathways are important risk factors for the development of cardiac remodeling, arterial hypertension, ventricular arrhythmias, atrial fibrillation, and heart failure. This figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license

9.2 Arterial Hypertension

9.2.1 Epidemiology

AHT is diagnosed when the office systolic blood pressure is ≥140 mmHg and/or the diastolic blood pressure is ≥90 mmHg [3]. Untreated AHT results in left ventricular hypertrophy and atherosclerotic processes and is a potent cardiovascular risk factor [4]. It is well established that AHT is very prevalent (50%–60%) among patients with OSA and that the risk of AHT increases with OSA severity [5–7]. In a large cross-sectional study (n = 2677), Lavie et al. [6] found that for every apneic event per hour of sleep, the odds of AHT increased by about 1%. In contrast, every 10% decrease in nocturnal oxygen saturation increased the odds by 13%. Moreover, OSA is regarded as one of the most important causes of secondary AHT and resistant AHT (uncontrolled AHT despite the use of ≥3 different antihypertensive drugs). Consequently, it is recommended to screen for underlying OSA in patients with resistant AHT [8].

9.2.2 Pathophysiology

It has been shown in an experimental human model that acute intermittent hypoxia elevates blood pressure [9]. The interplay of the following pathophysiologic mechanisms is thought to result in AHT in patients with OSA [10].

- Autonomic dysregulation with increased sympathetic drive: negative pressure against obstruction and repetitive intermittent hypoxia can activate renal, adrenal, and peripheral chemoreceptors. This leads to the release of catecholamines and the activation of the renin-angiotensin system with increased levels of angiotensin II and aldosterone.
- Endothelial dysfunction caused by intermittent hypoxia.
- Systemic inflammation.
- Metabolic dysregulation with impaired glucose tolerance and dyslipidemia.

9.2.3 Diagnosis

The diagnosis of AHT cannot be made by a single office visit. Still, it should be confirmed by repeated measurements at the office or, preferably, at home using a 24-h ambulatory blood pressure monitor to rule out white-coat hypertension (the phenomenon of blood pressures that are only elevated at the office) [3].

9.2.4 Treatment

Lifestyle modification, including diet, body weight control, and regular physical exercise, is the first-line antihypertensive treatment. Pharmacological treatment is recommended if blood pressures remain elevated despite lifestyle changes, or immediately in case of grade II hypertension (blood pressures ≥160/100 mmHg), evidence of organ damage (e.g., left ventricular hypertrophy) or in high-risk patients (cardiovascular disease, diabetes, chronic kidney disease) [3]. Several studies have shown that CPAP therapy and oral appliance therapy can lower systemic blood pressures [10, 11] and reverse left ventricular hypertrophy [12, 13]. The largest effect of CPAP treatment has been observed in patients with OSA and resistant AHT [14]. In patients with OSA and obesity, the combination of CPAP therapy and weight loss resulted in a greater reduction of blood pressure than either intervention alone [15], suggesting a synergistic contribution of both comorbidities on AHT.

9.3 Heart Failure

9.3.1 Epidemiology

Heart failure is a potentially life-threatening disease, and its development and progression are affected by many different factors, including OSA [16, 17]. Considering the well-known association of sleep apnea with cardiovascular conditions such as AHT, coronary artery disease, and atrial fibrillation, it is not surprising that sleep apnea is highly prevalent in patients with heart failure. Several studies have demonstrated that sleep apnea, including central sleep apnea and OSA, is present in around 50% of patients with chronic heart failure and up to 75% of acute decompensated heart failure patients [18, 19]. When considering only moderate to severe OSA

(AHI ≥ 15), the prevalence ranges from 10% to 35%. However, in clinical practice, OSA is often underdiagnosed and undertreated [20–24]. Importantly, the presence of OSA is similar in heart failure with reduced ejection fraction (HFrEF), defined as systolic dysfunction with left ventricular ejection fraction (LVEF) ≤40%, and heart failure with preserved ejection fraction (HFpEF), defined as diastolic dysfunction with LVEF ≥50% [19, 25].

9.3.2 Pathophysiology

The pathophysiologic effects of OSA related to heart failure can be explained by different mechanical, neurohumoral and inflammatory mechanisms [26]. During an apneic episode, the inspiratory effort against an occluded upper airway causes large intrathoracic pressure swings, increased left ventricular transmural pressure and increased afterload. In addition, left ventricular filling is decreased, which results in a reduced stroke volume [27, 28]. Following apnea, the sympathetic nervous system is activated, leading to increased blood pressure and heart rate. Finally, apneic episodes cause hypoxemia which induces oxidative stress and inflammatory pathways. Collectively, these factors contribute to a mismatch in myocardial oxygen demand/supply which predisposes to acute cardiac ischemia, and chronic left ventricular remodeling, and heart failure [26].

9.3.3 Diagnosis

Heart failure is a clinical syndrome that can be suspected when certain symptoms (e.g., dyspnea, orthopnea, exercise intolerance, fatigue…) and/or signs (e.g., peripheral edema, elevated jugular venous pressure, pulmonary crepitations…) are present. Most commonly, the diagnosis can be confirmed by routine echocardiography showing impaired contractility (systolic dysfunction) or impaired relaxation (diastolic dysfunction). In addition, elevated biomarkers such as BNP (B-type natriuretic peptide) or NT-pro-BNP (N-terminal pro-B-type natriuretic peptide) can help diagnose. As mentioned earlier, heart failure is classified based on the LVEF [29, 30]. Finally, it is important to determine the etiology, such as coronary artery disease, AHT, valve disease or cardiomyopathy.

9.3.4 Treatment

Patients with heart failure have high mortality rates and frequently require hospitalization for acute decompensation. Heart failure management is largely based on optimal medical treatment and differs between HFrEF and HFpEF. In patients with HFrEF, most recent guidelines recommend the simultaneous use of beta-blockers, angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor-neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists, and sodium-glucose

cotransporter-2 (SGLT2) inhibitors. Diuretics should only be used in patients with evidence of fluid retention [29, 30]. Only SGLT2 inhibitors have demonstrated a significant benefit on morbidity and mortality in patients with HFpEF [31]. Importantly, OSA is associated with increased cardiovascular events and mortality rates in acute or chronic heart failure patients [24, 32]. Based on the pathophysiological effects of OSA on the cardiovascular system, CPAP is expected to improve outcomes by reducing AHI and nocturnal hypoxia. After treatment with CPAP improved left ventricular systolic and diastolic function has been observed [33–36]. Furthermore, observational studies have shown better event-free survival in patients with heart failure who are treated for sleep apnea [37, 38]. Unfortunately, the beneficial effect of CPAP on survival or cardiovascular event rates could not be confirmed by large randomized controlled trials, potentially due to low CPAP adherence and exclusion of patients with severe dyspnea [39]. At present, there are no outcome data regarding the use of other therapeutic options, such as hypoglossal nerve stimulation or mandibular repositioning device, in patients with OSA and heart failure. Therefore, CPAP remains the recommended treatment for OSA patients with and without heart failure, despite its known limitations.

9.4 Atrial Fibrillation

9.4.1 Epidemiology

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation, leading to an ineffective atrial contraction and irregular heart rhythm. Currently, the estimated prevalence of AF in adults is between 2% and 4% [40]. Several studies have shown that the prevalence and incidence of AF are linked to OSA and its severity [41, 42]. In a study by Guilleminault et al. [43], 3% of 400 patients with moderate to severe OSA demonstrated AF on a 24-h Holter. In comparison, Mehra et al. [44] found an AF prevalence of 4.8% in patients with OSA vs. 0.9% in those without OSA. This is probably an underestimation; longer-term monitoring with implantable loop recorders in patients with severe OSA (most under CPAP therapy) demonstrated AF in 20% over a mean follow-up of 27 months [45]. Vice versa, the reported prevalence of moderate to severe OSA in patients with AF is up to 62% [46, 47]. If not at causal link, these data suggest at least a close relationship between the two entities. Indeed, AF and OSA share several risk factors, such as increasing age, heart failure, obesity, and hypertension, so both entities could manifest similar pathophysiological processes [48].

9.4.2 Pathophysiology

Arrhythmogenesis mainly occurs through three electrophysiological mechanisms: enhanced automaticity, reentry, and triggered activity. Most commonly, AF is postulated to result from an interplay between automatic triggers and substrate

(reentry). Rapid firing from a focus (such as the pulmonary veins) initiates propagating reentrant waves in a vulnerable atrial substrate. The perpetuation of AF relies more on the substrate than on triggers [49]. Slowing of conduction velocity (e.g., through fibrosis) and shortening of the effective refractory period increase the excitable gap and promote the ability of the atrium to harbor sustainable circuits [50]. Episodes of OSA can cause episodes of hypercapnia, hypoxemia, intrathoracic pressure oscillations, sympathovagal imbalance, and structural remodeling. Animal models have shown that chronically repeated OSA episodes caused an increase in AF inducibility, conduction slowing and cardiac remodeling with an increase of fibrosis [51, 52], while the application of negative tracheal pressure during obstructive respiratory events can shorten the effective refractory period and increased AF inducibility through vagal activation [53]. In humans, alleviation of airway obstruction through uvulo-palato-pharyngoplasty significantly reduced the risk of AF, suggesting a role of obstruction in arrhythmogenesis [54]. Right and left atrial voltages and conduction velocities were lower in patients with AF and OSA than those without OSA [55]. Low voltage areas are thought to correlate with zones of increased fibrosis. Thus, the findings of lower voltage in OSA patients might suggest a more diffuse substrate. The presence of inflammation, a condition shared by both AF and OSA, could worsen the substrate [26, 56]. The severity of OSA varies from night to night. Recently, it has been demonstrated that the risk of having a period of AF during a certain night was higher if the severity of OSA during that night was higher [57]. Similarly, atrial ectopic beats were higher during episodes of obstructive respiratory events right after cardioversion than during normal, nonobstructed breathing [58]. This suggests a dynamic factor on top of the more static, insidiously changing substrate (such as changes in refractory periods on return to eucapnia or sympathovagal balance alterations) [59].

9.4.3 Diagnosis

The diagnosis of AF, as per the most recent guidelines, is made through registration of an ECG with at least 30 s of an irregular heart rate and no discernible repeating P-waves [40]. This requires the arrhythmia to be present at the moment of the registration of the ECG. Given the potential paroxysmal nature of AF and 50%–87% of patients are initially asymptomatic [40], this inevitably gives rise to the underdiagnosis of the disease. Equally, the registration of a 24-h Holter monitoring will miss the majority of AF paroxysms [60]. In the light of these issues, the advent of more continuous screening tools, such as smart watches, hand-held devices, photoplethysmography, and wearables, hold promise, although they still have some limitations [61]. Especially in a high-risk population with a sufficiently high pretest probability, this could be a valid screening strategy in the future. Likewise, given the high prevalence of OSA in patients with AF, there is a need to screen these patients for underlying OSA [62].

9.4.4 Treatment

AF is an arrhythmia that tends to recur over time [50]. As many patients are asymptomatic, this has triggered the historic "Rhythm or Rate" debate: should we aim to maintain sinus rhythm or accept the existence of AF and try to manage the ventricular rate? Recently two randomized controlled trials showed a favorable effect of (early) rhythm control [63, 64]. In this light, we discuss the potential approaches to rhythm control in patients with OSA and AF:

- Weight loss: Obesity is a risk factor and in this context, weight loss has a beneficial effect on both AF recurrences and OSA [65, 66]. However, clinical experience demonstrates that many patients struggle to achieve sustainable weight loss and that OSA can exist without obesity. This implies the need for additional therapeutic approaches.
- Drugs and Cardioversion: The oldest approach to rhythm control is the use of antiarrhythmic drugs. Unfortunately, even with the most potent drug (amiodarone), mid-term maintenance of sinus rhythm is moderate [67]. In patients with OSA, recurrence rates are even higher [68]. After diagnosing an AF episode, direct current cardioversion is a standard procedure to restore sinus rhythm. Also, after cardioversion, AF recurrence rate is higher in patients with untreated OSA than in those without [69].
- Pulmonary Vein Isolation (PVI): PVI is an invasive electrophysiological procedure that emerged as a rhythm control strategy after identification of arrhythmogenic foci in the pulmonary veins inducing AF [70]. After PVI, patients with OSA showed more triggers outside the pulmonary veins than patients without OSA [55]. This might explain that in patients with untreated OSA the recurrence rate of AF after PVI is higher [71]. In a recent meta-analysis, a lower AF recurrence (after cardioversion or PVI) was found in OSA patients with CPAP compared to those without CPAP [72].

9.5 Sudden Cardiac Death

9.5.1 Epidemiology

Several large observational studies have shown that OSA is an independent risk factor for both all-cause mortality [73, 74] and sudden cardiac death (SCD) [75]. The first large observational study using 24-h Holter monitoring in 400 patients with OSA showed that ventricular cardiac arrhythmias and conduction disturbances are relatively prevalent, ranging from frequent ventricular premature beats (20%) to nonsustained ventricular tachycardia (3%), and from sinus arrest (11%) to higher degree atrioventricular block (3%) [43]. Moreover, more recent data showed that OSA is associated with ventricular tachycardia [76] and that SCD in patients with OSA mostly occurs during sleeping hours, in contrast to the general population [77, 78]. These data might suggest a causal relationship between OSA and SCD.

9.5.2 Pathophysiology

Apart from the association of OSA with specific cardiovascular conditions that carry an increased risk of SCD, following potential pathophysiologic mechanisms might play a role in ventricular arrhythmogenesis and SCD in OSA [79].

- Intermittent nocturnal hypoxia, resulting in intracellular acidosis, a decrease of enzyme activity and ATP synthesis, elongation of the QT-interval with myocardial electrical instability, and increased concentrations of reactive oxygen species, resulting in myocardial degeneration and inflammation.
- Autonomic dysregulation with increased sympathetic drive and release of catecholamines (see also pathophysiologic mechanisms of AHT).
- Increase in intrathoracic pressure with changes in heart geometry and electrical feedback.

9.5.3 Treatment

In a randomized trial that followed over 2500 patients with OSA over 3 years, no mortality benefit was shown for CPAP with usual care compared to standard care alone [39]. As mentioned before, this study was potentially hampered by a low adherence to CPAP and the exclusion of patients with daytime sleepiness. Interestingly, in an extensive real-life observational study, the termination of CPAP within the first year was associated with a significantly higher all-cause mortality rate [80]. However, further prospective data from large randomized trials are needed to draw definite conclusions regarding the effect of CPAP on SCD.

Take-Home Message

- Obstructive sleep apnea (OSA) is associated with a variety of cardiovascular diseases and is an established cardiovascular risk factor.
- Arterial hypertension is encountered in 50-60% of patients with OSA, and OSA is a significant cause of resistant arterial hypertension.
- Around half of heart failure patients have sleep apnea, associated with higher cardiovascular events and mortality rates.
- OSA is associated with atrial fibrillation, ventricular arrhythmia, and sudden cardiac death.
- These cardiovascular implications of OSA share common pathophysiological pathways, including autonomic dysfunction with increased sympathetic nerve activity, inflammation, metabolic dysregulation, hypoxia, oxidative stress, endothelial dysfunction, and intrathoracic pressure swings.

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Obstructive Sleep Apnea: A Neurological Approach

10

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10.1 Introduction

About 9% of women and 24% of men between 30 and 60 years of age have an AHI > 5 in polysomnography (PSG), and between 2% and 4% are associated with excessive daytime sleepiness (EDS), an incidence that increases with age [1, 2].

In the case of Alzheimer's disease, it has been seen that treating OSA can improve cognitive function and sleep quality and that patients with dementia can tolerate CPAP in the same way as other types of patients [3–5].

In patients with Parkinson's disease, altered upper airway muscle tone can facilitate OSA, and the severity of the disease is directly related to the severity of sleep disorders. Furthermore, Parkinson's disease (PD) is associated with autonomic dysfunction, which could alter respiratory control, and this mechanism may be associated with the incidence of respiratory disorders during sleep [6].

OSA is common in patients with cerebrovascular disease and is associated with poor functional and cognitive outcomes, and depression. Likewise, OSA can lead to cognitive deterioration due to increase in microvascular disease due to chronic systemic hypoxia and oxidative stress, and treatment with continuous positive airway pressure (CPAP) could prevent cognitive decline in these circumstances [7].

Neurologists need to consider the diagnosis and treatment of primary sleep disorders such as OSA and for the somnologist to appreciate the impact on cognitive function of the sleep disorder. This chapter reviews various aspects of these neurological conditions related to OSA.

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10.2 Alzheimer's Disease

Alzheimer's disease (AD) is by far the most frequent form of dementia, accounting for 60%–70% of all cases of dementia and is usually preceded by a predementia state called mild cognitive impairment (MCI). Forty percent of dementia cases are due to potentially modifiable factors such as obesity, diabetes, high blood pressure, physical inactivity, depression, smoking, hearing loss, low educational level, poor social contact, and environmental pollution. Sleep disorders have gained special importance, with OSA being a modifiable factor of great interest [8].

OSA has been frequently related to cognitive dysfunction and Alzheimer's disease in middle-aged and older adults [9]. Multiple comorbidities are frequently found in this type of patient with a lack of response to treatment to the cognitive dysfunction of some patients. Therefore, it is a priority to find the main factor contributing to cognitive deterioration and determine the impact of therapeutic interventions to improve this condition.

With increasing age, there are important differences in the prevalence of OSA, associated comorbidities, and phenotypic presentation, suggesting differences in cognitive performance between middle-aged and older adults. For example, in older adults, OSA is characterized by intermittent hypoxia, sleep fragmentation, increased sympathetic activity, and changes in intrathoracic pressure [8].

According to a systematic review of the literature, the prevalence in adults is between 9% and 38% for mild OSA, 6% and 17% for moderate to severe, and in older adults up to 84% for mild OSA and 16% for moderate to severe [8]. An even more worrying study shows up to 56% of adults over 65 years of age were at high risk of OSA, and only 8% had been studied. Therefore, many older adults remain undiagnosed and untreated. Of the patients diagnosed, only about 41% continue with CPAP after 1 year of treatment. This lack of adherence to CPAP is concerning, considering that this treatment could delay of cognitive function deterioration [4].

10.2.1 Mechanisms That Could Explain Cognitive Dysfunction in Older Adults with OSA

As it is well known, OSA causes intermittent hypoxia and sleep fragmentation; these frequent microalerts alter both the macro- (time spent in N3 and REM) and the microstructure of sleep (characteristics of slow waves and sleep spindles). Considering the role of sleep continuity, slow-wave sleep, REM sleep, and sleep spindles in neurogenesis, brain plasticity, alertness, and memory formation and consolidation, chronic sleep changes caused by OSA negatively affect cognitive function. REM sleep-dependent OSA is particularly damaging to the brain as respiratory events during this period are associated with reduced regional cerebral circulation, even in mild OSA.

In addition, REM atonia can increase hypoxic levels during obstructive events, and REM-dependent OSA is associated with more significant excessive daytime sleepiness than NREM-dependent OSA, which is more related to cognitive

impairment. Intermittent hypoxia and sleep fragmentation also alter brain function and structure. In addition, a biphasic pattern has been seen in imaging findings, with acute and transient or compensatory response pattern (in which gray matter hypertrophy and restriction of white matter diffusion) followed by evidence of brain damage (gray matter atrophy, white matter lesions, with increased hyperintensities and axonal injury [10, 11].

There is increasing evidence that OSA is associated with an increase in AD-related markers, specifically amyloid beta and Tau, measured in cerebrospinal fluid (CSF), positron emission tomography (PET), and serum. In several studies in which PSG diagnosed OSA, reduced CSF amyloid beta levels were demonstrated in age-matched controls without OSA [12]. When groups were stratified by ApoE allele status, the OSA severity was positively correlated with amyloidB42, phosphorylated tau (Ptau), and total tau (Ttau) in ApoE3 carriers and negatively correlated with amyloid B42 levels in those with ApoE2 [13]. In addition, PET amyloid tracer uptake levels are a predictor of amyloid burden, as well as the future development of AD; greater amyloid deposition has been found in the right posterior cingulate gyrus and right temporal cortex in OSA patients compared to controls [14–18]. Also, there is even a study that shows AD biomarkers in children with obesity and OSA, both risk factors for developing AD. Increased serum levels of presenilina1 and amyloid beta42 protein were found, these findings decreased after treatment (adenotonsillectomy) [19].

Several mechanisms could explain these pathological and neuroimaging findings such as inflammation [20], oxidative stress, metabolic alterations, cerebral edema, and endothelial dysfunction [21, 22].

10.2.2 Research Studies Linking OSA with Cognitive Decline

Most large cross-sectional cohort studies investigating the cognitive decline in middle-aged or older patients with OSA use objective measures such as PSG, polygraphy, and OSA screening questionnaires. While assessing impairment, some use a full battery of neuropsychological evaluations and others specific tests to determine the cognitive function or global functioning. The studies that show this association found alterations in long-term verbal memory, working memory, and global cognition. Markers of OSA severity or cognition-related symptoms were highly heterogeneous (snoring, apneas, hypoxemia, apnea–hypopnea index—AHI) and other studies found no significant relationship between OSA severity and cognition [23].

Despite heterogeneous results the greatest findings are found in the domains of attention, memory, information processing speed. At the same time there is less evidence in working memory, executive functions, visual and language skills in middle-aged or older adults. In contrast, in young people with OSA, the most compromised domains were attention, episodic memory, working memory, and executive functions.

These findings indicate that there are altered domains in OSA independent of age (memory and attention), while others are less impacted by age (working memory and executive functions [8, 24]. Longitudinal cohort studies have the advantage of quantifying cognitive decline over time. They use tools such as self-diagnostic questionnaires, PSG, or portable equipment to identify cases of OSA. Most use global cognitive measures such as minimental or screening tests. Only the complete neuropsychological battery was used in one study [25]. Among the main longitudinal cohort studies, the Study of Osteoporotic Fractures included 298 82-year-old women and found that 45% of women with OSA developed MCI or dementia at 5-year follow-up, compared to 31% of women without OSA [9, 26].

This suggests that longitudinal studies are more likely to identify long-term OSA-related cognitive impairment than MCI in specific domains. However, concerning meta-analyses and systematic reviews of the literature, most conclude that there is a significant association between OSA and cognitive impairment and that OSA increases the risk of AD [27, 28].

Notably, small cohorts of cases and controls from sleep clinics show an association between OSA and cognitive impairment, while large population studies do not detect it or present variable findings. Probably due to the type of studies, limitations of study design, etc., or perhaps because only the most severe cases show impairment [25, 28].

10.2.3 Risk Factors

Not all adults with OSA are at risk of developing MCI or dementia; there are individual characteristics that may add or interact with the severity of OSA to explain the increase in cognitive impairment such as age, gender, menopause, obesity, diabetes, high blood pressure, cardiovascular disease, smoking, excessive alcohol consumption, depression, environmental pollution or being a carrier of the ApoE4 allele [25]. This must be considered to assertively impact the treatment of cognitive impairment in a patient with OSA.

10.2.4 Regarding the Treatment

Treatment options for OSA include positive airway pressure devices, oral appliances, behavior/lifestyle modification, surgery, and/or a combination of these. A decision on the most effective treatment for a person diagnosed with OSA depends on the severity of the disease, the symptoms they are experiencing, and contributing causes.

CPAP is the most prescribed treatment. Analysis of the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort found that the presence of OSA was associated with an earlier age of cognitive decline and suggested that CPAP treatment may slow the progression of cognitive decline. A systematic review has found studies

whose participants were healthy older adults with OSA in which it was shown that their cognitive difficulties improved after treatment with CPAP [29].

Even in diagnostic imaging, it is observed that cortical thinning is attenuated, and connectivity in the neural network increases. In general, all randomized/controlled studies conducted in older adults with AD show that CPAP improves sleep parameters (N3, EDS), and cognitive function. These findings prove evidence that patients with mild AD to moderate may benefit from CPAP treatment.

Subsequent analyses have shown improvements in episodic verbal learning and memory and executive functioning (cognitive flexibility and processing speed) in a double-blind, placebo-controlled study examining the effects of donepezil, a central acetylcholinesterase inhibitor, on OSA [30]. Compared to baseline and placebo, patients with AD found that 3-month donepezil treatment significantly improved AHI and oxygen saturation [31].

In addition, REM sleep duration was significantly higher, and Alzheimer's Disease Assessment Cognitive Scale (ADAS-cog) scores improved dramatically. Regarding the improvement of biomarkers, it is known that a higher load of amyloid or tau in the brain, a higher load of tau in the cerebrospinal fluid (CSF) and a lower load of amyloid in the CSF are of worse prognosis. A study in middle-aged adults with OSA and with intervention showed that 1–4 months of CPAP use increased slow-wave sleep (SWS), and levels of amyloid beta in CSF were normalized.

In conclusion, there is sufficient evidence to recommend CPAP treatment as a treatment for OSA and AD or mild cognitive impairment. The fifth Canadian Consensus Conference highlights the importance of detecting dementia in patients with OSA and recommends that these patients be treated with CPAP. as it can improve cognition and lowers the risk of dementia. It emphasizes the importance of starting CPAP treatment early and improving follow-up to monitor compliance with this device.

Therefore, CPAP may be a promising treatment for slowing cognitive decline in older adults with comorbid MCI or AD and OSA. However, other pharmacological and nonpharmacological approaches need to be evaluated and tested [12, 25].

10.3 Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease, and its prevalence increases as the population ages. A recent multicenter study showed that sleep disorders are very common in patients with PD, with around 66% of these patients reporting sleep difficulties [32]. In addition, nonmotor symptoms of the disease, such as sleep disturbances, significantly affect the quality of life of patients with PD.

PSG studies show decreased total sleep time, and reduced percentage of SWS (N3). It is estimated that 60% of these patients have OSA, causing hypoxemia and fragmentation of sleep, which have been associated with cardiac arrhythmias, nocturnal arterial hypertension, nocturnal confusion, and neuropsychological alterations [33].

In PD, altered upper airway musculature due to muscle stiffness at night and bradykinesia may contribute to OSA development. However, there is no evidence to support an increase in central sleep apnea in PD. A significant decrease in muscle tone increases the propensity for upper airway collapse, during REM sleep, possibly worsening OSA.

The question then arises whether patients with REM sleep behavior disorder (RDB) who increase muscle tone at night have a lower risk of OSA. In a study of 239 patients with AD, 28% had OSA (AHI > 5), and logistic regression analysis showed that RDB was a protective factor for OSA. In comparison, another with 46 patients showed PD comorbid with OSA was more frequent in the RDB (+) group than in the RDB (−) group (51.4% vs. 9.1%). A greater decrease in nocturnal O2 saturation was found in the (+) group, and the increase in muscle tone in the chin did not affect the severity of OSA. The proportion of patients with RDB was higher in the group with PD + OSA [34]. The latest meta-analysis of PSG in patients with PD shows that these patients have decreased total sleep time, sleep efficiency, SWS, REM sleep, increased AHI, time awake after falling asleep (WASO), and periodic leg movements index (PLM-i), compared with normal controls. A supplementary analysis showed increased AHI, REM sleep, and PLM-i in PD + RDB patients.

It has been shown that PD patients spend twice as much time in the supine position compared to normal controls. This position is related to a longer time of illness, SED, and a high AHI. Additionally, an AHI > 5 and low sleep efficiency have been related to cognitive impairment, specifically in terms of attention, executive processes/working memory, and semantic memory [34].

10.3.1 Possible Pathophysiological Mechanisms That Relate PD and OSA

It has been suggested that the low incidence of OSA in patients with advanced Parkinson's is due to the low body mass index compared to the general population, which in turn suggests that PD in these patients does not follow the same pattern. However, some studies have shown no relationship between the severity of OSA and BMI in patients with PD. But have found a relation between the severity of PD with the severity of OSA, although causality cannot be inferred from these findings [6].

OSA is not more common in PD than in the general population, although they may coexist either because OSA is so common or PD-related changes predispose to OSA or both. Biologically, there is a possibility that PD is involved in the pathogenesis of OSA since the upper airway musculature may be affected by involuntary movements. It may have abnormal spirometry consistent with upper airway obstruction, which improves with levodopa. These alterations worsen during sleep, generating OSA. A decrease in sleep-disordered breathing has been found in patients who use long-acting levodopa overnight, compared with those who do not [32]. However, levodopa could generate respiratory alterations as a form of dyskinesias.

PD is also associated with autonomic dysfunction, which can alter respiratory control during NREM sleep, where breathing is predominantly dependent on chemoreceptors. This mechanism could be related to the high incidence of sleep-disordered breathing in Shy–Drager syndrome, in which abnormal afferent feedback to central respiratory centers has been implicated [6].

OSA itself can generate autonomic disturbances beyond sleep, particularly by increasing sympathetic tone that is associated with changes in chemo and baroreceptors, damaging respiratory control, and promoting OSA. In PD, there is a decrease in chemosensitivity to hypoxia despite adequate lung function, which reduces dyspnea in hypoxic conditions. It has also been found that the respiratory impulse to hypercapnia is reduced, probably related to the neurodegenerative process in the brain stem where the central chemoreceptors and respiratory centers are located. An abnormal response to hypercapnia predisposes to hypoventilation. Moreover, the activity of the dilator muscles of the upper airway is regulated by the respiratory drive and CO2 levels, a key element in the pathophysiology of OSA.

Although this mechanism has not been studied directly in patients with PD, another probable mechanism linked to OSA could be the fragmentation of sleep generated by the dysfunction that occurs as part of PD, due partially to the alteration of sleep circuits, medications, and comorbidities, increasing the possibility of upper airway collapse during sleep. It might be a factor in the progression of OSA in this disease [32].

10.3.2 Cognitive Impairment in PD + OSA

The mechanisms by which OSA generates cognitive impairment were previously explained when discussing AD; intermittent hypoxia has been implicated through the mechanisms of ischemia/reperfusion and oxidative stress. In addition, evidence of systemic inflammation in OSA could contribute to neuroinflammation that promotes neurodegeneration. However, these mechanisms could theoretically exacerbate the neuropathology of PD; they have not yet been studied in PD [6]. In PD, OSA-related hypoxemia is less marked than in patients without PD; this is due to the low body mass index (BMI) of patients with PD + OSA.

Sleep fragmentation has also been implicated in cognitive impairment in patients with OSA and is the best predictor of alterations in episodic memory [32]. And induce oxidative stress and inflammation as well as hypoxia. Interestingly, in animal models of OSA, decreased neuronal excitability has been found in the locus coeruleus (LC), an area involved in the pathophysiology of PD [6].

Regarding the glymphatic system, we know that it is a cleaning system that operates in the brain, transporting CSF through the perivascular spaces, connecting the flow through the brain parenchyma to the cervical lymphatic system, removing proteins and soluble metabolites; its function declines with age, and it has been suggested that this contributes to the accumulation of abnormal proteins in the extracellular space, such as amyloid-beta or alpha-synuclein, leaving the brain more vulnerable to neurodegenerative pathologies. The peculiarity of this system is that it

only acts during sleep, so any process that fragments sleep can alter it, generating alterations in brain homeostasis. We also know that dementia in PD results from a mixture of pathologies, including Lewy bodies, Alzheimer-related pathology, and a small component of microvascular pathology. It could then be speculated that glymphatic abnormalities could predispose to cognitive dysfunction in PD by nonspecific mechanisms [6].

The development of dementia in PD has also been related in case series to the role of noradrenergic defects on the LC. It has been implicated in cognitive impairment in the general population. In pathology studies in aging patients have been found a decrease in neuronal density in this area that correlates with a low cognitive level and faster cognitive deterioration [32], Intermittent hypoxia and fragmentation of sleep in the LC and other specific areas of the brain could have significant implications in PD [35].

In the pathophysiology of PD, the determining factor is the loss of dopaminergic neurons in the substantia nigra that generates dopamine depletion in the basal ganglia. Still, other regions have been implicated in neurodegeneration that is more associated with nonmotor symptoms. LC neurons specifically have been implicated in its pathophysiology, as the loss of their trophic influences may increase the sensitivity of dopaminergic neurons to neurotoxic insults.

Currently, the pathology of PD involves a combination of genetic, cellular, and environmental factors. There are no studies on humans, but animal studies show a decrease in the noradrenergic neuronal population in the LC and its functional alteration. OSA could not only generate cognitive impairment but also globally accelerate the evolution of PD. Furthermore, recent epidemiological studies suggest that OSA increases the risk of PD [36].

10.3.3 Neuroimaging in Relation to Cognitive Dysfunction in OSA + PD

Structural and functional changes have been found in brain imaging of patients with OSA, including decreased gray matter in the hippocampus and temporal lobe, anterior cingulate gyrus, and cerebellum, as well as in the frontal and parietal lobes, and the CPAP treatment appears to increase gray matter volume in the hippocampus and frontal structures.

In PD, cortical atrophy has been found in the hippocampus and frontal structures in patients with MCI but not in cognitively intact patients [37]. Many studies associate atrophy of the temporal lobe with memory alterations in PD, others with frontal or temporal regions. These variable findings could be partly explained by the effects of OSA [6]. Functional neuroimaging in OSA shows decreased activation of the cingulate, frontal, and parietal regions during sustained attention and memory tasks. In PD, poor performance in memory and executive functions was associated with decreased metabolism in frontal and parietal association areas and increased in the cerebellar vermis and caudate nucleus with PET-FDG. Other studies have found other sites of hyperactivation, probably as a compensatory mechanism [6].

10.3.4 Treatment of OSA in PD

The general recommendation is the use of oral devices in mild cases of OSA and CPAP in moderate to severe cases, as well as weight loss in obese patients. The efficacy of the use of CPAP has been demonstrated in patients with advanced PD with narcoleptic phenotype, the onset of sleep in the REM stage (SOREM) in the multiple sleep latency test (MSLT), and OSA. In addition, a prospective study demonstrated improvement in OSA, and daytime sleepiness measured by MSLT in 38 patients with PD with a mean duration of 5.3 years. Interestingly, improvement in OSA has been shown with long-acting levodopa at bedtime [38].

Additionally, the benefit has been seen in patients with PD with an average of 3 h 36 minutes of use with CPAP in terms of EDS, anxiety, and quality of sleep during 12 months of use. In patients with RDB + OSA, CPAP improved symptoms in 45.8% of those who used CPAP, which suggests that CPAP should be used first in this type of patient [34].

However, the long-term use of CPAP may be difficult due to the increase in motor and nonmotor symptoms of PD, particularly in the more advanced stages. Cognitive dysfunction, nocturia, RDB, and motor dysfunction are factors that could influence adherence to CPAP.

10.4 Small-Vessel Vascular Disease

Small-vessel vascular disease (SVVD) is a highly prevalent cerebral phenomenon that refers to a group of pathological processes with various etiologies that affect the small arteries, arterioles, venules, and capillaries of the brain. Age-related, arterial hypertension-related, and amyloid angiopathies are the most common forms [39].

It is often considered an incidental finding on brain MRI that manifests with white matter hyperintensities, silent cerebral infarcts, cerebral microhemorrhages, and perivascular spaces. Recent meta-analyses have associated it with an increased risk of stroke, cognitive impairment or dementia, and death. Reduced compliance in the cerebral arterioles resulting from chronic dysregulated vascular remodeling has been regarded as the fundamental pathomechanism of SVVD progression [39], which causes damage to the blood–brain barrier (BBB). Intermittent hypoperfusion alters the glymphatic system, which ultimately leads to chronic inflammation and subclinical ischemia in the brain parenchyma.

OSA is highly prevalent in the older population,, and shares common risk factors with SVVD, such as age, hypertension, diabetes, and obesity, and is associated with SVVD progression. In addition, it is involved in endothelial dysfunction and decreased vascular compliance. A recent study suggests that endothelial dysfunction in OSA is related to the consequent generation of reactive oxygen species and proinflammatory molecules that produce microvascular damage [22].

However, the effect of OSA on the progression of SVVD is independent of these cardiovascular risk factors. Its mechanism could be different from dysregulation of vascular remodeling. Probably more related to the abrupt increase in intrathoracic

pressure that interferes with adequate venous return and cardiac output, frequent alerts, intermittent cerebral hypoxia, and provocation of arrhythmias [40].

Frequent alerts and intermittent hypoxia recurrently activate the sympathetic nervous system, generating oxidative stress and inducing inflammation in the brain parenchyma. Furthermore, increased intrathoracic pressure and frequent arousals prevent activation of the glymphatic system. Although all these mechanisms are interrelated, discrimination of the main mechanism underlying SVVD progression in OSA patients could be important in predicting how appropriate OSA treatment might also modify SVVD progression.

Ultrasonography or transcranial Doppler (TCD) is a noninvasive method widely used to measure cerebral blood flow, and some parameters are helpful indicators to measure cerebrovascular elasticity. The pulsatility index evaluates the vessel stiffness and the resistance of the distal arterial bed. Recently, it has been reported that reducing this index along the middle cerebral artery may be an indirect marker of the compliance of the small cerebral vessels. A recent study in 97 patients compared TCD with PSG and SVVD markers in brain magnetic resonance imaging (MRI), such as volume of white matter hyperintensities, measures of increased perivascular spaces, and the presence of micro bleeding or lacunae, to determine the pathophysiological mechanisms that link OSA, impaired cerebrovascular compliance, and progression of SVVD. The results of this study indicate that the severity of OSA is related to markers of cerebrovascular compliance but not to other markers of vascular remodeling. The AHI is significantly related to the volume of subcortical white matter hyperintensities, while the desaturation index (ODI) was to the volume of white matter hyperintensities in deep structures [40]. This finding is consistent with a recent meta-analysis reporting that moderate to severe OSA is positively associated with white matter hyperintensities and silent cerebral infarction but not with microbleeds [40].

Although most of these studies are cross-sectional and a relationship between OSA and the progression of SVVD cannot be determined with complete certainty, it can be inferred that OSA may contribute to the pathogenesis of SVVD, through different mechanisms to vascular remodeling (chronic and irreversible process), which could be reversible to a certain extent.

10.4.1 Vascular Cognitive Impairment Associated with Subcortical Small-Vessel Disease

The hallmark of SVVD is ischemic white matter lesions that can present as lacunar infarcts, and global cerebral hypoperfusion in a common and homogeneous subtype of vascular cognitive impairment (VCI). It is often unrecognized. The unique nature and course of SVVD offer the opportunity to gather knowledge at all stages of its pathogenicity. Atherosclerosis, hypoxic hypoperfusion, and inflammation act synergistically, causing myelin degeneration and blood–brain barrier disruption. The clinical diagnosis of SVVD includes early executive dysfunction manifested by a diminished ability to use complex information, formulate strategies, and exercise self-control [41].

10.4.2 Regarding the Treatment of SVVD in Patients with OSA

The use of CPAP in previous studies has shown reversal of white matter lesions and increased gray matter volume in OSA patients, apparently due to amelioration of early osmotic changes in cells induced by mild ischemia and inflammation that disrupt the integrity of the cell membrane [39]. Surgical treatment of OSA with relocation pharyngoplasty, a UPP variant, also improves high-sensitivity C-reactive protein and reduces cardiovascular risk in patients with OSA [42].

10.4.3 OSA as a Risk Factor for Stroke and Transient Ischemic Attack (TIA)

OSA is increasingly recognized as an independent risk factor for high blood pressure, diabetes, cardiovascular disease, and stroke.

OSA is common after a stroke, and stroke seems to be more common in people with OSA. Also, there are shared risk factors for both. So, the question remains, does stroke cause sleep apnea, or does sleep apnea lead to stroke, or are they both caused by the same risk factors? This is important because it may have implications for the prevention, acute treatment, and rehabilitation of patients with acute stroke [43].

Stroke is a common disease, the second leading cause of death worldwide, generating high health costs. Recent studies suggest that OSA is common after stroke with 50%–94% prevalence and is likewise recognized as a risk factor for stroke [43]. At the same time, untreated OSA contributes to poor stroke outcome and is also a risk factor for subsequent cardiovascular disease, including recurrent stroke.

Sleep apnea treatment improves recovery from stroke and decreases cardiovascular morbidity and mortality. However, underdiagnosis of OSA in stroke patients is still common.

10.4.4 Relationship Between OSA and Stroke

OSA creates a substrate for stroke vulnerability and is particularly hostile to brain function. Exposure to intermittent hypoxia in rodents results in impaired executive function, excessive sleepiness, and sensitivity to sleep deprivation. Mediating mechanisms include free radical damage, lipid peroxidation, nitric oxide synthase induction, platelet activation, and apoptosis.

However, oxidative stress, especially moderate hypoxia, may have a protective effect on the brain and cardiovascular system by activating genetic programs that induce vascular remodeling and other protective responses; thus, it builds resilience in the brain (known as ischemic preconditioning) [44].

Moderate to severe OSA is associated with silent ischemic changes, including white matter changes and lacunae, and cerebral microbleeds. Carotid and intracranial atherosclerosis is also accelerated in OSA. However, it is not clear whether the

use of CPAP has any effect on these changes. Arterial hypertension and insulin resistance could mediate the development of stroke in OSA. Moderate-to-severe OSA is significantly associated with severity-dependent hypertension and is very common in patients with resistant hypertension. Therefore, effective CPAP therapy, alone or in addition to antihypertensive medication, substantially lowers blood pressure.

OSA can also increase the risk of developing type 2 diabetes through increased insulin resistance and elevated cortisol secretion. Continuously supervised CPAP therapy (7.92 h/night) improved glycemic control and insulin resistance. However, the effect of CPAP on glycemic control is less consistent than its effect on blood pressure. Therefore, concomitant obesity could have a more substantial impact than OSA, not mitigated by CPAP therapy. OSA is also associated with the risk of cardioembolism.

Nearly 40% of symptomatic atrial fibrillation events are seen between midnight and 8:00 AM. People with OSA are four times more likely to develop nocturnal atrial fibrillation, and oxygen desaturation is an independent risk factor for new-onset atrial fibrillation. In a recent cohort study of 6841 patients, the diagnosis and severity of OSA were associated with atrial fibrillation during a 12-year follow-up. Furthermore, OSA may potentiate the risk of cardioembolism or stroke in patients with atrial fibrillation [45]. In addition, several observational studies found improvement or resolution of cardiac arrhythmia and atrial fibrillation after CPAP therapy.

Furthermore, sleep apnea is associated with inflammation, endothelial dysfunction, hypercoagulability, and cerebral hemodynamic changes.

OSA is very common in acute stroke, with an estimated 50% to 70% of subjects with acute stroke or TIA, a higher frequency than observed in control groups. However, they share risk factors such as male sex, obesity, old age, hypertension, and smoking. An independent association between the two conditions is hypothesized by large-scale epidemiologic studies, including the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study. In these studies, OSA with an apnea-hypopnea index (AHI) ≥20/h or > 11/h was associated with prevalent stroke, with an OR of 4.31 (95% CI: 1.31–14.15) and 1.58 (95% CI: 1.02–2.46), respectively, when adjusted for age, sex, weight, blood pressure, smoking, and other confounding factors [44].

It has been found that with an average nocturnal use of CPAP for at least 4 h, the risk of incident cardiovascular events among subjects with severe or symptomatic OSA was comparable to that of controls or simple snorers (AHI < 5/h). The cardiovascular effects of OSA are not limited to subjects with severe OSA burden. A prospective observational study in a clinical population free of myocardial infarction or stroke at study entry found that the presence of OSA (AHI ≥ 5/h) increased the risks of events (stroke or death from any cause, during follow-up at 3.4 years). However, the treatment effect was not substantial.

In the SAVE and RIC-CADSA trials, a dose–response relationship was found between adherence to CPAP and cardiovascular outcome, in which adherence to CPAP was associated with a lower risk of stroke or cardiovascular events [46]. The increased rates of stroke and death despite OSA treatment may be explained by older age, long-term exposure to OSA prior to treatment, a relatively shorter

duration of intervention, and changes in treatment efficacy (weight regain, reduced adherence to CPAP, or loss of effect of surgery). The "healthy adherent" effect, which describes a better outcome in subjects compliant with any given intervention due to their health-conscious behavior or lifestyle, could bias the results in favor of CPAP therapy. Adherence to CPAP has modified efficacy in previous trials: the higher the adherence, the better the outcome.

Studies with randomized designs are required to provide a better understanding of the causal relationship between OSA and stroke, and the therapeutic efficacy of CPAP in stroke prevention [44]. OSA events during REM sleep are usually prolonged and associated with severe oxygen desaturation. Sleep apnea during REM sleep, but not during NREM sleep, has been associated with hypertension, nondipping effect in nocturnal arterial pressure, and insulin resistance, even in subjects not considered to have OSA (AHI < 5/h). In a recent observational finding from the Sleep Heart Health Study, severe REM OSA (AHI during REM sleep ≥30/h) was associated with a higher incidence of cardiovascular events in the group with prevalent cardiovascular disease. The cardiovascular effects of REM OSA have several important implications [44].

From a diagnostic standpoint, simple cardiorespiratory monitoring devices, for example a portable device consisting of flow and oximetry, should not be used in future trials. Such a kit cannot reliably detect REM OSA, central sleep apnea, and periodic limb movements (PLM). The latter two conditions not only commonly occur in populations at high risk for cardiovascular events (such as the elderly or those with cardiovascular disease or stroke), but also increase the cardiovascular risk of these individuals [44].

In conclusion, there is clear evidence that OSA is a complex pathophysiological condition with multiple disease factors that often interact. The benefit of CPAP therapy for the prevention of stroke and other cardiovascular events in OSA should be considered based on the results of currently available clinical studies. The overall findings suggest that what matters is therapeutic effectiveness, which is determined by CPAP adherence, CPAP efficacy, apnea burden, and possibly disease phenotype [44].

Take-Home Message

- Recent evidence suggests that OSA might be associated with the development or worsening of neurodegenerative disorders as Alzheimer´s and Parkinson disease.
- OSA is comon in cerebrovascular disease and is associated with poor functional outcomes.
- Treating OSA can improve the quality of live of patients with these comorbidities.

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Ear, Nose, and Throat (ENT) Aspects of Obstructive Sleep Apnea (OSA)

11

Casale Manuele and Moffa Antonio

11.1 Introduction

Sleep-disordered breathing (SDB) encompasses a broad spectrum of sleep-related breathing disorders, including obstructive sleep apnea (OSA), central sleep apnea, sleep-related hypoventilation, and hypoxemia. OSA is characterized by recurrent events of upper-airway (UA) collapse during sleep and affects nearly one billion people worldwide. About 9% of women and 24% of men between 30 and 60 years old have an AHI > 5 in polysomnography (PSG), and between 2% and 4% are associated with excessive daytime sleepiness (EDS), an incidence that increases with age [1]. OSA is considered a decisive risk factor for cardiovascular diseases, and its influence on the development of pulmonary arterial hypertension, cardiac arrhythmias, atherosclerosis, type 2 diabetes, cognitive dysfunction, and structural brain changes has been shown.

It is well known that OSA is a complex disease characterized by the collapse at the UA during sleep: the velopharynx, the lateral pharynx, and/or the tongue base. More often, the collapse is multilevel. However, it is equally true that OSA could have severe consequences on ENT districts.

In particular, recent evidence suggests that OSA might be associated with alterations in the auditory and vestibular systems [2], increasing the risks of hearing loss (HL), tinnitus, and dizziness [3]. It is estimated that over 41% of patients with mild to severe OSA showed HL. The incidence rate for peripheral vertigo, including benign paroxysmal positional vertigo (BPPV), Meniere's disease, vestibular neuritis, and other peripheral vestibulopathy, is 149.86 per 10,000 OSA subjects [4]. HL

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and peripheral vestibular disorders (PVD) are prevalent conditions associated with adverse health-related consequences such as falls, cognitive decline, and incident dementia. While aging is the most decisive risk factor for these conditions, identifying modifiable risk factors, such as OSA, may have significant public health implications [5].

Moreover, OSA could cause damage to other ENT organs by altering sensitive and motor functions of the pharynx and larynx. Dysphagia is one of the most common problems symptoms in OSA patients. Although the pathophysiology of dysphagia in OSA is not clearly understood, the literature suggests that dysphagia in OSA may result from sensory and motor changes of the pharynx and altered swallowing–breathing integration. Moreover, OSA patients are much more prone to developing laryngopharyngeal reflux (LPR), with an overall incidence of 45.2% of LPR positivity in OSA patients [6].

The first-line therapy for moderate–severe OSA is continuous positive airway pressure (CPAP); however, more than 50% of patients with OSA had interrupted treatment 1 year after the prescription [7]. It is uncomfortable to wear, and can cause many side effects such as dermatitis, mask leak, aerophagia, barotrauma, and claustrophobia. Moreover, OSA patients with CPAP usually complain of nasal obstruction, rhinorrhea, nasal dryness, sneezing, and mouth or throat dry.

For these reasons, in the last years, OSA and snoring surgical management underwent significant evolution to obtain therapeutic success and avoid CPAP therapy in selected patients. Newer intrapharyngeal remodeling surgical procedures, less invasive or morbid, improving patients' compliance, makes OSA surgery a reasonable alternative [8] with promising results and minimal side effects However, the managing of acute postoperative pain from these procedures remains a significant challenge. Usually, in the postoperative period, patients also experience throat phlegm, nose regurgitation, dry throat, and throat lump. Most of these tend to resolve within a few days.

The chapter aims to provide a brief overview of the major OSA consequences on the ear, nose, and throat (ENT) organs showing etiopathogenetic mechanisms, clinical evidence, and management strategies.

11.2 Hearing Functions in OSA Patients

11.2.1 Mechanisms That Could Explain Auditory and Vestibular System Damage in OSA Patients

Chronic intermittent hypoxia is one of the key OSA features and a significant contributor to adverse OSA consequences [9]. Usually, OSA is characterized by short episodes of intermittent and high-frequency hypoxemia (for 15–60 s) with a cyclic pattern during sleep. The episodic hypoxemia is followed by a reoxygenation or reperfusion state after each episode [9]. Hypoxemia induces chemoreflex stimulation and consequent vasoconstriction that persists even during normal breathing daytime wakefulness in OSA patients. Intermittent hypoxia results in an increased

production of reactive oxygen species, vascular inflammation, endothelial dysfunction, and elevated blood pressure. These vascular changes may induce direct damage to the inner ear, which is very sensitive to circulatory alterations since it is supplied by a single terminal artery and lacks adequate collateral blood supply [10]. Moreover, it is an organ requiring a large amount of energy, but the PO_2 level near the cochlea and vestibule is among the lowest throughout the body. Therefore, when blood PO_2 is reduced, or there is insufficient blood transport, cochlear and vestibular functions may be severely damaged [11]. In OSA, the base of the cochlea that receives high frequencies is more sensitive to damage than the apex (coding for low frequencies), something similar to what is seen in noise exposure and ototoxic drugs. In particular, the level of natural glutathione was significantly lower in basal outer hair cells than in apical outer hair cells, supporting a higher susceptibility of the basal cell population to free-radical damage. For these reasons, high frequencies represent the first and mostly damaged frequencies by snoring and OSA.

For the vestibular system, an induced OSAS vascular inner ear deficiency can cause a change in the otolith's chemical composition leading to BPPV and abnormal endolymph homeostasis, causing Meniere's disease. In vestibular neuritis, although the etiology of acute unilateral peripheral vestibular deficit remains unclear, it may suggest that the chronically repeated hypoxic episodes would affect the neuronal activities of the vestibular nucleus and immune responses to herpes virus [12].

The chronic hypoxic state seen in OSA results in the progressive reduction in the peripheral vestibular system, which consequently becomes asymmetrical. However, the central vestibular system initially tends to correct this disequilibrium between the two sides.

Chronic hypoxemia and consequent impairment in blood flow are not the only mechanisms producing inner ear damage induced by sleep apnea. Recently, another important contributing factor has been proposed: the noise exposure from snoring sounds leads to hearing dysfunctions in snorers and their bed partners [13]. In particular, the repeated loud snoring sound from the vibration of an overly long or floppy soft palate transmits through the Eustachian tube and conductive mechanism, causing acoustic trauma, particularly at the base of the cochlea, which corresponds to high-frequency hearing. The persistent acoustic trauma may explain the poor response to steroid treatment at a high-frequency in patients with OSA and sudden sensorineural hearing loss (SSNHL) [14]. Snoring also has detrimental effects on the bed partners. In particular, Sardesai MG et al. [13] observed a unilateral high-frequency pattern of HL consistent with noise-induced HL in the bed partners. These results pointed out how snoring is not just a "cosmetic" problem, but it can cause damage to the cochlea.

11.2.2 Research Studies Linking OSA and Hearing Loss

It has been shown that moderate OSA can cause a loss of high-frequency hearing functions and speech discrimination scores. In contrast, severe OSA has significant effects on all hearing functions, as reported by the study by Kayabasi et al. [15]

Pure-tone and speech recognition thresholds were positively correlated with AHI and ODI and negatively correlated with min. Oxygen saturation. Speech discrimination scores on both ears were negatively correlated with AHI and ODI and positively correlated with min. Oxygen saturation [15]. Martines et al. [16] did not detect hearing impairment in simple snorers. In contrast, in patients with moderate/severe OSA, significant hearing impairment was shown in the high-frequency range above 6 kHz, especially in the extended high-frequency zone of 10–16 kHz. Also, our group [17] reported cochlea impairment in patients affected with severe OSA, showing a pure tone average significantly higher than the control group, and lower transient evoked otoacoustic emission (TEOAE) reproducibility and distortion product otoacoustic emissions (DPOAE) amplitude, and prolonged mean latencies of waves I, III, and V. It is widely known that the otoacoustic emission (OAE) is the direct reflection of the cochlear active mechanisms, attributed to the active process of outer and inner hair cells; the reduction of the OAE levels can be attributed to a vulnerability of the hair cells to oxygen blood level. OSA can cause "subliminal" hearing damage without alteration of hearing thresholds [17]. Many studies showed a significant reduction in OAE amplitude in OSA patients without hearing loss modifications. OAE is a kind of sound energy produced in the cochlea, which can be recorded in the external auditory canal and reflect the functional status of outer hair cells in the cochlea. A possible explanation for this phenomenon is that chronic hypoxia of the cochlea in OSA patients may damage the outer hair cells, which are more vulnerable than the inner hair cells, thereby affecting cochlear function. Inner hair cells transform the sound vibrations from cochlea's fluids into electrical signals relayed via the auditory nerve to the auditory brainstem. In contrast, the outer hair cells mechanically amplify low-level sound that enters the cochlea. It has also been observed that the DPOAE change in amplitude was earlier than that of hearing thresholds. For these reasons, DPOAE could be used to monitor the cochlear function of OSA patients [18].

11.2.3 Tinnitus

Regarding tinnitus, some studies proposed that OSA-induced hypoxemia might have a negative impact on auditory function, leading to chronic tinnitus [19]. Secondly, tinnitus and SDB are closely associated with anxiety, depression, and short sleep duration; thus, they might be comorbidities or etiologically related [20, 21]. Many recent studies showed that the risk of tinnitus was found to be significantly higher among middle-aged and elderly OSA patients [22]. In addition, tinnitus can be considered an "alarm bell" for apnea and may prompt doctors to diagnose OSA early. In conclusion, OSA patients with Idiopathic SSNHL had significantly poorer responses to steroid treatment than patients without OSA, especially at high frequencies (4000 and 8000 Hz) [14]. There is conflicting evidence regarding middle ear function: one study indicated an increase in middle ear pressure (MEP) [23], and another showed a decrease in this parameter [24]. In contrast, two studies revealed no changes in MEP in OSA patients [25, 26]. MEP also

increases in OSA patients during sleep, with the increased pressure proportional to the number of hours slept [27]. Using a seven-question subjective questionnaire—the Questionnaire-7 (ETDQ-7)—patients were asked if they experienced symptoms like ear pain or pressure. One study reported statistically worse Eustachian tube Dysfunction symptoms in OSA patients despite an unequal sample size (31 OSA vs. 99 healthy controls) [28]. In contrast, another study revealed no difference in Eustachian tube dysfunction and nasal symptoms compared to the control [29].

11.2.4 Regarding the Treatment

There are no effective treatments for SNHL except for hearing aids, cochlear implants, and glucocorticoid treatment for sudden SNHL. The first-line therapy for moderate–severe OSA patients is CPAP. However, its failure in long-term adherence is well known, reaching 25%–50% of cases [8]. Through correction of hypoxia and improvement in cerebral blood flow and central oxygenation, CPAP therapy directly improves inner ear microcirculation and indirectly could improve auditory and vestibular functions. Chi JC et al. [30] investigated the effects of CPAP application to SNHL patients with OSA, suggesting that CPAP treatment for 6–12 months may improve pure tone audiometry threshold at low, medium, and average frequencies, when adjusting for age, gender, smoking, alcohol, coronary artery disease, hypertension, and AHI. Moreover, Alessandrini et al. [31] highlighted that postural instability and dizziness-related conditions due to OSA improved after 12 months of CPAP treatment. Some evidence investigated whether CPAP would effectively manage vertigo and hearing loss in Ménière's disease patients showing significant improvement in dizziness handicap inventory (DHI) and audiometric testing [32]. Further investigation is required to determine whether early application of CPAP can serve as a valid strategy for preventive or therapeutic purposes. Intriguingly, there is only a single study [33] evaluating the effects of uvulopalatopharyngoplasty (UPPP) on the auditory functions showing an improvement of transient-evoked otoacoustic emissions after surgery. However, to date, no other similar studies in the literature support an improvement in hearing functions after the "new" intrapharyngeal remodeling surgeries that are notoriously associated with better results and fewer complications in compared with the "old" UPPP [34].

11.3 Nose and Throat in OSA Patients

11.3.1 Pharyngeal and Laryngeal Alterations in OSA Patients

Dysphagia is often an underreported OSA complication. Furthermore, the pathophysiology associated with dysphagia in OSA patients remains poorly understood. A recent review estimated prevalence range from 16% to 78% [35]. Evidence suggests repeated trauma and tissue stretching resulting from low-frequency snoring vibrations can lead to palatal-pharyngeal injury. Further, this may be associated

with sensory impairments, contributing to not only upper-airway collapse but also swallowing dysfunction as well. Moreover, OSA perturbs the rhythmic swallowing–breathing coordination, as supported by study findings of increased duration of swallow-related respiratory cessation in patients with OSA. An additional factor to be considered is LPR. Caparroz et al. [36] studied the association of dysphagia and LPR in patients with moderate/severe OSA. Many authors are convinced that OSA and gastroesophageal reflux coexist because of shared risk factors like obesity or because one condition aggravates the other. The incidence of LPR is approximately 10% in the general population, whereas, in OSA patients, the incidence ranges from 30.6% to 89.2%. A few studies have suggested that OSA treatment relieves LPR. During OSA episodes, there is a change in the pressure dynamics inside the airway with a decrease in intrathoracic pressure and an increase in transdiaphragmatic pressure [37]. This could trigger gastric reflux mainly if there is transient lower esophageal sphincter relaxation. On the other hand, reflux is known to cause airway irritation and bronchospasm through direct or indirect (vagal) mechanisms. The more severe the apnea is, the higher the degree of reflux. This should be considered when treating this group of patients.

Other studies by Nguyen AT et al. [38] showed that upper-airway mucosal sensory function is impaired in the oropharynx and larynx of OSA patients than normal controls. This could arise from of mechanical injury due to trauma from vibration, suction collapse, and upper-airway tissue distortion during obstructed respiratory efforts. Reflux of gastric acid and proteases into the laryngopharynx, which has been reported in OSA, could be a factor [39]. Tissue hypoxia may also play a role. These insults could produce direct injury to the upper-airway mucosa and may lead to damage from the production of reactive oxygen species, inflammatory cell infiltration, and cytokine release. These findings, therefore, support the study hypothesis that mucosal sensory function is impaired at multiple levels of the upper airway in OSA.

OSA has been associated with upper-airway inflammation, thickened pharyngeal walls, hypertrophic tonsils, or a thickened and slack soft palate, which may adversely affect voice production and resonance and contribute to abnormal voice features [40, 41]. Moreover, it has been suggested that altered structure (including excess fatty infiltration into parapharyngeal tissues) narrows the upper airway and may contribute to hyperfunctional voice patterns related to efforts to overcome excess upper-airway resistance. Likewise, chronic snoring may cause dryness and inflammation in the upper respiratory system, which may adversely affect the health of the vocal folds and contribute to disturbances in phonation [42]. Expanding literature suggests that alterations in upper-airway structure and function may contribute to unexplained chronic cough (CC), diurnal breathing problems, and voice disorders. This triad of symptoms is commonly referred to as “irritable larynx syndrome” (ILS) or more recently “laryngeal hypersensitivity syndrome” (LHS), suggesting that the larynx becomes hypersensitive or hyperresponsive following overexposure to a variety of irritants that contribute to “hyperkinetic laryngeal dysfunction” [43]. Descriptions of ILS and related laryngeal motor dysfunction vary considerably, but most include: [1] dysphonia within the context of a structurally normal larynx

(combined with excess perilaryngeal muscle activation) [2], transient inspiratory dyspnea (with lateromedial glottic and/or supraglottic laryngeal narrowing), and [3] CC, throat clearing, or globus sensation. The exact mechanisms underlying ILS are unknown (and are likely multifactorial), but laryngeal hypersensitivity possibly related to sensory neuropathy and/or upper-airway inflammation is often proposed [44, 45].

Further studies will be required to elucidate the mechanisms underlying sensory and motor impairment and the potential role in the impaired defense of upper-airway patency during sleep, which characterizes OSA.

11.3.2 The Effects of CPAP Treatment on Upper Airway

Currently, CPAP therapy is the gold standard for treating moderate and severe OSA. The efficacy of CPAP in an ideal setting is apparent, but adherence to CPAP may limit its effectiveness in the home setting. It is well known that acceptance and compliance are often suboptimal in CPAP treatment. It is estimated that 30% to 80% of OSA patients can be classified as nonadherent when using CPAP for less than 4 h per night [46]. Several factors have been linked to CPAP rejection, including patient characteristics (e.g., age, race, and smoking status), disease characteristics (e.g., symptom severity), experienced side effects (e.g., skin irritation, dryness in the nose or mouth, and abdominal bloating), treatment titration procedures, and psychosocial factors (e.g., skills at coping with challenging situations, mental health problems, self-efficacy, and social support). The main complaints are dry nose, mouth, or throat [47]. In particular, dry mouth can be the reason patients are nonadherent to CPAP therapy. The absence of saliva in the mouth causes an unpleasant and scratchy sensation, difficulty swallowing, bad breath, and the growth of fungi and bacteria in the mouth with mucosal lesions because saliva's antimycotic and antibacterial action is lacking. It is thought that dry mouth is caused by an influx of air that dries up the oral mucosa. This would seem to be the case when using a full-face CPAP appliance or if a patient's mouth remained open when using a nasal-only CPAP appliance [48]. In most cases, the salivary flow rate in OSA patients was close to normal; only 20% of examined persons had objective signs of hyposalivation. Most cases are associated with mouth breathing but not with salivary gland hypofunction. CPAP's role in voice disorder development and maintenance remains a source of controversy. It is unclear whether CPAP improves or worsens voice function. For instance, two studies have concluded that CPAP has adverse effects on voice related to drying of the upper airway and vocal fold mucosa from "nonhumidified" airflow [49, 50]. In contrast, Atan D et al. [51] showed that phonatory function improved in the OSA group after 1 month of regular humidified CPAP use. Likewise, 11 CPAP-adherent participants reported a trend toward voice improvement (as measured by the Voice Handicap Index 10; VHI-10) and a significant reduction of reflux symptoms after 6 months of regular humidified CPAP use [52]. Thus, the relationship between duration, consistency, type of CPAP use, reflux symptoms, and voice problems remains unclear. To improve sleep and quality of life

of these patients and in particular dryness in the upper respiratory tract, it is recommended that the humidity and temperature of inspired air should be increased by heated humidification. During spontaneous breathing and mouth leakage, the relative humidity was reduced from 80% to 40%, and heated humidification improved the relative humidity to 60% [53]. Moreover, positive airway pressure can lead to nasal complaints, such as nasal obstruction, rhinorrhea, nasal dryness, and sneezing in up to 44%–65% of CPAP users [54, 55]. Balsalobre et al. [56] showed CPAP use by awake healthy individuals resulted in worsening of nasal obstruction, which was more evident in those with a known history of Allergic Rhinitis. Nasal complaints present prior or secondary to CPAP have also been identified as predictors of CPAP adherence. For these reasons, nasal obstruction surgical and medical therapy can still play an essential role in facilitating the treatment of patients with OSA by improving tolerance and compliance with CPAP.

It is the treating physician's role to understand the problems related to CPAP use to maximize adherence. However, due to the high incidence of noncompliance CPAP, otolaryngologists must offer other treatment options, including various surgical interventions, for these patients so that untreated OSA with its potentially severe consequences does not go untreated.

11.3.3 Postoperative Discomfort, Short and Long-Term Complications After Intrapharyngeal Surgery

Over the years, the surgeons' attention has turned to intrapharyngeal surgery, evolving from the older uvulopalatopharyngoplasty (UPPP) to the newer reconstructive palatal techniques [34]. Several studies have shown that UPPP and other older palatal surgery techniques were associated with a high incidence of unfavorable postoperative complications and comorbidities such as dysphagia, rhinolalia, velopharyngeal insufficiency, and nasopharyngeal regurgitation, phlegm in the throat, and abnormal scarring with velopharyngeal stenosis [57]. So, compared to the older techniques, these newer palatal surgery techniques, including Barbed Pharyngoplasty (BP) based on reconstructive principles respecting the lateral pharyngeal walls and preserving some or part of the uvula, are expected to have fewer long-term postoperative complications and comorbidities. The palate/pharyngeal mucosa has profuse tactile and pain innervations and is prone to considerable discomfort. Despite the belief that all of these surgeries lead to severe postoperative pain, pain the intensity varies according to different techniques [58]. It is typically present during the first postoperative days and tends to gradually disappear over 1 week. That the postoperative pain was significantly less in the patients if low temperature plasma surgery was employed [59]. These new intrapharyngeal surgical procedures, in particular the different Barbed Pharyngoplasties proposed, are very sure with significant short- and long-term complications. A recent review [34] found that thread/knot extrusion was the most frequent short-term complications. Concerning long-term complications, these patients infrequently experienced dry throat, throat lump, throat phlegm, mild and moderate dysphagia, rhinolalia, nose regurgitation, foreign body sensation, and a sensation of sticky mucus in the throat.

11.3.4 Postoperative Discomfort, Short- and Long-Term Complications After Hypopharyngeal Surgery

Hypopharyngeal obstruction is prevalent, and its presence is associated with increased OSA severity. Failure to address hypopharyngeal obstruction can lead to residual OSA and suboptimal treatment outcomes. Hence, sleep surgeons need to complete their armamentarium corrective treatment for hypopharyngeal obstruction. One of the most common surgical procedures is epiglottoplasty with or without tongue base reduction. Hypopharyngeal surgery is a safe and well-tolerated procedure for the treatment of OSA. Potential postoperative complications include hemorrhage, dyspnea due to tongue or residual epiglottic edema, infection of the cartilaginous stump of the epiglottis, aspiration, or dysphagia. Usually, patients who underwent epiglottoplasty with or without tongue base reduction proved to have a reasonable short-term swallowing outcome with no long-term sequelae [60]. OSA patients with initial swallowing difficulties, particularly during the pharyngeal phase of swallowing, are not candidates for epiglottic surgery. If there is a question regarding this, a barium swallow should be performed to rule out aspiration on penetration before considering the procedure.

11.3.5 Side Effects of Mandibular Advancement Devices for Snoring and Sleep Apnea

Mandibular advancement devices (MAD) are the most common oral appliances used to treat snoring and OSA. Although there are several MAD designs, all devices protrude the mandible and induce changes in the anterior position of the tongue, soft palate, lateral pharyngeal walls, and mandible, resulting in improved UP patency [61]. However, the response to MAD is variable and typically depends on the MAD design and patient characteristics. MAD is also associated with several side effects. In the short term, a patient could complain of the Temporomandibular Joint (TMJ) pain, myofascial pain, tooth pain, salivation, TMJ sounds, dry mouth, gum irritation, and the morning after occlusal changes. Most of these can be managed or even prevented with conservative behavioral therapy. In the long-term, the main side effects reported are represented by dentoskeletal changes, which are not clinically relevant [62, 63].

11.4 Conclusions

OSA is a complex disease with well-known adverse effects on multiple human body systems. It might affect ENT organs such as hearing and balance disorders, sensory and motor impairment of the upper airway, problems related to CPAP use, and short- and long-term side effects after OSA surgery. Otolaryngologists should be aware of these consequences while preventing or improving multiorgan damage in OSA patients.

Take-Home Message

- Recent evidence suggests that OSA might be associated with alterations in the auditory and vestibular systems, increasing the risks of Hearing Loss (HL), tinnitus, and dizziness.
- OSA could cause damage to other ENT organs by altering sensitive and motor functions of the pharynx and larynx.
- Newer intra-pharyngeal remodelling surgical procedures, less invasive or morbid, improving patients' compliance, and nasal surgery make OSA surgery a reasonable alternative. To patients that do not tolerate CPAP. Also, nasal surgery provides a way of improving CPAP adherence by reducing nasal resistance.

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12.1 Introduction

In the vast universe of sleep medicine, the dentist is also part of the multidisciplinary team described in this book.

The dentist must undergo training in dental sleep medicine. Apart from reviewing respiratory sleep disorders (OSA), it also deals with issues such as orofacial pain, oral moisture disorders, gastroesophageal reflux disorders, and jaw movement disorders [1].

There is an actual amount of information in the literature on this subject promoted globally by various academies and associations. The most important ones are the American Academy of Dental Sleep Medicine and the European Academy of Dental Sleep Medicine. In other countries, dental colleagues are organizing to promote, train and treat these patients suffering from obstructive sleep apnea (OSA).

Within this training, the dentist must explore beyond the topics of conventional dentistry, searching to understand the physiology of breathing and the diversity of tests available to measure sleep. There is also a need for collaboration with various medical specialists focused on this field of sleep medicine. It becomes a very important barrier for the dentist who wants to embark on this path in sleep medicine and treat the various respiratory sleep disorders such as Obstructive Sleep Apnea and Snoring.

In their daily practice, dentists can identify various observable clinical, such as the narrow maxillary, mandibular arches with high palatal vaults, tonsillar hypertrophy, macroglossia, retrognathia or micrognathia, and chronic periodontitis, tooth loss, deep overbite, and neck circumference size [2]. These signs make us suspect of OSA, especially if they are accompanied by daytime sleepiness (falling asleep during the dental procedure), the referral of with important snoring with respiratory pauses in our clinical history.

The presence of obstructive sleep apnea should be determined before proposing treatment with oral appliances.

There are many indications for the use of oral appliances:

1. Patients diagnosed with primary snoring,
2. UARS, patients with mild obstructive sleep apnea,
3. Patients with moderate obstructive sleep apnea and low BMI,
4. Patients diagnosed with moderate–severe obstructive sleep apnea with a failure of CPAP fitting,
5. Patients who have undergone oropharyngeal surgery by our otolaryngologist colleagues and who have failed the procedure,
6. Patients who are CPAP users and prefer the Oral Appliance (they must be candidates),
7. Patients who need to use the appliance when traveling,
8. And the use in conjunction with CPAP, which is rare [3].

12.2 Radiographic Analysis in Patients with OSA

Dentists and in particular, orthodontists can play a crucial role in identifying patients with facial features that may predispose them to OSA. However, another helpful tool is given by radio diagnostics.

Patients with a Class II skeletal malocclusion or maxillomandibular retrusion have a greater risk of presenting OSA due to greater ease of collapse of the soft tissues, which are contained by a skeletal compartment of insufficient size.

One of the most used radiological investigations to identify any predisposing features to OSA is the lateral x-ray of the skull in a lateral–lateral projection. Although this radiograph has the limitations of two dimensions, a cephalometric analysis can be done [4]. A hyoid bone positioned in a particularly caudal position with a distance from the mandibular plane greater than 15 mm is a risk factor for the onset of respiratory sleep disturbances. Mandibular retrusion and increased anterior facial heights, easily observed in the lateral x-ray, can also predispose to obstruction in the retrolingual site [5, 6] (Fig. 12.1).

In addition to the bone characteristics, it is also possible to evaluate any adenotonsillar hypertrophy.

Other measurements to be taken into account in cephalometry are tongue base-posterior nasal spine, sella-nasion-B point angle (SNB), maximum uvula thickness, tongue base-tongue tip, and nasion-anterior nasal spine (N-ANS) [7]. A retrospective cephalometric study on upper airway spaces in different facial types determined a difference in the median posterior-palatal space measurement, in the oropharynx region, that was reduced for individuals with a dolichofacial pattern [8].

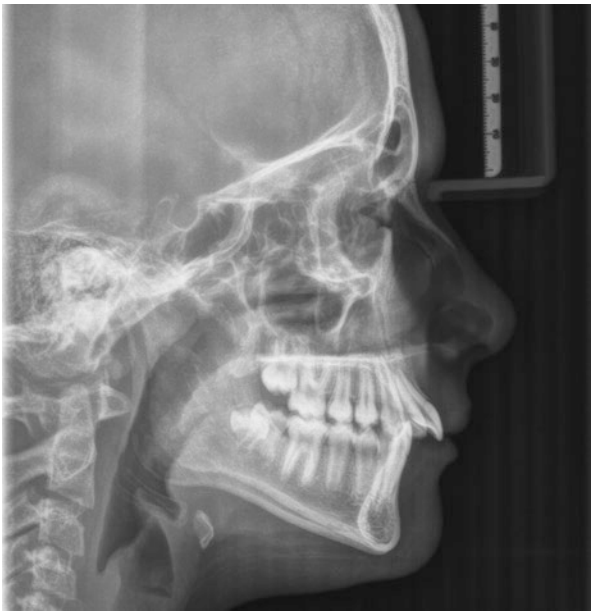

Fig. 12.1 Example of teleradiography in lateral projection of the skull in which the aforementioned structures can be observed

The advantages of the lateral x-ray are the ease of execution, noninvasiveness, reproducibility, and low cost. These characteristics are balanced by some disadvantages: the two-dimensionality, the upright position, the waking state in the execution, and the insufficient recognition of relevant anatomical landmarks.

In some cases, the two-dimensionality of teleradiography can represent a limit that can mislead the clinician: the sagittal size of the airways and pharyngeal airway space is difficult to evaluate using teleradiography.

This radiography is a support tool for the clinical evaluation of the patient, but it cannot represent a screening or diagnostic tool. In fact, there are no cephalometric values that identify the patient with OSA.

Radiodiagnosis also makes three-dimensional images available to the clinician thanks to Computed Tomography (CT). It allows for delineating the anatomy of the maxillofacial region with greater precision. CBCT provides detailed and three-dimensional images of the entire facial massif, overcoming the overlaps between the different structures and the distortion of the image of the lateral radiography [9]. Therefore, it is widely used to evaluate the upper airways and to identify predisposing factors of an anatomical nature in patients with OSA, be they adults or pediatrics. Through the CBCT, it is possible to evaluate, the size of the pharyngolaryngeal space through software analysis (Fig. 12.2).

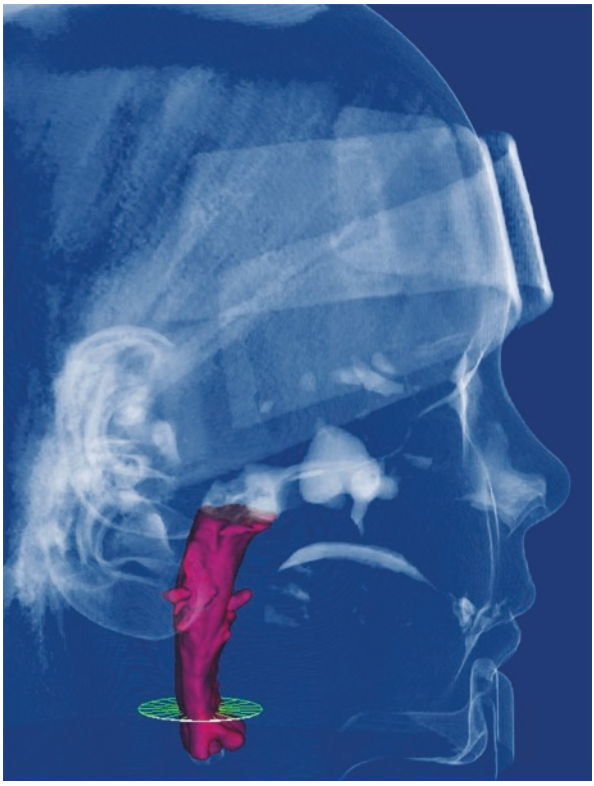

Fig. 12.2 The image highlights the airspace of the upper airways. The point with the smallest caliber is highlighted in green

Furthermore, there is the possibility to evaluate pharyngeal wall thickness in the presence of bone or some soft tissues anomalies. Some characteristics that alter physiological respiration and which are identifiable in CBCT are nasal polyps, nasal turbinates hypertrophy, concha bullosa or paradoxical curvature, hypertrophy of the soft palate or uvula, reduced transverse dimension of the jaws and dental arches, hypertrophy of the palatine tonsils or obliteration of the maxillary sinuses (Fig. 12.3).

Thanks to the sagittal projection reconstructions, it is possible to evaluate the length of the soft palate and the lingual structure, especially concerning the oral floor and the mandibular plane (Fig. 12.4).

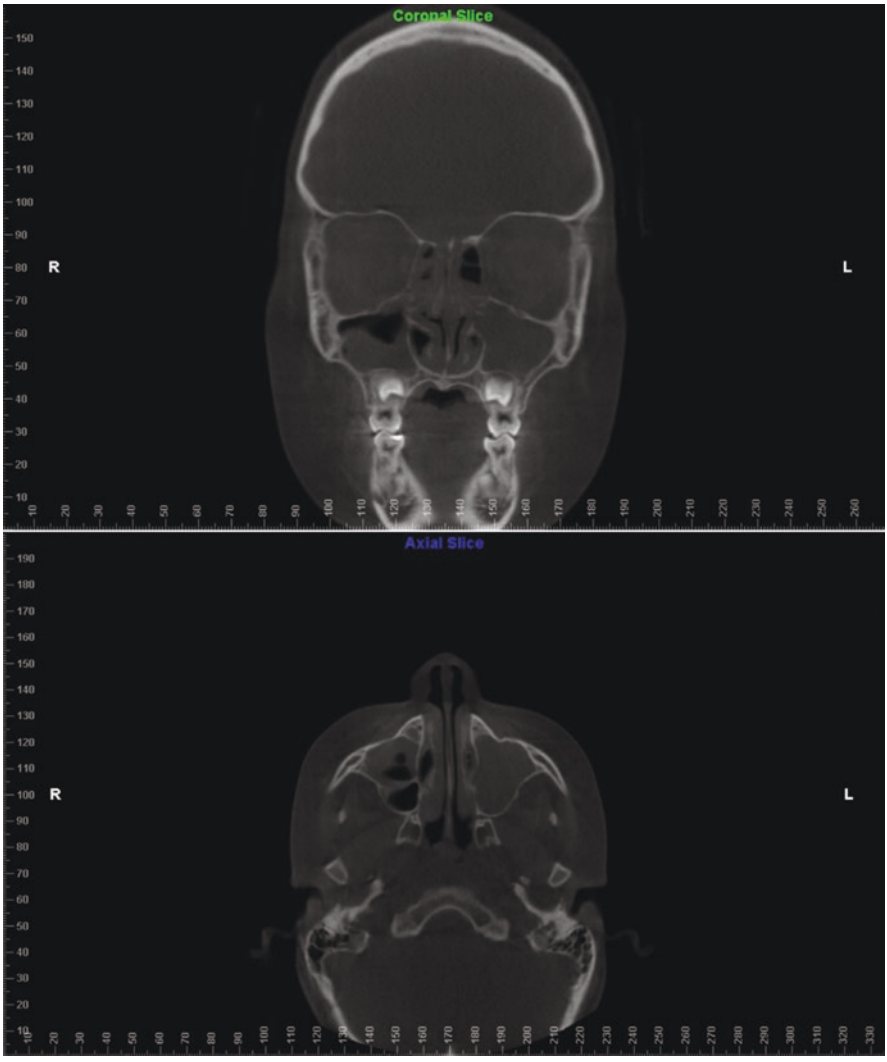

Fig. 12.3 Coronal and axial cuts highlight problems affecting the maxillary sinuses

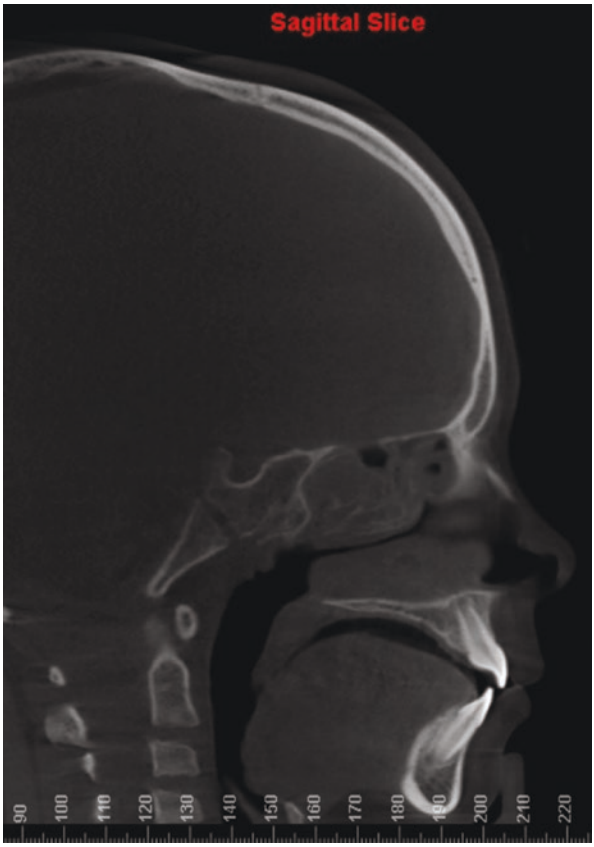

Fig. 12.4 Sagittal slice of a CBCT

CBCT of the skull can also be used to plan any oropharyngeal or maxillofacial surgery [10].

The anatomical features that influence the anteroposterior dimensions of the airways are multiple; however, the sagittal pharyngeal diameter is not seem to be affected by being overweight [11, 12].

Furthermore, CBCT is used more and more frequently by dentists who treat patients with OSAS using mandibular advancement devices (MAD) to investigate the state of health of the condyles, and the temporomandibular joint (TMJ).

In any case, it is necessary to consider the high cost of CBCT and the increased exposure to radiation. It has been suggested that a CBCT should be requested for an adult patient with a diagnosis or solid clinical suspicion of OSA before starting treatment identify all potential predisposing anatomical factors and establish the best therapeutic strategy [13].

On the other hand, in the case of children, they should be thoroughly examined before requesting a CBCT, and only in cases that are nonresponsive to treatment.

Magnetic Resonance (MRI) provides added information. Its use allows information of the soft tissues in the oropharyngeal area.. Evaluation of the lingual

morphology, the oral floor, and their relationship with the bone structure is possible. In addition, Dynamic sleep MRI can reliably characterize the actual site of dynamic airway obstruction and has the potential of improving predictions of successful surgical outcomes in OSA patients [14, 15].

12.3 Oral Appliances

Oral appliances have been described as an efficacious treatment for OSA. In a paper called "Defining an Effective Intraoral Device for the Treatment of Snoring and Obstructive Sleep Apnea Syndrome: 2019 in the Journal or Dental Sleep Medicine Update," five major changes were made concerning the effectiveness of the intraoral device. These changes focused on the physical characteristics and functions of an oral appliance (OA)

1. *An Oral Appliance must be made of materials that meet the physical needs of patients.*

   An OA must be made of biocompatible materials to be considered safe for patient use [16]. In addition, the materials must be suitable for the oral structure and physical needs of an individual patient. For example, such physical needs may include the need for nonmetallic materials for those with metal hypersensitivity.

   Approximately 10%–15% of the population is hypersensitive to metals [17]. Therefore, alternative, biocompatible materials should be used when fabricating intraoral devices for such patients. OA materials that were previously fabricated with metal can now be made with other materials. For example, the connecting mechanisms in Bibloc devices can be made of elastics, plastics, or even magnets [18].
2. *A custom-fabricated (customized) Oral Appliance may include a prefabricated component*.

   Current evidence indicates that custom-made oral appliances are superior to prefabricated devices [19–24]. In addition, custom-made appliances have been associated with patient comfort and treatment adherence [25] as well as reduced apnea–hypopnea index (AHI), improved daytime sleepiness, improved endothelial function, and increased muscle activity [25–35].
3. *The Oral Appliance (OA) mechanism is not limited to fixed mechanical hinges or metallic materials.*

   OA designs now feature connection mechanisms that are nonmetallic, for those who suffer from hypersensitivity to metals.

   As technology has progressed, several hingeless devices have been shown to be effective in treating OSA. However, there is still some controversy as some studies show improvements in AHI by protruding the mandible using elastics connected to Adams clasps [36]. Another study of OA's with elastic bands (to control mouth opening) compared to the same appliance without bands found no significant difference in AHI after use [37].

Other appliances (Bibloc) that are connected and fitted using nonmetallic flexible rods have been associated with significant improvements in OSA symptoms. In one study, 76% of patients were effectively treated with this device (AHI decrease ≥50%), and 64% achieved a complete response to treatment [30]. Another study with this OA showed that 56% of patients using the device achieved a response to treatment [38].

In other studies, devices using ball clasps to protrude the mandible significantly reduced AHI. These studies found that 57% of patients achieve an AHI <10 per hour and 31% an AHI <5 per hour. Overall, they concluded that the devices were successful in treating OSA in 58% of patients, excessive daytime sleepiness in 56% and snoring in 76% [31]. Therefore, connecting mechanisms other than fixed mechanical hinges can effectively treat snoring and OSA.

4. *An oral appliance must prevent dislodgement*

   An effective OA must have retention in one or both arches [6, 39]. Lack of adequate stability of the oral appliance can lead to worse outcomes. For example, it has been suggested that the Monobloc may be less effective than Bibloc devices due to poor stability (among other factors) [40]. Therefore, the OA must have good tooth retention and prevent dislodgement.

5. *Life of an oral appliance*

The original definition included a clause stating that an effective intraoral device must "maintain its structural integrity for a minimum of 3 years." In this update (JDSM 2019), it was determined that there was very little evidence outside of the AADSM definition that a device should last at least 3 years to be effective. Therefore, this aspect was removed from the definition.

12.3.1 Types of Oral Appliances

Currently, there are a many Oral Appliances (OA) designs available on the market. These Oral Appliances vary in attachment design, mode of fabrication and activation, titration capability, degree of vertical opening, and jaw laterality movements.

They also can be of a one-piece (Monobloc) or two-piece (Bibloc) design, either custom-made or prefabricated [41, 42]. Thermoplastic OA (boil & bite) has been proposed as a temporary device to be used while repairing a permanent OA, or a patient's waiting time is not enough to fabricate a permanent one [43]. It has the advantage of a feasible a low cost [44, 45].

A dentist with training in Dental Sleep Medicine should be the only one to provide OA therapy. The critical treatment approach includes coordination and communication (in writing) with the referring physician regarding the treatment plan and long-term follow-up.

12.3.2 Monobloc

These are OA (Fig. 12.5) composed of a single body and span both arches, mostly nonadjustable. It has been recommended that the dental pieces are totally or partially encapsulated inside the device to avoid dental overeruption or any other movement.

12.3.3 Bibloc

They are OA composed of two bodies (upper and lower arch) that interact with each other through different types of connectors. They are adjustable (depending on the connector type), making it possible for the dentist to have complete control of the protrusion during treatment. There are several designs worldwide; some examples of those are Somnomed Avant®, Telescopic/Herbst (Fig. 12.6), Elastic Device/EMA, Dorsal Fin (Fig. 12.7), OrthoApnea Classic® (Fig. 12.8), and the DreamTAP® (Fig. 12.9).

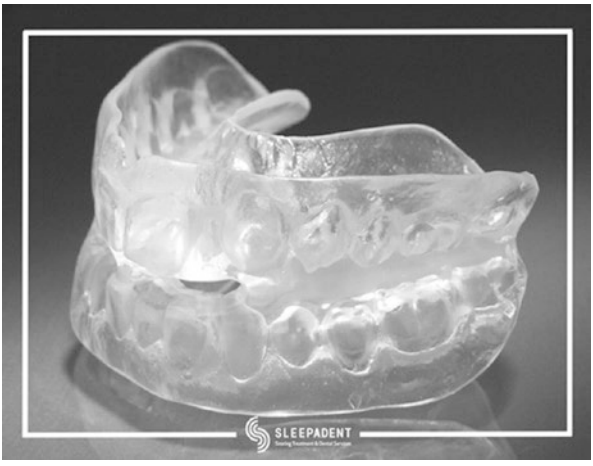

Fig. 12.5 Monobloc

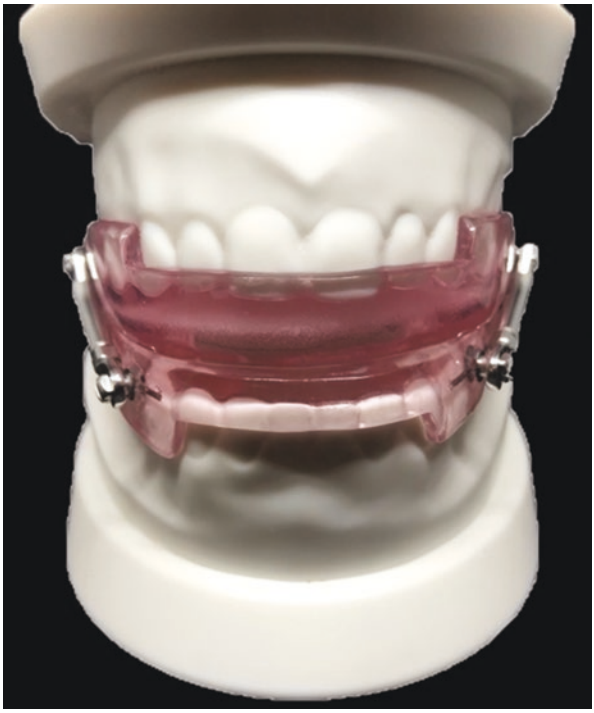

Fig. 12.6 Telescopic/herbst

Fig. 12.7 Dorsal fin

Fig. 12.8 OrthoApnea Classic®

Fig. 12.9 DreamTAP®

12.3.4 Telescopic/Herbst

12.3.5 Dorsal Fin

12.3.6 OrthoApnea Classic®

12.3.7 DreamTAP®

12.3.8 Thermoplastics (Boil and Bite)

These are prefabricated devices (Fig. 12.10) that are not custom-made, and their durability is not predictable. Instead, adaptation is made directly at the moment, either in the office or by the patient at home.

There are both monobloc and bibloc, adjustable, and nonadjustable.

There are also the tongue retainer devices (Fig. 12.11) among these intraoral devices, which are an alternative for those partially or edentulous patients. All of them are prefabricated, and the most common design is the one shown below:

Finally, emphasize that technological and innovative advances in Intraoral Devices have occurred in recent years by elaborating them using 3D Printing and CAD-CAM technology such as OrthoApnea NOA® (Fig. 12.12) and ProSomnus® (Fig. 12.13). At the same time, more and more markers or "chips" are being incorporated into the devices, where we can receive information about the three-dimensional position, time of use, patient's temperature, etc.

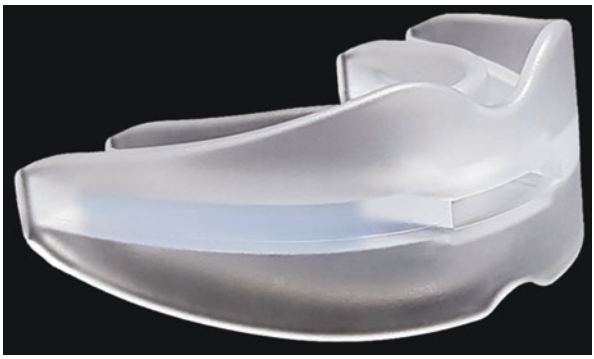

Fig. 12.10 Thermoplastics

Fig. 12.11 Tongue retainer device

Fig. 12.12 OrthoApnea NOA®

Fig. 12.13 ProSomnus®

12.3.9 OrthoApnea NOA®

12.3.10 ProSomnus®

12.3.11 Effectiveness of an Oral Appliance

An Intraoral Device aims to treat obstructive sleep apnea, primary snoring, and associated symptoms. Historically, the most frequently measured outcomes in therapeutic efficacy and effectiveness of OSA treatment have been the apnea–hypopnea index (AHI) to measure the severity of OSA and the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness. However, as OA research has matured, the results have expanded to include the effect on cardiovascular function, neurocognitive behavior, and quality of life.

12.3.12 Improvements in Respiratory Variables and Daytime Sleepiness

The efficacy and effectiveness of Oral Appliances therapy have been confirmed by several high-quality studies, including randomized controlled trials, systematic reviews, and meta-analyses [38, 46–60]. Through nocturnal polysomnography (PSG), these studies have validated the usefulness of MA (mandibular advancement) in decreasing the frequency and/or duration of Apneas, Hypopneas RERAS and/or snoring, as well as in improving nocturnal oxygenation. As a measure of daytime sleepiness, the ESS score has normalized or improved by 2–4 points [54].

In one of the first reports of a study conducted comparing pre- and postpolysomnographic recordings using Oral Appliances Yoshida demonstrated that posttreatment AHI was significantly reduced by more than 50% from pretreatment values [61]. Polysomnographic parameters did not normalize, but these findings showed that intraoral device therapy can improve sleep-disordered breathing significantly.

Subsequently, Marklund reported that in 72% of patients with mild to moderate obstructive sleep apnea, AHI was reduced to <10. In the severe group, AHI significantly improved from a mean of 53 to 14 [62]. Other reports corroborated these early findings and demonstrated longitudinal stability of improvement in sleep parameters with OA [63–69].

In perhaps the most extensive study to date, Holley and colleagues described the results of their retrospective study in a sample of 497 OSA patients with all levels of disease severity, all treated with Oral Appliance therapy [70]. OA therapy reduced mean AHI from 30.0 to 8.4, and ESS was significantly improved. In addition, there is a comparison of PSG parameters between OA therapy and CPAP therapy of the 397 subjects. OA therapy demonstrated equivalent efficacy relative to CPAP in the mild subjects ($p = 0.15$), where treatment successfully reduced AHI <5 in 76% of the CPAP and 62% of the oral appliance group. In the moderate and severe groups, CPAP was more effective than OA in reducing AHI <5 (71% vs. 51% in the moderate group and 63% vs. 40% in the severe group). However, when comparing the

magnitude of reduction in AHI between treatments, the decrease in AHI was significant only for the severe group, where CPAP decreased AHI by an additional 5.9 events/h ($p < 0.001$). The amount of reduction in AHI by both treatments in the mild and moderate groups differed by less than 2 events/h and was not statistically significant.

12.3.13 Effect on Cardiovascular Function

There was an improvement in High blood pressure [71–77] and cardiovascular function [78, 79] in addition to respiratory and daytime sleepiness improvements. The effect of OA therapy on hypertension has been summarized in Iftikhar's systematic review and meta-analysis of seven randomized controlled observational studies [74].

A reduction of approximately 2 mm in systolic, diastolic, and mean blood pressure was reported among the 399 pooled participants who met the inclusion criteria for these studies. In another study, an evaluation of the impact of OA therapy on blood pressure revealed a significant improvement in overnight diastolic blood pressure compared to CPAP [72]. In addition, Lam studied the effect of OA therapy on blood pressure and found a significant improvement in systolic blood pressure maintained after 1 year of follow-up [75]. Gotsopoulos demonstrated a reduction in 24-h mean diastolic blood pressure in patients with AHI > 10 and concluded that these findings mirrored those found with CPAP [58]. Otsuka reported a significant reduction in mean arterial pressure and diastolic blood pressure during monitoring over a 20-h period, and significant reductions in systolic, diastolic, and mean arterial pressure during sleep [76].

12.3.13.1 Impact on Quality of Life and Neurocognitive Behavior

The overall quality of life [71, 80–86] and neurobehavioral outcomes [73, 80, 81, 85, 87] have improved with OA therapy. Walker-Engstrom examined three dimensions of quality of life (vitality, satisfaction, and sleep quality) in randomized subjects between patients with uvulopalatopharyngoplasty or intraoral device therapy [86]. One year after the intervention, both treatment groups demonstrated significant improvements in all three dimensions of quality of life. Levendowski et al. studied quality of life in patients who underwent OA therapy after failing CPAP therapy [81]. They found statistically significant reductions in sleepiness (76% of subjects) and depression (73% of subjects), as well as improvements in the disease-specific quality of life index (60% of subjects).

In addition, Saletu designed a study to examine respiratory variables and different outcomes of OA therapy in a group of patients with all levels of disease [85]. Active and inactive oral appliances were used to compare the effects on morning mood, subjective impression of sleep quality, and cognitive and psychophysiological performance. All respiratory variables improved in the active OA group compared to the sham appliance group. In addition, subjects demonstrated a significant benefit in sleep quality, morning cognitive performance, fine motor activity, and reaction time.

Fig. 12.14 MyTAP PAP®

12.3.14 Potential for Improved CPAP Adherence

Finally, Oral Appliances may offer improvements in CPAP efficacy. Using phrenic nerve stimulation to assess the dynamic properties of the upper airway, Borel et al. established that continuous use of CPAP (nasal mask) in conjunction with an OA reduces velopharyngeal resistance to a greater extent than using CPAP alone [83]. When OA's were used with nasal CPAP, peak flow velocity was significantly improved. Take for example: MyTAP PAP® (Fig. 12.14).

12.3.15 MyTAP PAP®

The simultaneous use of OA therapy with CPAP is a relatively new concept in dental sleep medicine. While preliminary studies are promising, further research is warranted to validate the improved effectiveness.

12.4 Dental Side Effects of Oral Appliances (Mandibular Advance Devices Mad)

Mandibular advancement devices aim to advance and stabilize the mandibular during sleep, allowing the passage of air through the upper airway without obstruction. This forward position of the lower jaw can cause discomfort with pressure and sometimes pain in the muscle, the joint and, the teeth. Extreme circumstances can lead to the failure of the therapy.

Managing side effects depends on the dentist clinical expertise and sensibility to identify and establish the best approach.

Oral appliances are attached to the teeth, and therefore, this therapy is highly dependent on a healthy dentition [88, 89].

The clinical relevance of dental occlusal side effects is strictly related to the baseline dental occlusion [90].

Dental side effects can be clinically minor, but the dentist should be experienced in dental sleep medicine to inform the patients and to deal with these events. Side effects may worsen with time and patients need to be monitored over time [90].

12.4.1 The Device's Force

Forces will arise on the teeth during appliance use, and there is a risk for bite changes [88].

Device design will also influence the risk of bite changes. For example, one study describes that a device attached mainly to the front teeth will produce a faster and more significant change in dental occlusion than a device connected to the whole dentition.

The advanced position of the jaw during the night will create forces on the teeth, and patients can experience some discomfort, temporary bite change with the loss of occlusal contact some hours after taking off the device [89, 91].

A study showed that device materials have no influence in centric occlusion and centric relation and no differences were found during the follow-up [92]. However, side effects were more pronounced in patients using hard acrylic devices and soft elastomeric devices with a large mandibular protrusion [92].

Some factors, such as a high percentage of advancement and poor oral health conditions (poor periodontal disease, insufficient bone support) and noncustom-made or nonadjustable devices, can lead to increased risk for negative impact and produce changes [91, 92].

The occlusal and structural changes registered are a consequence of the joint forces elicited by the MAD on masticatory muscles, which tend to bring the mandible back to its original position, discharging the tension on the teeth [90].

12.4.2 Short-Term Side Effects

OSA treatment with a mandibular advancement device can lead to side effects that are short-term and reversible in most cases.

Patients can experience bite changes in the early morning after a night using a MAD, but the occlusion comes normal during the day [92]. Subjective side effects are common, and the most frequently include temporomandibular joint (TMJ) pain, myofascial pain, tooth pain, TMJ sounds, gum irritation, and morning-after occlusal changes [89, 91, 93].

Also, dry mouth and excessive salivation can occur at the beginning of the treatment [6, 91, 93].

With high vertical dimension and advancement, a MAD creates more muscular and joint discomfort [91].

Puttin et al., in their study, examined the temporomandibular joints and revealed noises in 9 of the 106 patients (8%) who did not have joint noises before treatment. There wasn't a decrease in mouth opening. However, an increase was found in 30 (28%).

12.4.3 Long-Term Side Effects

With time only tooth movement and bite changes are more prevalent and can lead to discontinuation of treatment [91].

The overjet, i.e., the horizontal distance between the upper and lower front teeth, will decrease. Patients may lose antagonistic contact between the molar teeth, although there might be variability between patients [88, 91].

The initial type of bite is associated with the degree of bite changes. Patients with a deep bite, i.e., a significant vertical overlap between the front teeth, may be protected from overjet changes [88]. Those with normal bites or Angle Class III, i.e., lower front teeth located anterior to the upper front teeth, seem to be more at risk for negative bite changes [88, 91, 93].

Patients with Angle Class II, i.e., lower front teeth much posteriorly located from the upper front, might receive positive orthodontic effects of oral appliance treatment [88, 91, 93].

A study stressed the significant correlation between the duration of the therapy and the decrease of overjet, overbite, and U1 inclination, and increase of L1 inclination [90]. During a period between 2 and 11 years of therapy, there is a decrease in overjet from about 0.2 to 2.0 mm and a decrease in overbite from about 0.6 to 2.3 mm [90].

12.4.4 Changes in Dental Occlusion

The bite changes are noticed early during the first years of treatment and will gradually continue [88].

Although most patients are unaware of bite changes, the changed dental occlusion might influence the device's efficacy. For example, the advancement of the mandible by the device might diminish if the device is left unadjusted in patients with more considerable bite changes [88].

Some patients could also have skeletal changes by advancing the mandible [88, 91, 93]. After 5 years of MAD treatment, patients can experience less overbite and overjet, and also the mesial relationship of the lower molar [88, 91].

One-third of patients report posterior open bite after 1 or 2 years of treatment. Loss of interproximal contact is usually reported in the cases of attachments to increase retention of the device, leading to food impaction [91].

Also, the posterior teeth can change with the distal tip of the upper molars and the mesial tip of lower molars [88, 91].

Some studies describe the yearly migration of central incisors and jawbones, and patients' lower central incisors were significantly tilted forward [94].

Pantin et al., in their study, reveal that the proportion of patients with occlusal change increased with the use of the mandibular advancement splint for up to 2 years. Beyond 2 years, the ratio remained relatively constant.

Consequently, bite changes do not necessarily need to be considered disadvantageous to a particular dentition, and, indeed, some patients could benefit [88].

Changes occur in occlusion during snoring and obstructive sleep apnea treatment with MAD, especially in patients with protrusion below 6 mm. Although a follow-up after 2 years is recommended as individual patients may experience marked orthodontic side effects [92].

Same studies refer that occlusal changes were managed conservatively, using temporary cessation or reduction in the use of the device and remedial exercises each morning following its removal. With exercises, the occlusal changes resolve within 2 weeks of treatment cessation in most cases [95].

Patin et al. [95] found a satisfactory response of most patients to exercises, either to treat occlusal change or subsequently as a prophylactic measure, which suggests that these problems develop because of a failure to reposition the mandible during the day following use rather than as the result of immutable changes in occlusion caused by the device overnight.

12.5 Side Effects Related to the Use of Mandibular Advancement Devices

(Device selection to prevent dental side effects)

The dental effects attributable to the prolonged use of oral devices for the treatment of obstructive sleep apnea have long been investigated in the literature. Occlusal modifications are found in 86.7% of patients [96]. The authors agree to observe a reduction of overjet and overbite over time (1.5 mm in 7 years), and loss of dental contacts in the posterior region. Maxillary incisors palatal tipping and mandibular incisor labial tipping were also observed [97].

A recent study analyzed the effects on periodontal ligaments and tooth surfaces during the use of 4 different oral devices. The analysis was carried out using the Finite Element Method (FEM). It was developed in synergy between the dental department of the Università degli Studi di Padova (Italy) and the department of industrial engineering of the Università Politecnica delle Marche (Italy) [98, 99].

The Finite Element Method is an instrument that simplifies a complex physical object into many simple elements and analyzes these stresses and deformations in response to different conditions. FEM has been used in numerous medical and dental studies.

A 3D model of the skull of a 29-year-old patient was created from the Cone Beam CT and Magnetic Resonance. After creating a 3D model of the skull of a 29-year-old patient was based on his Cone Beam CT and Magnetic Resonance images. After scanning with a laser probe, four different digital models of Mandibular Advancement Devices were coupled (Fig. 12.15).

These MADs were chosen among the most used for OSA therapy and had different advancement mechanisms. (1) OrthoApnea Classic® consists of two splints connected by a reverse connecting anterior rod screw; (2) Somnodent Flex® (Dorsal Fin) has two advancement screws placed bilaterally on the upper splint that interface with the fins of the lower part. (3) Also, chose a Herbst-type device with telescopic sidearms. (4) Somnodent Avant®, which connects the two splints using a

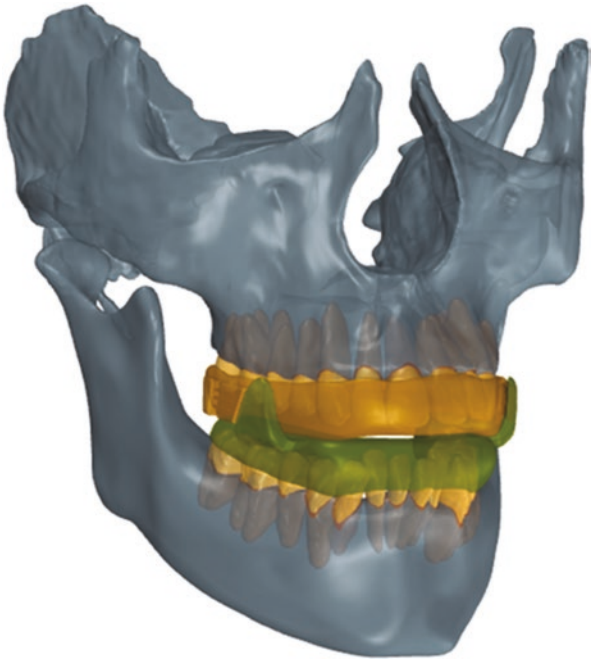

Fig. 12.15 3D model of the skull with MAD

nylon string that hooks anteriorly in a lane placed on the upper splint and in two pins at the level of the mandibular molars.

Periodontal ligaments were modeled by offsetting each tooth root surface of 0.3 mm to fill the space between each tooth and the alveolar socket [100, 101].

A force of 11.18 N was applied to the MAD on the connection points of the splints; equivalent to a device advancement of 9.5 mm [102, 103].

OrthoApnea Classic® generated stress with a maximum value of 4.26 kPa on the periodontal ligaments and 600 kPa on the tooth surfaces; that affected the teeth of the upper and lower anterior sector (Fig. 12.16).

The Herbst-type device created a maximum of stress corresponding to 3.56 kPa on the ligaments and 302 kPa on the dental surfaces; the stress, in this case, was distributed more homogeneously, with prevalence in the lateral sectors (Fig. 12.17).

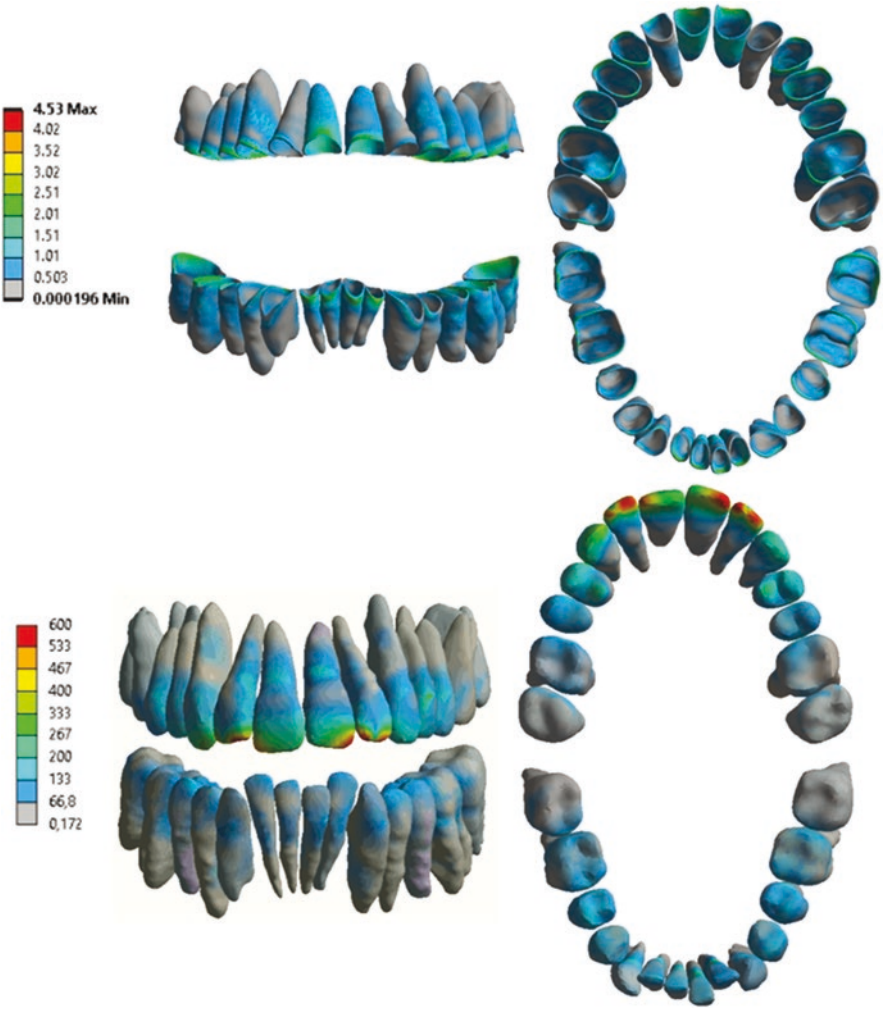

Fig. 12.16 Stresses caused by orthopnea

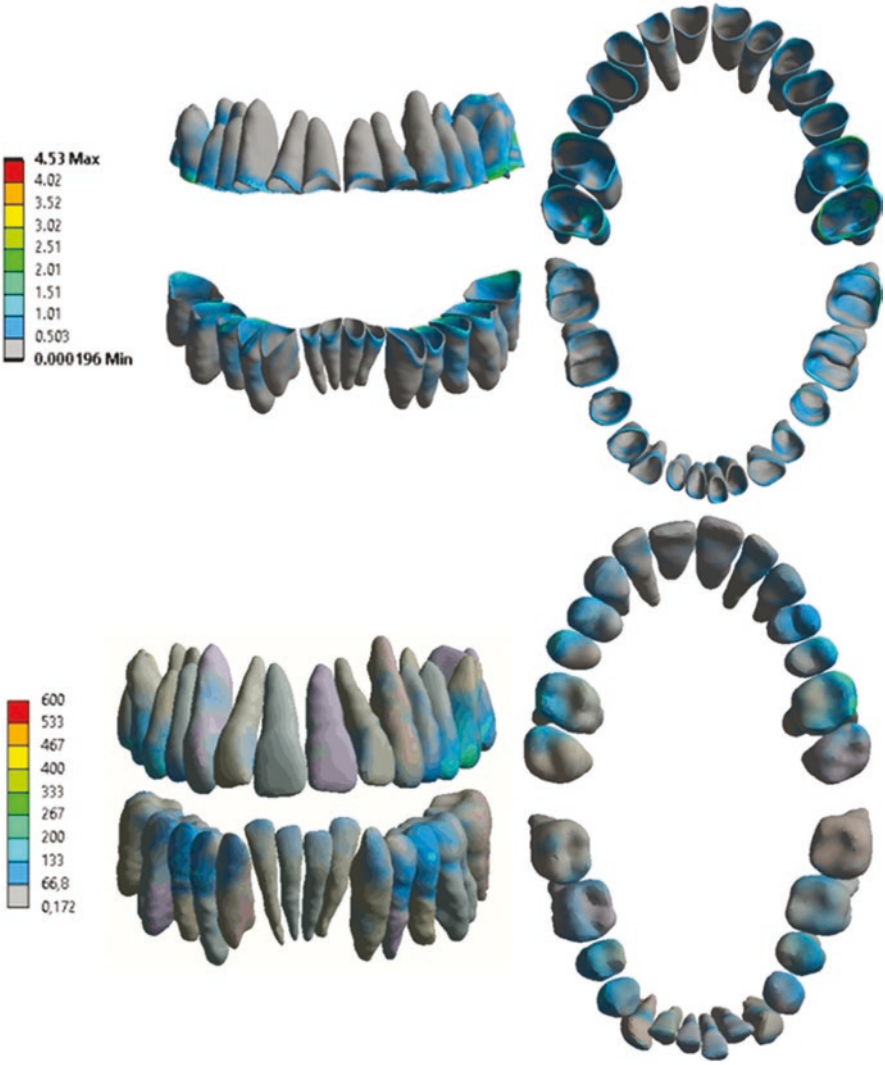

Fig. 12.17 Stresses caused by telescopic/herbst

Aleta Dorsal/Somnodent Flex® exhibited very similar behavior, presenting the absolute least lower stresses (maximum values of 3.27 kPa on the ligaments and 287 kPa on the teeth) that concentrated on the lateral sectors (Fig. 12.18).

Somnodent Avant® is the device that presented the most significant stresses with intermediate distribution between OrthoApnea Classic® and devices with bilateral propulsion mechanisms. The maximum stress values were 4.53 kPa on the periodontal ligaments and 467 kPa on the tooth surfaces; the stress distribution was prevalent on the lower molars and in the upper anterior sector (Fig. 12.19).

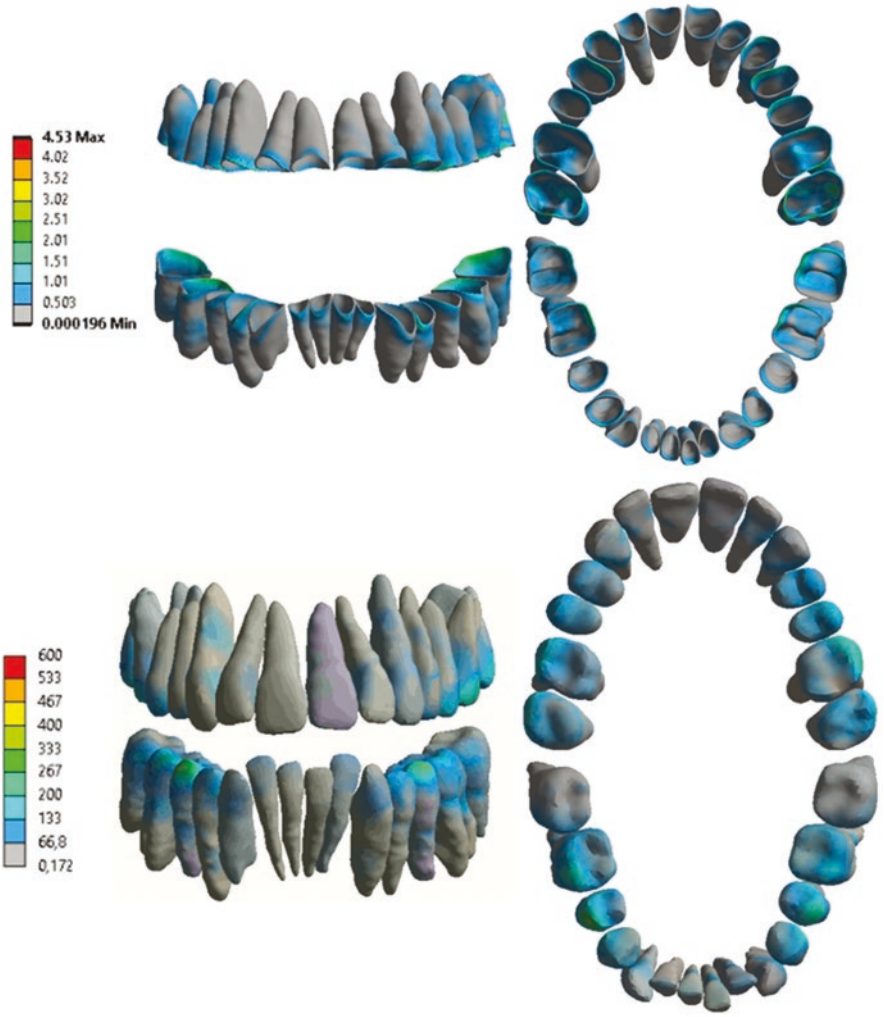

Fig. 12.18 Stresses caused by Aleta Dorsal/Somnodent Flex

The study also analyzed the deformations to which the teeth are subject during the use of MAD, using vectors that indicate the direction of movement and the value expressed in millimeters. The model showed a right-side view, but the left side is considered symmetrical. The forces tend to move the upper jaw teeth downward and backward when considering the anterior teeth in all four devices. Conversely, the deformations of the posterior teeth were directed backward and upward. Regarding the lower arch teeth, there is a displacement oriented forward.

The images obtained do not reproduce the exact advancement of the devices but are examples of the tooth movement that derives from the activation forces of the MAD (Fig. 12.20).

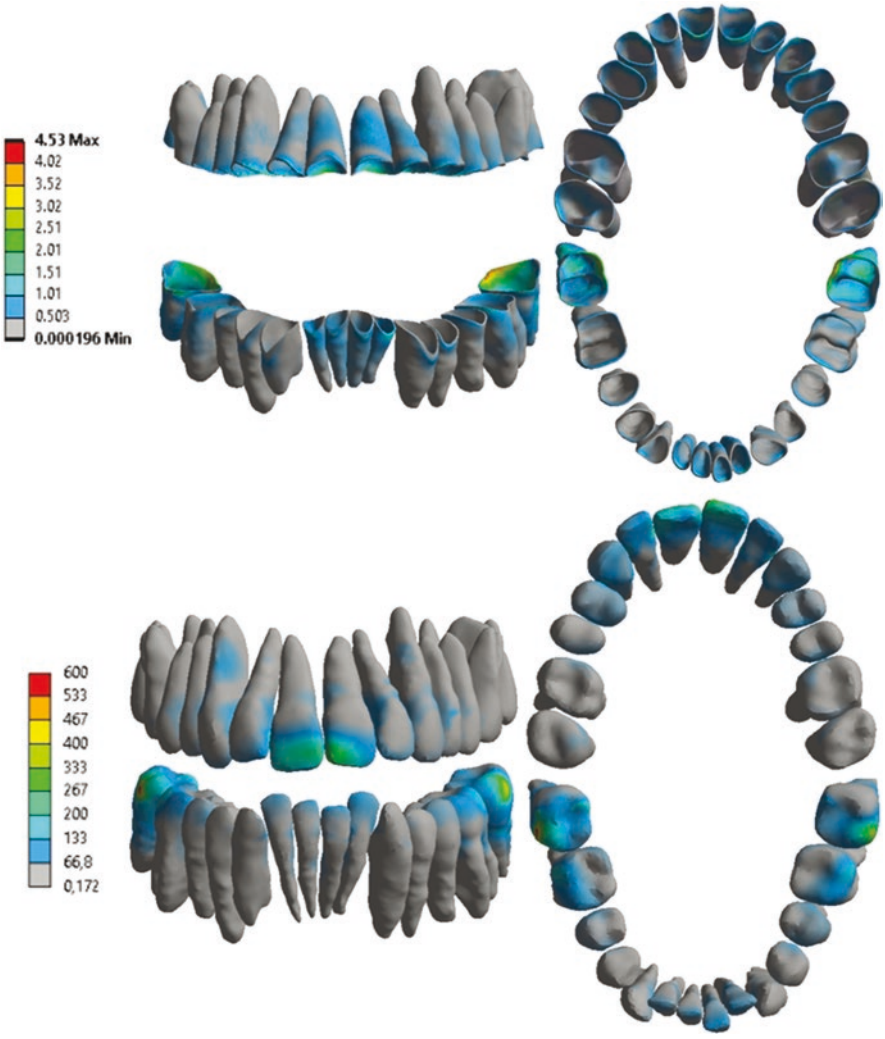

Fig. 12.19 Stresses caused by Somnodent Avant®

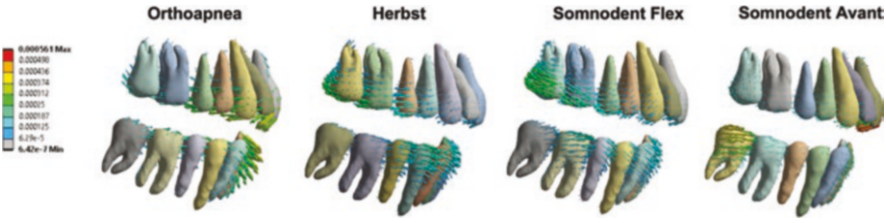

Fig. 12.20 Examples of the tooth movement that derives from the activation forces of the MAD

The devices that generate the most significant displacements were OrthoApnea Classic® and Somnodent Avant®. The deformity mainly concentrated at the incisal level.

According to the authors, the different distribution of tensions was explained by the various operating mechanisms: OrthoApnea Classic® uses a reverse front connecting rod that enhanced stress. Herbst and Somnodent Flex® exploit a bilateral propulsion mechanism despite being of different designs (telescopic arm for Herbst and advance screw for Somnodent Flex®). This explained the lateral stress distribution at the points of application of the propulsion forces. Somnodent Avant® has an intermediate behavior between OrthoApnea Classic® and Herbst/Somnodent Flex®: its propulsion mechanism is based on a string that connects from the molar portion of the lower splint to the anterior part of the upper splint; in this case, the forces are concentrated in the areas on which the feed mechanism acts. Since there is a single pin on which the string is anchored below, the point stress values are the greatest ever; in general, however, it can be assumed to be intermediate between an anterior activation device such as OrthoApnea Classic® and bilateral propulsion devices.

OrthoApnea Classic® and Somnodent Avant® are the devices that generate more stress at the anterior level: this derives from the fact that the splints are connected, unlike Somnodent Flex® which has two independent portions and generates the absolute lowest stresses.

The results of the analysis are in agreement with a previous study that compared the differences between Somnodent Flex® and TAP®, which is a device with a completely similar design to OrthoApnea Classic®: it is reported that TAP® generates more significant occlusal changes, in response, therefore, to higher stress, compared to Somnodent [104].

The clinician needs to consider the effects that MAD cause at the periodontal level, choosing the device that best suits the individual patient.

To summarize, devices with activation with an anterior connecting rod generate more concentrated and quantitatively significant stresses in the anterior areas of the teeth. In contrast, devices with lateral activation cause less intense and more distributed stress.

12.6 The Relationship Between Obstructive Sleep Apnea and Temporomandibular Disorders

Temporomandibular disorders (TMDs) are a heterogeneous group of musculoskeletal disorders in the masticatory system that represents chronic orofacial pain's most common cause. Prevalence of TMDs has been estimated between 5% and 12%, with higher rates among women [104, 105].

Different biomechanical, neurobiological, neuromuscular, and biopsychosocial factors may contribute to the presence of TMD. The main risk factors include age, genetic factors, sex, stress, anxiety, malocclusion, poor posture, rheumatoid or other systemic arthritis, and breathing sleep-related disorders. TMD develops at a markedly higher rate in individuals with relatively poorer health status, in conjunction

with the presence of other painful conditions, comorbid diseases, smoking, and poor sleep quality [106–108].

One plausible risk factor for TMD is the presence of sleep-disordered breathing (SDB). A preliminary report suggested that around 75% of patients diagnosed with TMD have clinical characteristics suggestive of SDB, and this last contributes to the presence of sleep bruxism, a classically considered an etiologic factor for the development of TMD [109–112].

In the OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) study, which followed subjects for 4–6 years, the signs/symptoms of OSA were associated with a higher risk of incidence of TMD. This large-scale prospective cohort study, a multicenter study, followed adults age 18–44 years at enrollment for 2.8 years. The goal was to identify the incidence of first-onset TMD and potential risk factors for TMD development. Initially, TMD-free adults with two or more signs/symptoms of OSA had a 73% greater incidence of first-onset TMD, in relative terms, than adults with fewer signs/symptoms independently of confounding demographic, autonomic, and behavioral characteristics [113, 114]. OPPERA subjects at risk for OSA had 1.7 times TMD incidence over the median 2.8-year follow-up period, independently of demographic, autonomic, and behavioral characteristics [110, 113, 115, 116].

Although the findings indicated a significant overlap between the OSA and TMD, further studies are required to define the nature of this relationship. Because both OSA and TMD are associated with several comorbidities, the association between OSA and TMD could be very complex [114].

We need consequently a large-scale cohort study that takes comorbidities into the analyses.

These OPPERA studies lack OSA diagnosis through PSG which limits the interpretation of the results [110].

A recent case-control study found a higher prevalence of TMD in subjects at high risk of OSA (30.7%) than with subjects at no risk of suffering OSA (18.5%). However, the study may be skewed as many participants were classified as having OSA by a sign or symptom questionnaire and may have milder forms of SDB such as upper airway resistance syndrome (UARS) [110, 117].

Smith et al. demonstrated in their study that a great majority of their patients with TMD complaints were diagnosed with at least one sleep disorder through a PSG study. Insomnia (36%) and OSA (28.6%) showed the highest frequencies. Sleep bruxism was also a comorbid sleep disorder in this TMD sample, although the frequencies varied from 75% to 17%, dependent of the clinical vs. PSG criteria for the diagnosis of SB. Surprisingly about 43% of the sample were diagnosed with more than just one sleep disturbance [118].

Several mechanisms might be underlying the close relationship between OSA and TMD [119].

1. Disrupted or inadequate sleep in OSA patients might enhance pain sensitivity, contributing to hyperalgesia, an important feature found in many TMD patients [120, 121].

2. OSA patients usually display chronic intermittent hypoxemia, which raises circulant inflammatory cytokines levels, contributing to the pathogenesis of multiple comorbidities presented with OSA.

   These inflammatory cytokines have also been reported in TMD. Therefore, OSA might contribute to the pathogenesis of TMD by enhancing systemic inflammation. Therefore, it is not surprising that OSA patients have higher TMD incidence [122, 123].
3. Malocclusion and other craniofacial abnormalities may induce the upper airway collapse during sleep. This is the reason why mandibular advancement appliances are suggested to treat OSA. In fact, accompanying OSA, there might be diverse craniofacial structure anomalies and/or muscle dysfunction predisposing to TMD development [124].

   Also, the co-occurrence of TMD and UARS has led investigators to postulate a TMD/UARS phenotype that develops during growth in response to disordered breathing during wakefulness [124].

   However, paradoxically mandibular-advancement intraoral appliances to treat or manage OSA may also cause TMD or increase its risk.
4. TMD and sleep bruxism may concomitantly present in OSA patients. Bruxism episodes index (BEI) positively correlated with the AHI in patients with mild-to moderate OSA, whereas patients with severe OSA had lower BMI than those with mild-to-moderate OSA [125–130].

   This relationship between OSA and bruxism has been previously discussed in this chapter.

Patients referred for OSA treatment also present to the clinic with signs and symptoms of TMD. This is a solid clinical feature for deciding what problem should be addressed first or if we can treat both simultaneously [131].

Cunali et al. reported a group of patients diagnosed with mild to moderate OSA referred for oral appliance therapy. Nearly 52% of the patients presented TMD, with a high prevalence of pain in OSA patients [132].

Since the development of TMD has also been reported after the treatment of OSA with oral appliance therapy, it is crucial to detect the presence of previous TMD in the patients referred for OSA treatment [131].

As with other forms of treatment, the use of MADs is not exempt from side effects. While relatively common, most of the side effects associated with MADs tend to be relatively minor and transient and do not usually prohibit the use of the appliances.

These have been mentioned above [132, 133].

It has been hypothesized that by inducing forward and downward position of the mandible, MAD can impact clinical signs of TMD and objective perception of them [132–134].

The most common temporomandibular joint-related side effects are:

- Transient morning jaw pain.
- Persistent temporomandibular joint pain.
- Tenderness in muscles of mastication.
- Joint sounds.

Transient jaw pain includes pain or discomfort occurring in the morning upon oral appliance removal that disappears spontaneously during the day. Usually is mild, originating in muscles of mastication, and unlikely to cause OAT abandonment.

Persistent TMD pain is less frequent and usually occurs in OSA patients with previous TMD disorders, especially those or arthrogenic origin. However, the advancement effect of the MAD on the TMJ capsule and lateral pterygoid can aggravate this problem over time and can lead the patient to abandon the treatment. Palliative care with NSAIDs, isometric contraction and passive jaw stretching exercises, verifying, or correcting the midline position, decreasing the titration rate, decreasing the total amount of advancement, and conducting a comprehensive TMD evaluation and management are mandatory [132, 134–136].

Advancement of the mandibular position wearing the appliance may contribute to tenderness of mastication muscles. Management should be as in the previous scenario. However, symptoms persist a modification in the design of the appliance, physical therapy measures, or wearing a daytime appliance should be necessary [137, 138].

Lastly, the patient may develop joint sounds after treatment with MAD. These are usually transient and resolve with time. First-line treatment is watchful waiting. If the joint sounds are accompanied by persistent TMJ pain, temporary or permanent discontinuation of the oral appliance is needed. However, a precise diagnosis of the TMJ disorder should be made before taking that clinical decision [138, 139].

In summary, TMD can be a transient adverse effect associated with the use of MADs, particularly during the initial phases of treatment. Patients with prior signs and symptoms of TMD may experience a worsening of symptoms. For this reason, patients with OSA should be screened for TMD before the initiation of MAD therapy and during the subsequent follow-up appointments to prevent the discontinuation [140].

12.7 Highlights

- The odds of TMD are significantly greater in individuals at high risk for SDB supporting the idea of coexistence.
- Studies employing PSG for SDB and RDC-TMD find an increased prevalence of OSA or UARs in subjects with TMD supporting the idea of co-existence.
- OSA often precedes the first onset of TMD in initially TMD-free adults, supporting a relation of causality.
- Multiple hypotheses can explain an association between OSA and TMD, and how OSA might lead to TMD in susceptible individuals or might exacerbate the severity of previously existing TMD.
- All patients referred for OSA treatment should be screened for the presence of TMD.

- Patients with TMD should be screened for SDB and treated if present, of this life-threatening condition.
- Treatment of SDB is anecdotally reported to improve TMD in some patients.
- However, no clinical trials or controlled clinical studies have been conducted to determine whether treatment of SDB alters the natural course of existing TMD or its first occurrence in TMD-free patients.
- Prior treatment of TMD symptoms is often required before the initiation of OSA treatment to prevent TMD aggravation.
- TMD side effects from oral appliances are often transient and don't produce discontinuation of the treatment.

12.8 Orthognathic Surgery in Patients with OSA

Treatment for patients with obstructive sleep apnea (OSA) aims to prevent the collapse of the pharynx during sleep. There are several alternatives as a treatment. These range from noninvasive therapy with the use of CPAP (continuous positive air pressure device) to invasive surgical procedures that can modify the facial pattern of patients [141].

The goal of CPAP is to create a pneumatic stent in the airway during sleep to prevent obstruction and the resulting episodes of apnea and hypoxia; although it is the most reliable method to correct the collapse of the airways, it is far from being the most comfortable and ergonomic device during sleep, so the adherence to the use of these devices is very variable and decreases over the time, therefore the morbidity and mortality in those patients who do not adapt to its use is higher [141]. Patients who do not adapt to CPAP therapy have an absolute increase of 10% in the risk of mortality at 5 years, for which various surgical techniques have been described in an attempt to resolve the condition permanently [142].

Advances in surgical therapy have improved significantly since the description and understanding of the syndrome. The first invasive treatment described was the tracheotomy performed by Kuhlo for the treatment of upper airway obstruction in the "Pickwickian" subject [143].

Soft tissue surgical procedures to increase airway volume and/or space in patients who cannot tolerate CPAP have sometimes improved subjectively or just with a decrease in snoring during sleep, however, the actual rate of success for these procedures is relatively low and ranges from 40% to 60%, so patient acceptance of these results is highly questionable [144–146].

One of the soft tissue interventions for the treatment of upper airway obstruction in patients with sleep apnea described by Ikematsu and later popularized by Fujita is uvulopalatopharyngoplasty (UPPP) [147, 148]. There are several hypotheses for which there is a limited effectiveness of surgical interventions in soft tissues, it is due to the fact that there may be multiple anomalies in the entire extension of the pharynx which is not limited to one area, so it is essential to take into account the dimensions of the pharynx in terms of its average length that is 12–15 cm (14 cm in

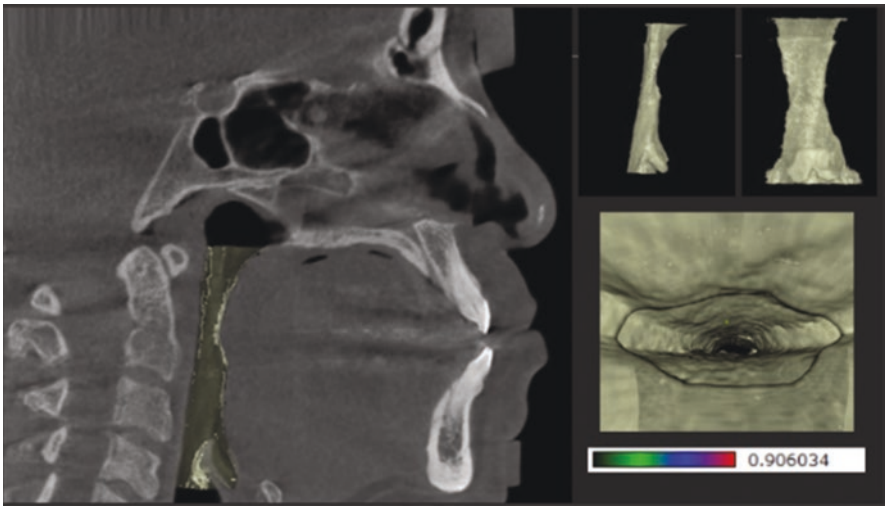

Fig. 12.21 Linear and volumetric airway measurement in cone bean tomography

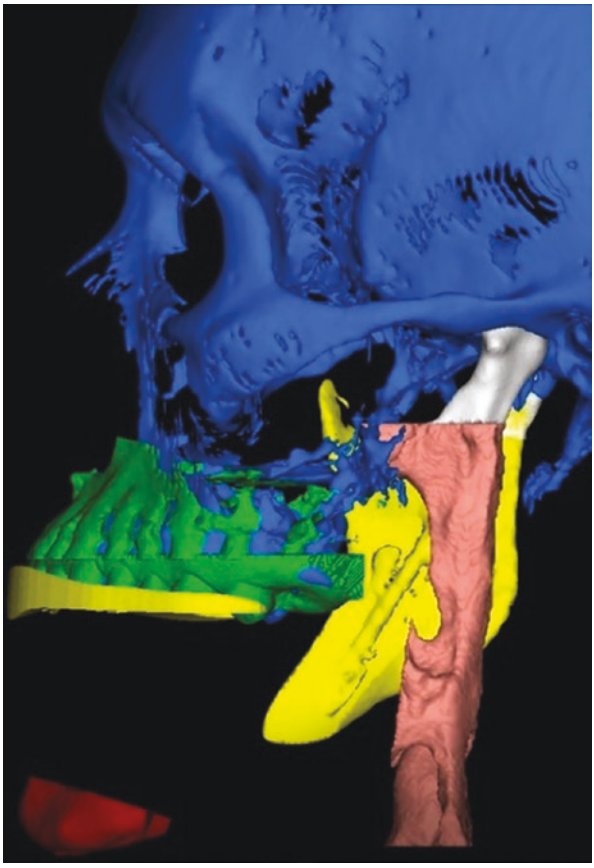

Fig. 12.22 Digital planning of orthognathic surgery, having the airway as reference

men and 13 cm in women), diameter in the transverse direction of 4–5 cm and in the anteroposterior direction of 2–3 cm, with a vertical extension from the base of the skull to the C6 level (corresponding to the cricoid cartilage), where it continues with the esophagus [149–151].

It is essential to remember the muscles involved in the permeability of the airway, one of the main ones is the genioglossus muscle, which is shaped like a triangle whose vertex is located behind the mental symphysis and its convex base corresponds to the dorsal aspect of the tongue this muscle contraction helps in stabilizing and lengthening the upper section of the tongue, maintaining its anterior location, thus allowing the patency of the airway to be maintained. During sleep, muscle fibers relaxes, causing posterior displacement of the tongue and obstruction in susceptible patients [152].

Advancement mentoplasty has been proposed as an alternative treatment. The intervention is based on an osteotomy of the mental symphysis to bring the genioglossus and geniohyoid muscles forward, causing an advancement of the tongue, avoiding obstruction of the upper airways in the hypopharynx during sleep [153].

The first publication of an intervention in the jaws for OSA treatment was made in 1984 by R. Riley, te. Guilleminault, *N. Powell, and tS. Derman. They described a 24-year-old male patient with OSA, daytime sleepiness, and nocturnal arrhythmias who had undergone palatopharyngoplasty surgery without significant improvement. A new surgical procedure was proposed combining an advance of the hyoid bone and a mandibular horizontal sliding osteotomy; Later, the same authors published a more extensive series of cases through the treatment of Maxillomandibular Advancement (MMA) in patients with severe OSA. They described a combined maxillary, mandibular, and hyoid advancement. They observed an objective improvement through PSG after 4–18 months of surgery t [154].

Maxillomandibular Advancement (MMA) described a surgical intervention has shown significant surgical success in OSA treatment. A preoperative surgical assessment should be performed when considering Maxillomandibular advancement surgery. It should include x-ray studies, orthopantomography, and lateral cephalometry to study craniofacial alterations, the facial biotype, and the probable site of airway obstruction. Obtaining a volumetric tomography may improve information, which we can navigate within the airways (Fig. 12.21). In addition, it is possible through computer programs to carry out preoperative surgical planning, providing a helpful guide and an accurate reconstruction of the bone structures so we can predict and plan the aesthetic and soft tissue changes obtained through the movements of the bone structures (Fig. 12.22).

This customization improves prediction and accuracy, allowing visible and precise relationships between the different soft tissue and bone structures.

We consider it crucial to obtain CAD-CAM models (Computer-Aided Design-Computer-Aided Manufacturing) to carry out the bone movements objectively and, if necessary, to confirm the plates or select the correct length of the screws to be placed (Fig. 12.23) [155, 156].

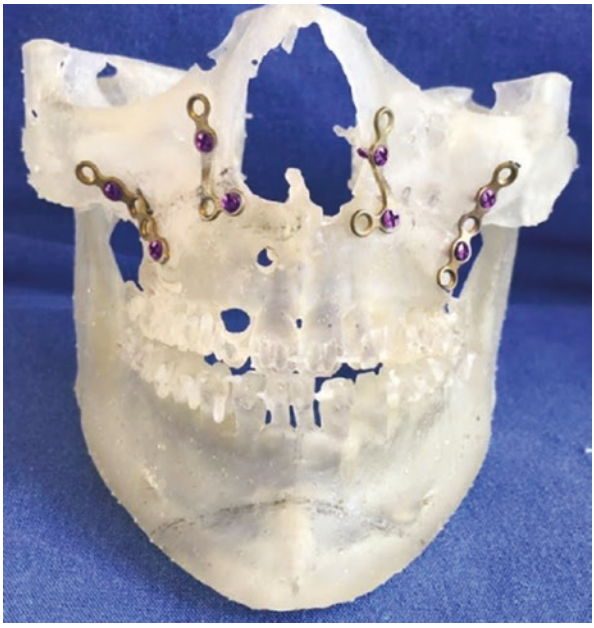

Fig. 12.23 Orthognathic surgery planning in stereolithography

The selection criteria for patients who are candidates for MMA are the following:

- Diagnosis of OSA by polysomnography.
- Site of obstruction determined by Mallampati classification, cephalometry, tomography, or ideally by drug-induced sedation endoscopy (DISE).
- Body mass index (BMI) less than 30 kg/m^2 (we consider it essential to reduce the BMI as much as possible to obtain stable long-term results since we must remember that the redundant soft tissue of the upper respiratory tract becomes lax over time due to natural aging).
- Age between 18 and 65 years.
- Adequate health status to undergo a surgical procedure.
- Intolerance to CPAP after a trial period of at least 3 months.

Maxillomandibular Advancement (MMA) should not be performed if patients have a systemic condition for which they cannot tolerate surgery or if there is an obstruction site at the level of the nasopharynx or hypopharynx [156].

For many physicians who work in OSA, the MMA is considered a very invasive procedure, and therefore, they indicate it as a last resort. We believe that patients who present dentofacial alterations such as mandibular retrognathia, maxillary hypoplasia, microgenia, or a combination of the above should be candidates for orthognathic surgery as the first choice [157].

Many patients with OSA present bone alterations that can be corrected using orthognathic surgery [157].

it is known that a poor development, mainly of the jaw, is associated with a lower volume of the airways [158].

On the other hand, Grauer et al. evaluated the shape and volume of the airway in subjects with different facial patterns and concluded that the volume and shape vary in patients with different anteroposterior relationships; however, when it comes to vertical relationships, only the shape varies. The class II pattern had the lowest oropharyngeal volume (VO) in this study, while class I and class III had similar values [159].

The goal of MMA is to increase posterior airway space (PAS) to decrease airway resistance and eliminate sites of airway collapse. In addition, MMA has decreased retropalatal air velocity and improved lateral pharyngeal wall collapse [160].

High success rates are reported [141, 143, 146, 154]. Most studies show a surgical success rate of approximately 80% and a cure rate of 30%–40% [161], with equivalent improvements in sleep quality to CPAP therapy.

The mechanism behind the improvement of OSA symptoms after MMA is complex and based on many factors, the primary means being the modification of the dimensions of the posterior airways [162–164].

Changes in preoperative and postoperative polysomnography measure the success of MMA in OSA. Surgical "cure" is defined as an apnea–hypopnea index (AHI) or Respiratory Impairment Index (RDI) of less than 5. In contrast, "success" is defined as a combined AHI/RDI of less than 10–20 and a decrease in IAH/RDI of 50% or more. The definition of surgical success varies between publications. However, the therapeutic success definition prevails [146].The success or cure, is ultimately achieved by advancing the bony structure of the face to change the associated soft tissues and airway dimensions [165–167] A large neck circumference has been suggested as negative factor for MMA success in patients with OSA [164].

Zaghi et al. [168] have described the preoperative severity of OSA to be the most reliable predictor of outcome. More specifically, the more severe cases of OSA tend to benefit more after MMA by lowering the AHI, but the cure rate was only 20% among patients with a preoperative AHI of >90 events/h. Patients with a preoperative AHI of <30 events/h showed cure in 56% and therefore showed a higher probability of success.

There seems to be a more important effect on the pharyngeal airway produced by mandibular advancement than at maxilla, due to the role played by the advancement of the skeletal insertions of the suprahyoid musculature. But, there is some disagreement on this issue of preponderance of an area [169].

A hot topic of controversy in OSA with MMA is the amount of surgical advancement required to achieve the desired effect in the posterior airway space. It has been suggested by Riley et al. that a 10 mm advancement showed a statistically significant improvement in the postoperative with confirmation by subsequent studies [168, 170].

However, there is still some disagreement, as some studies have not found statistically significant correlation between the amount of advancement and improvement in polysomnography results. A minimum advancement of 10 mm has not yet

been studied exclusively in patients with normal or class I malocclusion (neutroclusion) [171].

Regarding the amount of advancement, there is no specific amount in the literature necessary to obtain better results, Boyd et al. [172] in their study reported an advancement of 7 ± 2.3 in the maxilla and 9.2 ± 3.3 in the mandible, Vignono et al. reported 10.4 ± 4.3 in the maxilla and 12.9 ± 4.2 in the mandible, and Li et al. [173] a maxillomandibular advancement of 10.8 ± 2.7. This is close to the commonly accepted standard in most studies of achieving advances of approximately 10 mm.

Butterfield et al. [174] reported that maxillary, but not mandibular, advancement was significantly correlated with changes in IAH and SBP, while others reported a negative correlation between the magnitude of Le Fort advancement and changes in IAH [175].

Mareque et al. [176] proposed a protocol for surgical action in patients with an associated facial deformity, following a sequential pattern, depending on the location of the defect and the response to initial treatment as follows:

1. Class I patients with bimaxillary hypoplasia: Bimaxillary advancement.
2. Patients in class II and mandibular hypoplasia:
   (a) Accept orthodontic treatment. Mandibular advancement.
   (b) Not acceptance of orthodontic treatment:
      - No aesthetic compromise: Geniohyoid advancement through anterior mandibular osteotomy.
      - Aesthetic compromise: This study shows that jaw advancement surgery, particularly in the maxilla, does not continuously increase airway volume. There is essentially a plateau effect in maxillary advancement up to 7 mm; in all three regions, the airway increased in volume with maxillary advancement up to 7 mm of maxillary advancement. Beyond 7 mm of promotion, airway volume (whole airway or segmented airway regions) decreased despite further advancement. The most significant percentage change was seen in the nasopharynx but showed the most significant standard deviation [177].

In a cohort study of 62 patients who underwent maxillary advancement, two variables were associated with a successful or unsuccessful outcome: the first was age, which was higher in unsuccessful patients, and the second was circumference of the neck, which was greater in patients with treatment failure. Regarding age, a possible explanation for this could be the degeneration of muscle fibers in the pharyngeal airways, which gives greater relaxation and softness. The mechanism behind MMA is to widen the pharyngeal airway by gently stretching tissues, but with increasing age of the tissues, this mechanical effect maybe more susceptible to failure, associated with significant gravity and neck circumference [164].

Comparison of results of the procedures through different imaging studies is found. Orthognathic surgery offers great variability of treatment possibilities for the same problem. It is challenging for different surgeons to repeat the same surgical

procedure accurately. On the other hand, it is impossible to carry out an identical movement in different patients since each one has a very individual diagnosis and facial characteristics, requiring highly individualized treatment. Finally, there are inherent difficulties with volumetric measurements of the airway. Postural changes significantly modify pharyngeal dimensions. The natural position of the head is the standardized method proposed for performing cone-beam tomography; however, it is difficult to reproduce precisely. The control of breathing and the tongue's position during the examination is challenging to achieve, and not all researchers consider these variables [169]. Maxillomandibular advancement (MMA) is considered a safe and well-tolerated procedure by patients; Boyd et al. [172] reported as main adverse events that 40% of the patients presented long-standing paresthesia in the chin region and 13.8% of the patients perceived an unfavorable change in their facial aesthetics after treatment. No patient reported serious adverse events.

Camacho et al. [178] 2019 published a meta-analysis on the long-term results of MMA as a treatment for OSA. They analyzed 120 patients and concluded that patients maintained an improvement in AHI, sleepiness, and oxygen saturation. However, the average AHI may increase in the long term with some reports studying longer term effects (≥8 years). These have concluded excellent immediate results with an increase of AHI that varies between 11.3 and 40.6 events [179, 180]. Some factors that might influence this include redundant upper airway tissue that might become laxer over time, skeletal recurrence, and normal patient aging.

Zhou et al. (2020) [181], published a systematic review and meta-analysis comparing the efficacy of different surgical treatments based on MMA in adults with OSA, including 227 patients and eight other treatments. The treatments studied were:

- Traditional maxillomandibular advancement (MMA).
- Modified maxillary advancement (MMA and advancement mentoplasty).
- Maxillomandibular advancement with counterclockwise movement (MMACM).
- Maxillomandibular advancement and drug-induced sedation endoscopy (MMA + DISE).
- Maxillomandibular advancement and trans oral robotic surgery (MMA + TORS).
- Maxillomandibular advancement and uvulopalatopharyngoplasty (MMA + UPPP).
- Maxillomandibular advancement and uvulopalatopharyngoplasty with uvula preservation (MMA + UPFPUP).

Of these treatments, the one that offered the most significant improvement in terms of AHI, Oxygen Saturation, and Epworth Scale was maxillomandibular advancement with uvulopalatopharyngoplasty with uvula preservation (MMA + UPPPUP); however, analyzing isolated procedures, good results were seen in maxillomandibular advancement (MMMA) with counterclockwise maxillomandibular advancement (MMACM), offering benefit for patients with moderate to severe OSA [181].

These data contrast Camacho et al. [178] report that did not find improvement for performing a maxillomandibular advancement alone or combined with uvulopalatopharyngoplasty.

Whether or not to perform procedures on the soft palate (either UPPP or UPFPCPU) depends on the site of obstruction.

When the obstruction is in the hypopharyngeal area, the advantages of this procedure are limited, Bettega et al. [182] report that the success rates of these procedures are 40.8% in general and are reduced to 5% when there is a narrowing in the retrolingual space. Therefore, drug-induced sedation endoscopy (DISE) has become popular today since it allows for the establishment of the sites of obstruction with greater precision and, in this way, to plan the treatments that can offer the best results. However, the systematic review carried out by Zhou et al. [181] did not find a significant improvement in the therapeutic success of performing an MMA alone or previously with DISE, which is why it is considered a diagnostic tool rather than therapeutic success tool.

12.9 Conclusions

- Whenever the patient presents a skeletal discrepancy, MMA treatment should be considered as the first treatment option.
- The main criteria for a patient to be a candidate for orthognathic surgery are diagnosis of OSA by polysomnography, identification of the site of obstruction, (by tomography or DISE), and a BMI of less than 30.
- The goal of MMA is to increase posterior airway space while decreasing airway resistance and eliminating sites of collapse.
- Although considered by some health professionals to be an invasive treatment, MMA is a safe and effective alternative for the treatment of moderate to severe obstructive sleep apnea.
- The success rate of MMA in OSA treatment has been reported to be approximately 80% and a cure rate of 30%–40%.
- Within the different modalities of this procedure, the best results are the MMA with advancement mentoplasty and MMA with counterclockwise rotation.
- In some cases, MMA and uvulopalatopharyngoplasty with uvula preservation can offer superior results to MMA alone.
- Mainly when DISE previously verifies the site or sites of obstruction.
- More methodologically well-designed studies are required to verify the success of these treatments in the longer term to verify their stability over time.
- The dentist specializing in oral and maxillofacial surgery must be a part of the multidisciplinary teams that care for patients with OSA's and participate in the initial evaluation of patients and in maxillofacial surgical treatments when these are indicated.

12.10 Sleep Bruxism

There has been a lack of consolidated knowledge to several kinds of physiological and pathological motor occurrences within the orofacial and craniomandibular regions that have frequently led to a no man's land, with clear implications on the design of both diagnostic and therapeutic algorithms and decisions seriously impacting patients' outcomes. After brief description of the basic mechanisms subsidizing the circadian and sleep-related motor control, an updated definition of sleep bruxism is provided within this section, as well as the current proposed classification.

12.10.1 Circadian and Sleep-Related Motor Control

In humans, motor control is dictated by a complex, well-organized system linked to oscillatory components associated with a central biological clock [183]. A background muscle activity represents the circadian dynamics of such control during the day, which is progressively silenced during a typical No Rapid Eye Movement (NoREM) - Rapid Eye Movement (REM) sleep cycle usually occurring during nighttime [184]. The behavioral reduction in muscle activity during the nocturnal phase results from both circadian and homeostatic influences leading to a generalized inhibitory flow [185]. While this inhibition, which is evident mainly during REM sleep, is expected, periodic phasic motoneuronal excitations leading to brief movement moments do occur in the same physiological matrix [186]. Yet, abnormal/deviated patterns of motor inhibition, excitation, or both may also occur during sleep as a cause of recurring motor phenomena, eventually leading to sleep-related motor exacerbations [187]. Sleep bruxism is, in this context, a motor construct derived from sleep. Wakeful bruxism is commonly considered another construct which is arguably a less common circadian phenotype differing from the sleep variant in several ways. Yet, considering circadian phenotypes linked to bruxism may be more complex than simply separating according to the state of arousal from which it derives. In a recent study, our team showed that a circadian profile of bruxism manifestations might symmetrically occur during the day, eventually with different clinical impacts depending on the moment in which is mostly perceived [188]. One clear implication of such neglected circadian distribution is their temporal relationship with some daily routines. For example, Bruxism perceived near bedtime (awake bruxism), and during sleep (sleep bruxism) may interact with mechanisms generating the onset and maintenance of insomnia.

12.10.2 Defining Bruxism

Sleep bruxism (SB) involves exacerbated activation of the masticatory muscles, often resulting in a dynamic contact of teeth during sleep.

Three definitions of sleep bruxism have been provided by the American Academy of Sleep Medicine (AASM). The first one, in 1990, was inscribed in the ICSD within the parasomnias chapter, e.g., a disorder intruding on sleep but not associated with complaints of insomnia or excessive sleepiness, as a stereotyped movement disorder characterized by grinding or clenching of the teeth during sleep [189]. In 2005, the second edition of the ICSD integrated bruxism into the category of sleep-related movement disorders, defining it as an oral parafunctional activity characterized by a sleep-dependent tooth grinding or jaw clenching, usually associated with arousals [190].

However, several issues remained unsolved until 2013, when from a consensual meeting of experts, redefined bruxism as "a repetitive jaw muscle activity characterized by clenching or grinding of the teeth and/or bracing or trusting of the mandible" [191]. The latest international consensus updated however the previous definition with the statement that SB is "a masticatory muscle activity during sleep that is characterized as rhythmic (phasic) or nonrhythmic (tonic) and not a movement disorder or a sleep disorder in otherwise healthy individuals" [192].

12.10.3 Epidemiological and Developmental Aspects of Sleep Bruxism

Bruxism has been studied from the epidemiological point of view in large populations. Although, methodological constraints are related to subjectively reported manifestations in most studies, both cross-sectional surveys and self-reports showed that SB affects 15%–40% of children and 8%–10% of adults [193–198].

Pediatric bruxism can start as soon as the first teeth erupt, and its prevalence rises until the age of 6, reaching about 30% [199], lowering its frequency in adults (12%) and advanced age (2%–4%) [194]. While there seems to be no difference in the proportion of males and females affected, bias regarding potentially etiological factors cannot be discarded.

12.10.4 Risk Factors, Comorbidities, and Genetics

Every condition tending to superficialize sleep may pull the trigger for motor activation and therefore predispose to bruxism. Consequently, it is not surprising that comorbid sleep disorders would be the main risk factors. Primary psychiatric and neurological disturbances may also account as essential contributors.

Although obstructive sleep apnea alone has shown to significantly increase SB risk, an increase in arousals and circadian misalignment as frequent comorbidities can also potentially trigger SB [200]. The co-occurrence of insomnia and sleep apnea is frequent among population, showing a misalignment of the circadian clock [201], in addition of sharing common pathophysiological pathways toward autonomic activation [201, 202]. Comorbid Insomnia and Sleep Apnea (COMISA) is also a putative contributor to such oromotor phenomena. As recently reported, SB is common in patients with COMISA [203] and therefore should be adequately assessed.

The reasoning behind the interaction between SB and OSA is not enterally understood and is still under debate. However, it was proposed a protective role of the motor events during respiratory-related arousals [204] which has not yet been confirmed [205].

Also, SB was proposed to be related substances intake. However, the cause–effect relationship is lacking for many of those pharmacological agents and therefore evidence supporting specific medications as risk factors for bruxism is low [206].

The relationship between SB and certain neurologic and psychiatric disorders has not been established although their co-occurrence is frequent.

In children, some parasomnias and sleep-related behavioral issues mostly derived from sleep-related dissociative states have been found to be prevalent in patients with SB [17]. Also, psychosocial stressors in children and adults are frequent among SB patients and exacerbated gastroesophageal reflux has been found in the same segment of ages [207].

There are also several tentative genetic-etiological contributors, such as the serotonin receptor encoding gene (HTR2A) and dopamine (DRD1) receptor gene, and several polymorphisms seem to affect SB or being involved in its development, pathogenesis, or its relationship with other sleep disorders [208].

12.10.5 Treatment

The therapeutic success in bruxism treatment will depend on the clinical approach taken; it is essential to adopt a new model from the perspective of the individual rather than the partial vision of the teeth and their alterations, which can offer answers about bruxism, understood as a dysfunctional muscular activity with neurobiological origins that explain it beyond its evident peripheral effect.

The approach to the treatment of bruxism has varied according to the etiological theories proposed in the past. Today, considering bruxism as a multifactorial parafunctional activity, treatment should be focused on etiological factors.

The therapeutic alternatives in the control of bruxism are independent for each case since multiple conditions can cause this entity: However, personality type, allergies, nutritional deficiencies, malocclusions, central nervous system disorders, drugs, deficiency in oral proprioception, and genetic factors are some of the causes for its development, so treatment should be focused mainly on the etiological factors. Although the trigger it is potentiated by certain emotional states such as anxiety and stress [209].

The functional evaluation of occlusion static and dynamic is of great importance because it depends on any treatment's success or failure. Although, we have multiple clinical studies, we still do not have sufficient scientific evidence for treating bruxism.

Different treatment modalities have been applied (behavioral techniques, intraoral devices, medications, and stimulation); however, a clinical evaluation is essential to differentiate between awake bruxism and sleep bruxism and rule out any

medical disorder or medication causing its presence (secondary bruxism). In some cases, an overnight sleep study is necessary.

Below we will mention some of the treatments most frequently used in traditional practice for the control of bruxism within the dental office [210].

12.11 Sleep Hygiene Measures

Modifying habits before sleeping and as relaxation techniques will be essential to contribute to the joint therapy of bruxism, being the first step in treatment.

The treatment for dental bruxism will depend on knowing what is causing this problem. The dentist must determine the potential cause with precise questions and a dental exam. Then, depending on the cause and the damage, the treatments applied to treat dental bruxism aim to reduce pain, prevent tooth wear, and permanent damage to the jaw. These therapies can reduce the habit of clenching and grinding the teeth, although they are often not a definitive solution. Splints are considered as the initial treatment for the control of bruxism. However, it has been clinically observed that the effects in the reduction of electromyographic events (EMG) of long-term bruxism are transient.

One study compared occlusal splints versus doses of a gabapentin drug and found that both treatments similarly reduced muscle activity associated with sleep bruxism after 2 months of therapy [211].

Traditional splints or dental protectors have been used to prevent dental bruxism during sleep. Splints can make the pain go away while worn and help prevent the damage this disorder can cause. However, they do not solve the problem since the inconvenience reappears if they are no longer used. There are different types of splints. Some fit on the lower teeth and others on the upper ones. These protectors are designed to keep the jaw in a more relaxed position.

Traditionally, splints or dental protectors have been used to prevent dental bruxism during sleep. Splints can make pain go away while they are worn and help prevent the damage this disorder can cause. However, they do not solve the problem since the inconvenience reappears if they are no longer used. There are different types of splints, some fit on the lower teeth and others on the upper ones. These protectors are designed to keep the jaw in a more relaxed position.

12.11.1 Drug Therapy

Some experimental studies have been carried out on the use of medications in patients with BS; however, more clinical research is still necessary for their use this therapy in bruxism.

Lobbezzo et al. [212] used levodopa in severe bruxers, comparing them with a placebo group. They observed a decrease in the number of sleep-related masticatory events. Mohamed's group [213] evaluated the use of amitriptyline in patients with sleep bruxism and symptoms of temporomandibular disorder. The study showed similar results, a decrease in masticatory events too.

Huynh N et al. [214], showed the effect of 2 sympatholytic drugs, propranolol, and clonidine, on sleep bruxism; the reduction of bruxism activity by 60% was observed, but with significant adverse effects such as dry mouth, morning hypotension, and suppression of REM sleep. Saletu et al. observed that in patients with psychiatric and sleep comorbidities, clonazepam reduces bruxism and improves the general quality of sleep [215].

12.11.2 Botulinum Toxin

Botulinum toxin is one of the alternatives implemented for aesthetic use; it is used for various treatments, including bruxism, reducing muscle strength in the masseter, providing a reduction of bruxism events and activations in the brain during the night.

Bruxism has been evaluated with nocturnal polysomnography, showing a reduction of muscle contraction after 4 weeks, but without changes in the rhythm or number of bruxism episodes per hour of sleep [216]. Lee et al. found similar results after 8 weeks after application of botulinum toxin [217]. There is a need for more e scientific evidence for the use of botulinum toxin as an alternative treatment for bruxism.

12.12 Role of the Dental Professional in Drug-Induced Sleep Endoscopy (DISE)

Currently, the dentist's role during DISE (Fig. 12.24) is earning interest among our otolaryngologist colleagues who perform these procedures while the patient is under sedation.

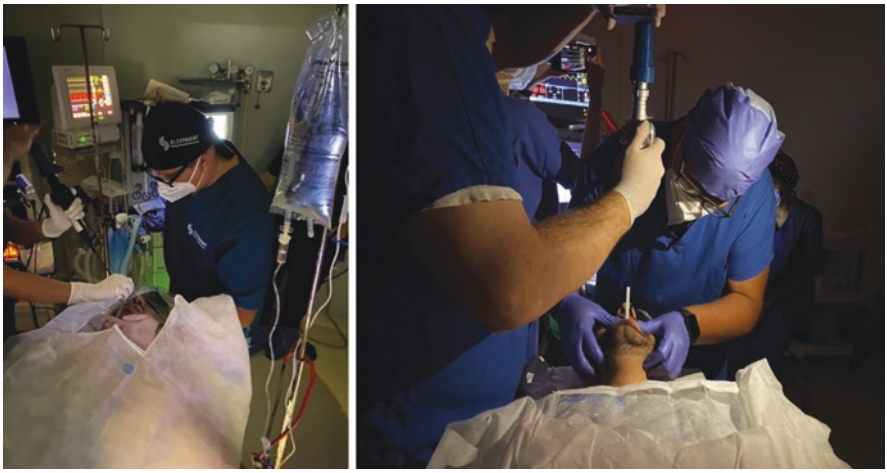

Fig. 12.24 Dentist maneuvers during DISE procedures

The dentist with training in dental sleep medicine can participate during DISE, trying to fit diverse appliances using vertical dimension and protrusion to assign the right tool to modify the airway.

It can also be combined with CPAP if it is eligible.

Several protocols are currently being developed for the role of the dentist during the DISE nowadays [218].

Take-Home Message

- Oral appliances have been described as an efficacious treatment for OSA. Studies have shown a decrease in the frequency and/or duration of Apneas, Hypopneas RERAS and/or snoring, as well as in improving nocturnal oxygenation, improvement of blood pressure, and quality of life. They may enhance CPAP adherence when used nightly.
- However, their use is limited by side effects.
- Temporomandibular disorders and Bruxism are related to Obstructive sleep apnea.

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Obstructive Sleep Apnea (OSA) and Gastroenterology

13

Carlos A. Cortez-Hernández and Jose C. Cessa-Zanatta

13.1 Obstructive Sleep Apnea (OSA) and Gastroenterology

Obstructive sleep apnea (OSA) is a disease with a high prevalence worldwide. High costs are needed for identifying the disease and for the treatment and care of associated conditions such as obesity and metabolic syndrome. The severity of sleep apnea and chronic intermittent hypoxia is thought to be the key trigger for inflammation that causes progression of nonalcoholic fatty liver disease (NAFLD). Colorectal cancer represents the third most common cancer in men, and the second in women, the hypoxia caused by OSA could be associated with the development and growth of colorectal tumors, and if this is confirmed in future studies, OSA could be considered an additional risk factor for starting screening programs at a younger age. Finally, the association with OSA and gastroesophageal reflux disease (GERD) can be associated with hormonal disorders observed in OSA, but more studies are needed before concluding that there is a solid relation between both diseases.

Obstructive sleep apnea (OSA) is a disorder with a very high prevalence all around the world, and it is associated with negative health outcomes. It is associated with many metabolic disorders, which include metabolic syndrome. In addition, it has been associated with nonalcoholic fatty liver disease (NAFLD) in adult and pediatric populations.

NAFLD is a disease with a very high prevalence in obese patients, affecting more than 70% of this population [1]. The first studies describing the association of OSA severity with the progression of NAFLD were published 20 years ago. To date, more than 20 studies in different populations have confirmed this association.

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The severity of sleep apnea and, specifically, its manifestation, chronic intermittent hypoxia (CIH), is the critical trigger for higher levels of stress oxidative and generation of reactive oxygen species (ROS), which cause the liberation of inflammatory cytokines, provoking systemic inflammation that causes exacerbation of NAFLD and progression to liver fibrosis. CIH results in reduced oxygen tension in the liver, specifically in the hepatocytes surrounding the central vein (zone 3), and causes the expression of hypoxia-inducible factors (HIFs), which are fundamental oxygen sensors that regulate the capacity of the cell to respond to a hypoxic environment. HIFs are implicated in developing hepatic steatosis, insulin resistance, and liver fibrosis, resulting in a fundamental link between OSA and NAFLD [2].

OSA severity and, specifically, its manifestation, chronic intermittent hypoxia (CIH), triggers high levels of oxidative stress and reactive oxygen species (ROS), which release inflammatory cytokines, producing systemic inflammation with exacerbation of NAFLD and progression to liver fibrosis. CIH results in reduced oxygen tension in the liver, specifically in the hepatocytes surrounding the central vein (zone 3), and causes hypoxia-inducible factors (HIFs), which are fundamental oxygen sensors that regulate the capacity of the cell to respond to a hypoxic environment. HIFs are implicated in the development of hepatic steatosis, insulin resistance, and liver fibrosis, resulting in a fundamental link in the association of OSA and NAFLD [2].

A French study of 1285 patients with OSA found a linear relationship between OSA severity and hepatic steatosis index [3].

Continuous positive airway pressure (CPAP) therapy has proved to prevent serious coronary events and reduce blood pressure [4]. In patients with OSA, treatment with CPAP in a chronic way diminishes mortality risk in the OSA population, but the effect of CPAP treatment on liver disease in patients with OSA is controversial [5].

The pathogenesis of NAFLD has not been fully elucidated, but a "Two-hit" model has been proposed as the mechanism underlying the pathogenesis of NAFLD. The insulin resistance and excess hepatic lipid accumulation due to the dysregulation of fatty acids cause the first hit, while oxidative stress and inflammation cause the second hit.

These mechanisms are suggested to be significant risk factors in the progression of NAFLD. OSA is consistently associated with some of these risk factors, including insulin resistance, dyslipidemia, visceral fat deposition, increased serum leptin levels, and low-grade inflammation. CPAP may positively affect the liver by interfering with these factors of the "Two-hit" model [6, 7] (Fig. 13.1).

Despite the "Two-hit" hypothesis being very popular and is often quoted, recent data show that it is not enough to explain the elaborated interaction of the multiple factors involved in the development of NASH. Some other factors and mechanisms that participate in the pathogenesis of NASH are included in the "Multiple-hit hypothesis" [8].

This hypothesis places insulin resistance as a key factor in the progression of nonalcoholic fatty liver disease (NAFLD) [9] because it causes a chain of reactions including higher peripheral lipolysis, with an increased flux of free fatty acids

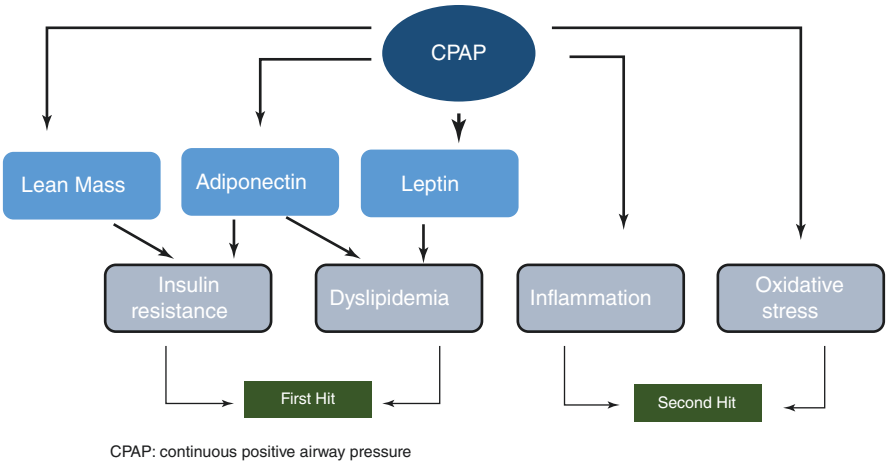

Fig. 13.1 Effect of CPAP on components of "two-hit." *CPAP* continuous positive airway pressure

(FFAs), and also more hepatic *de novo* lipogenesis (DNL). Insulin resistance also affects adipose tissue, causing altered secretion of adipokines and increased levels of inflammatory cytokines, interleukin (IL)-6, and tumor necrosis factor (TNF)-α. Alteration of gut microbiome causes high gut permeability, systemic levels of lipopolysaccharides, and absorption of FFAs [10].

All of these factors cause an increased flux of FFAs into the liver. This results in excess triglyceride (TG) deposition in the liver (hepatic steatosis) that parallels the generation of lipotoxic metabolites of FFAs. Further, these toxic metabolites cause mitochondrial dysfunction with increased oxidative stress, generation of ROS, and endoplasmic reticulum stress, which manifests in hepatocyte injury and inflammation.

As mentioned before, CIH is the most crucial trigger for increased oxidative stress, generation of ROS, and release of inflammatory cytokines, resulting in systemic inflammation that drives the exacerbation of NAFLD and progression to liver fibrosis.

CIH raises sympathetic activity and induces a state of insulin resistance. This promotes lipolysis in the adipose tissue and increased flux of FFAs in the liver. Under normal oxygenation conditions, FFAs are metabolized by oxygen-dependent mitochondrial combustion through β-oxidation. Hence, hypoxia creates a state of excess FFAs and their reduced utilization through mitochondrial β-oxidation. More FFAs become available for TG and cholesterol synthesis, resulting in fatty liver, liver injury through oxidative stress, and NASH. CIH has also been shown to selectively inactivate the adipose tissue lipoprotein lipase and reduce the very low density lipoproteins (VLDL) clearance from circulation. In summary, CIH can cause dyslipidemia by upregulating *de novo* lipogenesis (DNL) and lipoprotein secretion, reducing lipoprotein clearance, and enhancing peripheral lipolysis and influx of FFAs in the liver.

Also, obstructive sleep apnea is related to liver fibrosis. Stellate cells and portal fibroblasts are essential sources of fibrillar collagen and lysyl oxidase (LOX) enzymes in the normal liver and after early hepatic injury. Hypoxia is a potent stimulator of LOX activity, which plays an essential role in the covalent cross-linking of collagen and elastin, increasing liver stiffness. This increased stiffness causes increased mechanical tension that is crucial for the differentiation of hepatic stellate cells and portal fibroblasts into myofibroblasts, which are responsible for the deposition of extracellular collagen and, eventually, the development of fibrosis. Mesarwi and colleagues have recently demonstrated that serum LOX is elevated in patients with NAFLD-associated hepatic fibrosis relative to those without fibrosis [11]. These same investigators also proposed the potential role of serum LOX as a biomarker of liver fibrosis in patients with severe obesity and OSA. HIF-1α has also been independently implicated in the development of liver fibrosis in a mouse model of NAFLD [12]. Hence, it can be concluded that hypoxia induces HIF-1α, which in turn causes the expression of the LOX enzyme and the subsequent development of fibrosis.

Given that CIH plays a vital role in mediation of NAFLD in OSA, treatment with CPAP would be expected to yield unequivocal benefits in NAFLD patients. However, the available studies have yielded mixed results.

13.2 Obstructive Sleep Apnea (OSA) and Colorectal Cancer

Colorectal cancer is the third most common cancer in men, and the second most common in women, accounting for almost 10% of all cancers in both groups [13]**.** Elevated rates of colorectal cancer in western countries suggest that lifestyle could play an essential role in the etiology of this disease [14].

Today, there is strong evidence that healthy habits like being physically active, consuming whole grains, and foods containing dietary fiber decrease the risk of colon cancer. In addition, consuming red meat, processed meat, or two or more alcoholic drinks per day, and being overweight or obese increase the risk of colorectal cancer [15]. Plus, low consumption of fruit and nonstarchy vegetables could be associated with an increased risk of colorectal cancer [16].

Less than 10% of colorectal cancer cases account for hereditary causes, like those with hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis. Most cases are related to sporadic colorectal cancer with genetic and environmental causes, emphasizing the importance of being aware of these risk factors and taking action to change them [17].

The studies to find the association between OSA and colorectal cancer are not easy because they have many confounding factors because most of these patients are obese, and obesity may contribute to the development of colorectal neoplasia.

The association between OSA and colorectal neoplasia remains unclear. But some studies have found an association between OSA and the development of colorectal neoplasia.

S. Lee and collaborators were the first to demonstrate that OSA was associated with colorectal cancer [18], and they attempted to eliminate the potential confounding effects of obesity by controlling BMI. They performed a retrospective study diagnosing OSA in patients who underwent overnight polysomnography (PSG) and compared the prevalence of colorectal neoplasia between patients with or without OSA according to the PSG results. For each patient with OSA, they matched one or two controls by age, BMI, sex, and smoking and did a screening colonoscopy for the first time. This study found an OR for detecting colorectal neoplasia in patients with OSA of 3.03 times greater than controls.

Another study by Yang-Chen and collaborators in Taiwan identified more than 4000 patients with a new diagnosis of OSA, and they were compared with more than 16,000 controls from a National database. They found that patients with OSA were associated with a significantly higher risk of colorectal cancer (HR 1.80; 95% CI, 1.28–2.52). This association was related to more frequent visits to the doctor [19].

Tumorigenesis has three stages: initiation, promotion, and progression [20, 21]. The first stage is initiated by DNA mutations that activate oncogenes and inactivate tumor suppressor genes. Tumor promotion involves the reproduction of the mutated cells. Inflammatory cytokines such as interleukins 1 and 6 and tumor necrosis factor α contribute to the growth of the tumor. However, the role of OSA in colorectal tumorigenesis remains obscure.

Abrams and colleagues suggest that hypoxia during OSA could be associated with the regression of tumors [22]. Hypoxia induces reactive oxygen species, which activates the NF-κB signal pathway that regulates various genes associated with colorectal tumor development and growth [23].

Therefore, further studies are needed to establish the mechanisms between OSA and colorectal cancer. At the same time, physicians should be aware of the association between OSA and the development of colorectal neoplasia and explain the need for colonoscopy to patients with OSA. The latter are eligible for colorectal cancer screening (Fig. 13.2).

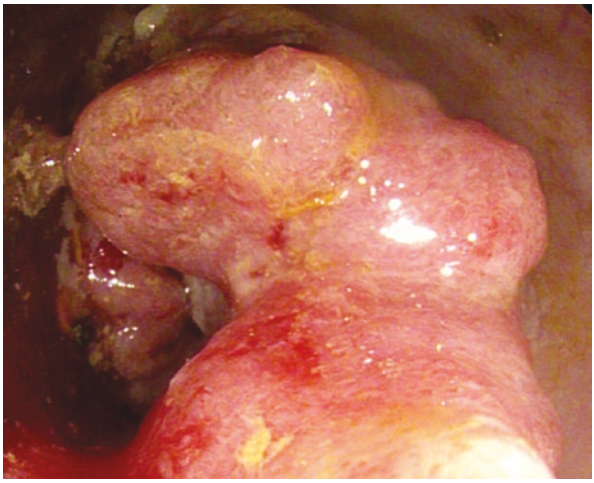

Fig. 13.2 Rectal adenocarcinoma as seen in colonoscopy

13.3 Obstructive Sleep Apnea (OSA) and GERD

GERD is a frequent disorder; one in five adults will have this disease in the United States. It is an entity essential to recognize because it can cause Barrett's esophagus and esophageal adenocarcinoma. Worldwide studies demonstrate obesity as a risk factor for GERD and esophageal adenocarcinoma [24].

Epidemiological studies demonstrated that obese people have a higher GERD prevalence compared to nonobese patients. Over more than 10,545 patients participating in the Nurses' Health Study were asked to fill a supplemental GERD questionnaire, which showed that weekly symptoms had a linear increase in the adjusted OR for reflux symptoms for each BMI group [25]. Similar results were obtained in a cross-sectional study with more than 80,000 patients [26].

Also the higher prevalence of erosive esophagitis in obese patients was demonstrated in a study by El-Serag et al. in which an endoscopy was made to 196 patients with weekly heartburn or regurgitation symptoms. They found esophageal erosions in 39% of overweight patients and in 41% of obese patients. This study concluded that obese participant (BMI > 30) had twice the chance of having esophageal erosions or reflux symptoms compared to nonobese participants (BMI < 25) [27]. Another study by Jacobson et al. showed that raising BMI by more than 3.5 kg/m^2 was associated with more frequent reflux symptoms, compared to no increase at all [25].

OSA is believed to be related to GERD, but evidence at the moment hasn't been conclusive. A meta-analysis performed [28] to identify the association between obstructive sleep apnea hypopnea syndrome and gastroesophageal reflux disease, analyzing a total of 2699 patients, found a significant relationship between obstructive sleep apnea syndrome and gastroesophageal reflux disease, with a pooled OR of 1.75 (95% CI 1.18–2.59, $p < 0.05$).

Hormonal disorders observed in OSA may be relevant to the development of GERD. A study performed by Pardak and collaborators [29] aimed to assess the correlations between ghrelin, obestatin, leptin, and GERD intensity in patients with OSA through a survey. This was performed relating symptoms of GERD, gastroscopy, and esophageal pH monitoring. They concluded that in patients with OSA, GERD was twice as common compared to the group without OSA. Among subjects with severe sleep apnea (apnea hypopnea index (AHI) > 30; $n = 31$; 53%), we observed lower ghrelin levels, especially in the second half of the night and in the morning ($p5.00 = 0.0207$; $p7.00 = 0.0344$); the presence of OSA did not affect obestatin and leptin levels.

Finally, Shepherd et al. compare reflux events day and night in obese and nonobese individuals with obstructive sleep apnea (OSA) and obese individuals without OSA. They found that BMI significantly predicted the number of acidic reflux events ($r^2 = 0.16$, $p = 0.01$) during the 24 hours, but OSA didn't show an association with GERD severity [30] (Fig. 13.3).

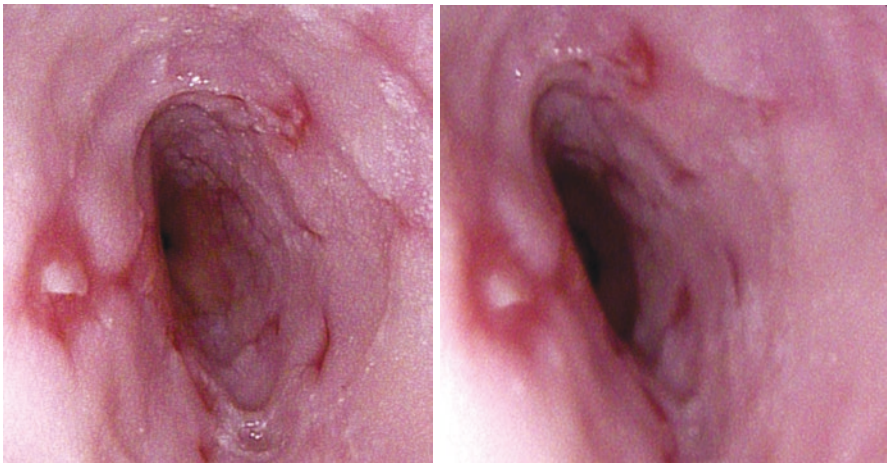

Fig. 13.3 Los Angeles Grade B esophagitis as seen on superior endoscopy

Take-Home Message

- Obstructive sleep apnea (OSA) has been associated with nonalcoholic fatty liver disease (NAFLD) in adult and pediatric populations, liver fibrosis, and colorectal cancer. The mechanisms that produce these problems are multiple.
- OSA is believed to be related to GERD, but current evidence is inconclusive.

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Sleep-Disordered Breathing: An Expanding Spectrum for the Pulmonologist

14

Qanta A. A. Ahmed

14.1 Sleep Medicine as Clinical Frontier: Personal Perspectives

It is difficult to convey to those outside of the field of sleep medicine how even today, we are practicing at the nascent frontier of this extremely exciting field. Those of us practicing sleep medicine today have been directly trained and educated by the godfathers and pioneers of this discipline. While this is wondrous of its own accord, it also means that transitions within our field are dramatic and confront us rapidly. It also means that each of us as a sleep specialist has a role to play in the development and advancement of sleep medicine, most impactfully, from within our own clinical practice.

While I have come from a background of pulmonary disease and critical care medicine, I was first introduced to sleep medicine during my fellowship in New York in 1996 through 1999. Shortly after fellowship, I had the privilege of exploring the field more deeply with the Stanford School of Sleep Medicine, led by Dr. Sharon Keenan as a school distinct from Stanford University but where many Stanford University pioneers of sleep medicine would come to teach newly trained academic and clinical sleep specialists. Those classes left a deep impact on me and have defined my clinical practice since. Every day, I encounter the lack of knowledge about sleep, sleep disorders, healthy sleep, the biological need for sleep, and the

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impact of sleep loss and sleep disorders on both health and illness. Everyone involved in his field must develop an appetite for becoming an ambassador to both the public and our learned colleagues to advance awareness of what is the most important frontier impacting health, disease, and wellness and because of the relationship of sleep disorders with noncommunicable disease in terms of cardiovascular disease, diabetes, and obesity, also determines public health around the world.

It is therefore with this perspective that I bring you not my vantage from the pulmonology standpoint concerning obstructive sleep apnea syndrome but also the expanding spectrum of disorders we encounter and the increased amount of expertise beyond the traditional range of breathing abnormalities during sleep that a true sleep specialist in the pulmonary office must respond to.

14.2 Timeline of the Discipline

Until 1972, when Stanford University declared the study of clinical sleep medicine a new field and opened the first sleep clinic in the world, our understanding of illness and health had been confined to the waking patient over centuries of medical study and practice. Sleep medicine had been the purview of esoteric researchers working in isolated research labs. Onlookers were not clear as to how this field of exploration would ever lend value to the lives of patients. A mere 20 years after REM sleep was first identified in 1953 (and named) by then medical student William Dement [1] who would go on to become the founding father of modern sleep medicine, clinical sleep medicine opened enquiry of both clinical physiology and pathology of the sleeping patient, creating new frontiers in the understanding of disease. In 1973, in Italy, Dr. Elio Lugaressi [2] identified heavy snorers disease reporting the first series of what would become the world's first cohort of obstructive sleep apnea patients demonstrating excessive daytime sleepiness obesity and snoring. Less than a decade later, in Australia, Dr. Colin Sullivan [3] would patent the first prototype for continuous positive airway pressure manufacturing each facemask manually and connecting it to device that was essentially a reversed vacuum cleaner treating over 300 patients in this manner beginning in 1981. Within 10 years of that I had graduated medical school and 15 years later, I was treating sleep-disordered patients. A decade into my practice as a sleep specialist I referred a patient to receive one of the first upper airway nerve stimulators for treatment of obstructive sleep apnea syndrome. And less than 5 years later, during this global pandemic, my patients are now being regularly implanted with intelligent nerve stimulators to treat central sleep apnea with transvenous phrenic nerve stimulation. This kind of proximity to the origin of my field makes it extremely exciting to meet patients every day, diagnose, and then treat them—so many of them have been reporting symptoms to an array of clinicians before the clinical constellation can be recognized by a seasoned, interested sleep specialist. I therefore underline that anybody that is in his field can exercise an astonishing impact on the surrounding community not only of the patients entrusted to our care but also on our clinical colleagues and the very practice of our clinical discipline.

While collective focus has been primarily on the physiology, circadian biology and mechanisms of both normal sleep and primary sleep disorders themselves, insights into the impact of systemic disease on sleep and vice versa are only beginning to come into view. Those discoveries have been discussed in chapters elsewhere. This chapter will focus not only on the presentation of obstructive sleep apnea syndrome to the pulmonologist in the setting of lung disease, but the related and unrelated diagnoses that may incidentally appear in our clinical practice. Very important is the recognition of the spectrum of sleep breathing disorders beyond obstructive sleep apnea syndrome and the critically important need to distinguish obstructive sleep apnea from central sleep apnea which today is being clarified as novel and cutting-edge technology becomes accessible.

Sleep disorders specialists within pulmonary medicine will encounter diverse patient populations in both adult and pediatric practice. It is very important that we treat both the adult patient that may initially present to us while we additionally perform a comprehensive family history to identify children and younger relatives who may at the moment not be seeking attention. Treating entire families of patients is not uncommon in my practice and I believe a hallmark of good practice while our field of professionals remains so small.

Sleep disorders are present in a number of systemic conditions that will be discussed in other chapters but will almost always be at play within the pulmonary patient population. It is insufficient for the sleep specialist to know and recognize only the sleep disorder. It is imperative the seasoned sleep specialist understand the impact and interaction of the sleep disorder on the systemic disease. Equally, it is important for the sleep specialist to understand the impact of the systemic disorder on sleep architecture and sleep itself. This is seen very commonly for instance in the coexistence of obstructive sleep apnea with chronic lung disease.

Above all a true sleep specialist must become deeply expert in all aspects of the field of sleep medicine in order to inform the broader medical community, assist medical colleagues devoted in a discipline to recognize the nuances and manifestations of sleep loss, sleep disorders, circadian rhythm disorders, insufficient sleep hygiene, insufficient sleep syndrome, and many other challenges as to how they impact the patients within their care. Sleep disorders often cluster within families, as do poor habits of sleep. We must care about both challenges. Every time we educate even one of our colleagues, the impact on their patient population will be enormous and raising awareness both of the nature of sleep disorders and the impact on specific populations is an enormous public service which I urge you to always keep in mind.

I would also like to underline that here in the United States, sleep medicine is dominated by subspecialists in pulmonary disease and this is not always to the betterment of the field. With most sleep centers in America being managed and directed by pulmonologists, there is a tremendous emphasis and bias toward identifying the most common sleep disorders which relate to obstructive sleep apnea syndrome at the expense of neglecting many other sleep disorders which have tremendous comorbidities associated with them. As we will see in the second part of this chapter one of the most overlooked disorders of breathing and sleep is central sleep apnea

syndrome and we must work hard to help those patients be recognized and reach definitive treatment. Additionally, also because the field in the United States is led by pulmonologists, this has resulted in a domination of therapy despite alternatives by positive airway pressure, sometimes at the expense of other extremely well-indicated treatments, surgeries and devices which are not offered to patients including oral appliance therapy of the mandibular advancement type, upper airway nerve stimulation and targeted oral maxillofacial surgery. It is imperative that every serious sleep specialist that is deeply invested in the field and her patients cultivate a multidisciplinary practice incorporating expertise relating to the upper airway outside of the pulmonologists range but incorporating our head and neck otolaryngology colleagues, our dental sleep medicine colleagues, our EP cardiology colleagues who can place transvenous phrenic nerve stimulation and many other parallel disciplines.

I recognize this is not the mainstream view at the moment in the United States, but it certainly is the future of this field. If pulmonologists fail to recognize these shifts and treatment options in an environment of an increasingly educated patient populace and policymakers, they will lose their domination of the clinical discipline and that may not be a bad thing for patient care.

14.3 Sleep Is a Biological Necessity, Not an Expendable Luxury

This is the first maxim I teach every patient, every family member of every patient and every fellow training in my discipline. In the modern world, a culture of sleep loss is admired cultivated and emulated. This has disastrous effects and true metabolic impacts. Sleep loss must be identified as a physiologic stressor and while it is difficult to address in our contemporary culture of "sleep machismo" it is the first lesson toward diagnosis and treatment for every person presenting with a sleep complaints. The United States, Japan, and Western Europe even in the twenty-first century continue to see sleep as an expandable luxury rather than a biological necessity. Japan is the first place where a word "karoshi" identifies death through lack of sleep as occurred at a Toyota manufacturing plant and was first categorized as an industrial injury in 2001 [4].

Rechtschaffen's investigations [5] are among the first and most emphatic confirming that sleep is a biological necessity and that sleep deprivation, whether total or chronic partial deprivation, posed a serious risk for basic metabolic function. Bacterial invasion and gastrointestinal erosions seen in the rats prior to death mimic the findings of many critically ill patients in intensive care units—environments notorious for sleep deprivation—who go on to die of sepsis and multiorgan failure.

Even more prevalent is the role of sleep deprivation in hyperphagia, blunted satiety signals, and resulting weight gain which is undoubtedly a major driver in the obesity pandemic we find here in the United States. Additionally, we have seen acutely and painfully in the recent COVID-19 global pandemic that impacted the

United States so severely as to how obesity strongly drives vulnerabilities in adaptive and innate immunity responses to SARS Cov2 and is responsible for a component of the very high death rate we saw here in the United States [6]. Sadly, despite decades of escalating national obesity rates the role of sleep loss driving obesity and metabolic syndrome, the role of sleep-disordered breathing also driving obesity and metabolic syndrome remains severely unrecognized and still unacknowledged in our emerging post pandemic era.

14.4 Sleep Deprivation Poses Enormous Public Health Burden

Sleep loss is more prevalent and increasingly recognized. Some experts noting its catastrophic impact on some of the most notorious public health disasters in living memory, and its role in driving non communicable disease.

Consequences of sleep loss can be physiologically catastrophic for both the individual and society. Notorious public health disasters have been caused by sleep deprivation. The Exxon Valdez oil spill (often wrongly attributed to the inebriation of the ship's captain) was due to the sleep-deprived shipmate who assumed control of the doomed vessel. The shipmate had been working for over 36 h before he assumed control of the oil tanker that would lead to the world's most devastating oil spill in history.

The Chernobyl explosion in the Ukrainian city of Pripyat killed hundreds of people directly and indirectly in the worst nuclear power plant in history due to worker error caused by sleep loss.

Three Mile Island Plant Unit 2 Reactor in Pennsylvania, shift-workers on duty failed to recognize and react to the lack of core coolant which had been obstructed by a defective valve. While the mechanical problem of a dysfunctional valve was to blame for the near meltdown, Mitler and colleagues determined it was worker fatigue and sleep loss which resulted in the human error.

Much more common than meltdowns in nuclear reactors are motor vehicle accidents. The busy pulmonologist will often encounter people who present to the sleep specialist either mandated by the Department of Motor Vehicles and the police or so frightened by the experience that they finally come to seek attention with a sleep specialist [7]. Every sleep patient that comes to see me in my practice will leave educated about driving and sleep. This is where a sleep specialist can have a tremendous public health impact and each visit documents the driving sleep education provided to the patient.

We examine the impact of sleep disorders and sleep deprivation in the commercial driver—and by extension all drivers—later in this chapter. The high prevalence of driving in the United States sleepy driving poses a tremendous public health burden: the National Transportation Safety Board (NTSB) estimates more than 100,000 motor vehicle accidents each year can be attributed to drowsiness at the wheel or "fatigue."

14.5 Sleep and Chronic Respiratory Disease

Sleep-disordered breathing (SDB) is a spectrum of breathing abnormalities confined to the sleeping state but with significant physiologic impact and profound waking impact. Recognition of obstructive sleep apnea syndrome—periodic airway collapse during sleep resulting in apnea—cessation of airflow—followed by recovery hyperpnea events causing EEG arousals and recurrent oxygen desaturation and reoxygenation—is now most widely recognized.

Both obstructive sleep apnea syndrome and chronic obstructive pulmonary disease noted Chronic Obstructive Pulmonary Disease (COPD) are very highly prevalent. Distinct clinical phenotypes of COPD influence the likelihood of coexistent OSA. Some experts believe that increased lung volumes and lower body mass associated with the predominant emphysema phenotype might protect against obstructive sleep apnea syndrome, but this does not account for craniofacial abnormalities which can predispose obstructive sleep apnea syndrome even in the lean patient. Certainly, a higher body mass which is often associated with the predominant chronic bronchitis phenotype may well strongly promote obstructive sleep apnea syndrome and complicate and already vulnerable patient during the breathing in sleep.

Always an awareness of obstructive sleep apnea syndrome in patients with COPD is necessary and requires clinical suspicion, screening questionnaires and careful clinical and anatomical evaluation to identify patients who would benefit from overnight polysomnography [9].

Managing the obstructive sleep apnea COPD overlap patient differs for managing COPD alone and survival of overlap patients who receive positive airway pressure during sleep is superior to those who would like to treatment. This makes the recognition even more important.

Patients with chronic respiratory disease report impaired sleep quality been measured to have reduced sleep efficiency. Reduction in dream sleep and this reduction correlate with oxygenation measured when they are awake with arterial oxygen tension but not with the degree of obstruction of airflow measured on pulmonary function testing. Some argue that reduction in REM sleep percentages could be protective from the exacerbation of OSAS which occurs during REM sleep. COPD patients with lung hyperinflation have been associated to report poor sleep quality. Using measures of quality-of-life sleep disturbance and COPD is measured in association with reducing quality of life suggesting that treating sleep disorders in this patient population will improve quality of life scores [10].

14.6 Pathophysiology of Sleep-Related Breathing Disorders in COPD

Respiratory mechanics and ventilatory control are disturbed during sleep in the COPD patient due to a number of factors. These disturbances in ventilation and gas exchange occur during sleep and are related to hypersensitive or accentuated

physiologic responses to the disease including alveolar hypoventilation which is negatively impacted by sleep in COPD resulting in worsening hypoxemia, reduced functional residual capacity, increased airway resistance and worsening VQ mismatch. Sleep also results in respiratory muscle hypotonia which gets worse in REM sleep. There is additionally a reduced respiratory drive during sleep and the upper airway is narrowed in sleep, all of which promotes negative impact on various aspects of respiration resulting in hypoxemia and the COPD patient's respiratory mechanics and ventilatory control are also disturbed during sleep due to several factors.

COPD patients are often hypoxemic during wakefulness, and the resting oxygen saturation levels tend to reside on the steeper portion of the oxygen–hemoglobin dissociation curve—during sleep, there will have disproportionately greater falls in oxygen saturation related to respiratory events in the major sleep episode. These patients desaturate dramatically, as we measured them in polysomnography. Additionally, they experience further VQ mismatch and reduced functional residual capacity because of emphysema (absolute loss of alveolar units available for gas exchange) and because of hyperinflation of the lungs and subsequent flattening of the diaphragm and that further worsens nocturnal hypoxemia in COPD.

14.7 Exaggerated Physiologic Hypoventilation Due to Central Respiratory Effects

In normal health the respiratory control system consists of a matrix of central and peripheral chemoreceptors and central nervous system respiratory rhythm generators interacting continuously in relation to the lung dynamics, chest wall expansion and arterial gas content to maintain tightly controlled oxygen and carbon dioxide tightly regulated between a narrow window. The system maintains a negative feedback loop. In wakefulness, normal breathing is impacted by both metabolic and behavioral stimuli. For instance, exercise-induced metabolic acidosis or diuretic-induced metabolic alkalosis alter $paCO_2$ due to altered CO_2 production and drive changes in respiratory rate, tidal volume, and (combined) the work of breathing. These changes in respiratory rate and effort are in response to feedback from peripheral and central chemoreceptors. Behaviors—stress—which can cause involuntary breath holding, speech, swallowing (all of which cause voluntary pauses in respiration) also modify respiration.

Sleep eliminates behavioral stimuli, leaving only metabolic stimuli to exert influence. Thresholds for control of respiration change from waking to sleeping state, and in fact, in normal healthy individuals with normal sleep parameters, ventilation become less rigorously controlled, tolerating a physiologic state of relative hypercapnia—in other words, the respiratory control responses to $paCO_2$ during healthy sleep are blunted to avoid excessive respiratory drive causing EEG arousals and eventually awakening from sleep.

Also during healthy sleep, in normal individuals, PCO_2 becomes the only stimulus driving respiration during sleep—an increase of PCO_2 driving respiration, a

decrease suppressing respiration. If $PaCO_2$ falls below a tightly regulated apneic threshold, respiration ceases entirely, and a central sleep apnea event prevails continuing until only a sufficient rise in $PaCO_2$ triggers a respiratory effort and resumes respiration.

COPD patients experience ventilatory control much like other normal individuals and we will return to this in the discussion on central sleep apnea syndrome. During all stages of sleep the respiratory center signals respiratory drive and response to chemical, i.e., chemoreceptor inputs which are blunted during sleep and respiratory muscle responses to the drivers for respiration are also reduced, particularly during REM sleep, exacting a marked impact on COPD patients who may be reliant on accessory muscles for respiration [11].

During REM sleep healthy individuals experience marked alveolar hypoventilation and ventilation maybe 40% lower than during wakefulness because of reduction in tidal volume and increase in upper airway resistance and reduced inspiratory drive centers so normal individuals will experience a fall in arterial oxygen saturation during REM sleep. In normal individuals this does not cause physiologic distress. The COPD patient will also experience these changes, but the physiologic hypoventilation is worsened, resulting in profound hypoxemia and patients—especially if they have respiratory insufficiency which is marked—have increased physiologic dead space, worsening of the alveolar hypoventilation with lower-than-normal tidal volumes during sleep—a perfect storm. The COPD patient therefore is already very vulnerable during sleep and vulnerable to a rise in CO_2 and falls in oxygen before any comorbid obstructive sleep apnea syndrome is considered.

Additionally, these patients experience much more light sleep stage N1 and light sleep stage N2, much more stage shifting—meaning that the sleep is markedly less consolidated than normal, and they tend to have more nocturnal awakenings and greater sleep fragmentation. If they do have comorbid obstructive sleep apnea syndrome it will be markedly worse during REM sleep, and therefore, the REM sleep also tends to be fractured interrupted and deficient.

14.8 Altered Airway Resistance and Respiratory Muscle Contractility

In normal sleep, upper airway resistance is increased compared to during wakefulness. This is related to the loss of muscle tone in the upper pharyngeal muscles and changes in the ventilator responses to hypoxemia and hypercapnia and probably contributes to hypoventilation. These changes also occur in COPD patients but the compensatory dilatory response of supraglottic airways which results in increases in CO_2 tension is significantly lower. COPD patients who lack the ability to respond properly to the lowering of the upper airway resistance that can make nighttime or sleep-related hypercapnia and hypoxemia worse are more compromised in sleep and will experience more work of breathing and more sleep-disordered breathing.

Additionally, because of circadian changes in airway dimensions which are normal, bronchoconstriction can become more exaggerated in the COPD patient, further worsening airway resistance in the lower areas of the tracheobronchial tree. Clinically significant bronchospasm ensues.

The sleeping state is also associated with hypertonia of skeletal muscle including the tongue, the pharynx, the larynx, and the intercostal muscles. There is a change in the relative contribution of the thoracic cage and the abdominal compartment to breathing and during REM sleep where we see muscle atonia in all striated muscle there is marked loss of tonic activity in the intercostal muscles which are imperative in the COPD patient dependent on accessory musculature for work of breathing. This loss of muscle tone is related to a supraspinal inhibition of gammon motor neurons and also some alpha motor neurons and additionally some presynaptic inhibition of afferent terminals from muscle spindles. Contrast this with the diaphragm that is driven almost entirely by alpha motoneurons and has many fewer spindles, and the intercostal muscles have little tonic or postural activity and thus escape the reduction of this kind of drive during REM sleep which is fortunate, allowing the primary muscle of respiration to continue functioning during the most perilous stage of sleep.

As the COPD patient enters REM sleep and loses or has a reduced accessory respiratory muscle activity, hypoventilation which is normal in healthy sleep, becomes markedly worse and especially so in the COPD patient who is very reliant on accessory muscle activity to maintain ventilation. This patient will develop CO_2 elevation, i.e., ventilatory failure during sleep.

In the advanced COPD patient with a diaphragm stretched related to lung hyperinflation, the diaphragm is less efficient at contracting and that will make the thoracic cage more reliant on accessory muscle contribution to breathing. Advanced COPD is associated with sarcopenia, skeletal muscle atrophy and dysfunction worsening the contribution of accessory muscles. Sleeping in the supine position or semirecumbent position further worsens diaphragmatic efficiency because abdominal contents counteract diaphragmatic contraction and with all of the muscles of respiration quiescent during REM sleep except the primary muscle of respiration the diaphragm that becomes so compromising to the COPD patient, we can expect to see paradoxical breathing and further hypoventilation. The COPD patient with advanced disease thus sleeps very poorly and will demonstrate profound sleep maintenance insomnia and daytime sleepiness.

If we now consider respiratory mechanics during sleep and COPD, as COPD progresses in severity, the mismatch between VQ relationships also worsens—the result of progressive airflow limitation and escalating emphysematous destruction of the pulmonary vascular bed which limits to the ability for gas exchange. A small but significant reduction in functional residual capacity also occurs during sleep related to the reduction in tonic muscle activity we described above and increase in airway resistance will make the VQ relationships worse in dependent lung zones while the patient is lying down, when small airways will become further closed and worsen gas exchange and ventilation relationships even more.

14.9 Sleep in the COPD Patient

Sleep quality is frequently impaired in these patients and contributes significantly to reports of daytime fatigue daytime sleepiness and reduction in quality of life is been reported by these patients when surveyed. Most COPD patients report disturbed sleep and report their COPD symptoms also disturbing their sleep. COPD patients report insomnia sleep onset insomnia, sleep maintenance insomnia nonrestorative sleep and increased reliance on hypnotic medications that themselves can sometimes suppress respiration. These patients been found to be sleepier than average in the daytime and furthermore the pulmonary symptoms in the form of nocturnal cough, nocturnal wheezing, also contribute to sleep fragmentation and sleep maintenance insomnia. As COPD becomes more severe sleep complaints escalate and will have profound pathophysiologic effects.

These patients tend to have very fragmented interrupted sleep with frequent arousals and awakenings reduced stage III sleep and reduced REM sleep. It has been reported that there is an association between degree of hyperinflation and reduction in sleep efficiency in patients with overlap syndrome independent of any coexisting obstructive sleep apnea or disease severity of any coexisting obstructive sleep apnea.

Quality of sleep in the COPD patients is not improved by adding supplemental oxygen and it is believed that higher levels of hypercarbia during sleep, i.e., nocturnal hypercapnia related to the alveolar hypoventilation that gets worse in these patients during sleep is a much stronger stimulant in provoking EEG arousals and awakenings. Also, because of the increased work of breathing related to the disadvantageous mechanics of the chest during sleep in the COPD patient, results in stimulation of mechanoreceptors in the chest wall and lower airways also fragmenting sleep.

This patient is often on medications including bronchodilators and medications like theophylline that can cause tachycardia and insomnia themselves. Cigarette smoke exposure results in EEG arousal in the active smoker COPD patient and even in those exposed to passive smoke including newborns were exposed to passive cigarette smoke develop insomnia. If the COPD patient has discontinued smoking, withdrawal from nicotine can also result in frequent EEG arousals, predominance of stage I sleep and a sensation of nonrestorative sleep.

Even though COPD is so well known, well recognized, readily diagnosed and has many treatment strategies, most pulmonologist are not considering the impact of sleep on the COPD patient and the impact of COPD on the sleep of the patient nor other considering comorbid obstructive sleep apnea in these patients. This is where pulmonologists with sleep medicine expertise can have an enormous impact [12].

14.10 Sleep in Pulmonary Overlap Syndromes (OVS)

Over 30 years ago, recognizing patients who have both had COPD and obstructive sleep apnea syndrome, David Flenley coined the term Overlap Syndrome. The term "pulmonary overlap syndrome" was first used in reference to only patients with comorbid COPD and obstructive sleep apnea syndrome, though now the definition

is extended to patients with comorbid obstructive sleep apnea syndrome and other chronic lung diseases including interstitial lung disease. A distinct definition remains lacking and the patient population with OVS remains diverse encompassing both chronic lung disease and obstructive sleep apnea syndrome of any severity, both of which span a broad spectrum. The current definitions of obstructive sleep apnea syndrome may be insufficiently rigorous for assessing obstructive sleep apnea in the setting of chronic hypoxemic lung disease particularly as obstructive sleep apnea syndrome is defined by specific desaturation criteria and distinguishing hypoxemia due to chronic lung disease from concurrent sleep-disordered breathing event may be difficult [13].

Basic interactions between COPD and OSAS are not completely understood including, for example, the full spectrum of effects of COPD on upper airway collapsibility.

Even so, the commonest diseases presenting in the office of the pulmonologist will be COPD, asthma, and obstructive sleep apnea syndrome and many of these patients will have coexisting disease.

Nocturnal hypoxemia is one of the most distinctive and important abnormalities measured in both COPD and obstructive sleep apnea syndrome. The overlap syndrome patient will have marked worsening of nocturnal hypoxemia than patients who have either one or other of the disease alone. It is the nocturnal hypoxemia that drives sympathetic nervous system activation which is the pathognomonic hallmark of sleep-disordered breathing and drives systemic and pulmonary increases in blood pressure, drives arrhythmias, and increases reactive oxygen species production and many other negative sequelae.

One of the profound frustrations of the sleep specialist is trying to quantify disease severity using the apnea-hypopnea index which would not necessarily account for the severity of desaturations seen in these patients even if events are rare. Fortunately investigators are searching for other surrogates to compensate for the known pitfalls of the AHI but until then we must consider the entire clinical picture. In patients with the overlap syndrome AHI use is a surrogate for obstructive sleep apnea syndrome severity seems to play a small role in the development of pulmonary hypertension compared to the extent of the severity of the COPD. Daytime hypoxemia hypercarbia and reduction in obstructive lung function will be more likely to be predictors of right heart failure and severity of AHI) This also related to the failure of AHI to distinguish longer duration events from shorter duration events, to provide equal weighting to apneas and hypopneas—probably not physiologically equivalent, and failure to distinguish hypoxic from nonhypoxic events.

While management of obstructive sleep apnea syndrome is recognized and discussed elsewhere in this book it is imperative to raise awareness of sleep-disordered breathing in these pulmonary patients who are already so compromised in pulmonary function. Overlap COPD patients who have obstructive sleep apnea carry greater mortality and obstructive sleep apnea syndrome patients who had coexistent COPD were also at an increased risk of death. Even when adjusting for disease severity of COPD presence of obstructive sleep apnea increases risk of death. Data showed that treatment with continuous positive airway pressure in this patient population reduces the added mortality risk and confers a survival benefit.

It is very important to diagnose obstructive sleep apnea in this compromised patient population with irreversibly progressive disease who are living with an entirely treatable sleep disorder. Treating the sleep disorder could have a significant impact on the overall survival and quality of life.

While optimization of the underlying lung disease is the first step in treating these patients, rapid diagnosis and an implemented management plan for underlying obstructive sleep apnea discovered in this patient is paramount.

Oxygen therapy may be indicated in these profoundly hypoxemic patients, but care must be taken that correction of hypoxemia does not worsen hypercarbia—in some patients, the primary respiratory drive may in fact depend on hypoxemia, removed by supplemental oxygen. This means that supplemental oxygen should be carefully adjusted with the lowest amount of supplemental oxygen needed to avoid CO_2 narcosis and our preference in our practice is to always achieve airway patency with positive airway pressure in the sleep center in the obstructive sleep apnea syndrome patient before resorting to supplemental oxygen if possible. We also recommend optimization of body mass and positional therapy in addition [14].

Careful review of the patient's pharmacologic therapy of COPD should be considered to minimize the effect of steroids and bronchodilators and nebulizers on promoting insomnia including timing of these agents where possible away from bedtime and to optimize control of the obstructive lung disease to minimize interference with sleep.

Certainly, these patients will often request medications to promote sleep and there may be a role for benzodiazepine and nonbenzodiazepine hypnotics which facilitate sleep onset short sleep latency improve sleep efficiency reduced EEG arousal capability and may provide some benefit, but I would be very reluctant to commence these until any sleep-disordered breathing has been fully treated with positive airway pressure and even then for as limited a dose and duration as possible. These patients may benefit from cognitive behavioral therapy for insomnia while they are awaiting to adjust to positive airway pressure for obstructive sleep apnea syndrome before considering any pharmacotherapy. For the more severe COPD patients, benzodiazepine and nonbenzodiazepine hypnotics may be out of the question because of the degree of respiratory depression they may produce [15].

While there are separate indications for noninvasive positive pressure ventilation in the patient with COPD and marked respiratory insufficiency in our practice, we are very aggressive with treating even mild sleep-disordered breathing with positive airway pressure or mandibular advancement therapy because of the benefits of treating obstructive sleep apnea in this patient population.

Also it has been shown that there are improvements in long-term nocturnal noninvasive positive pressure ventilation in COPD patients with hypercapnia respiratory failure including improvements in respiratory muscle strength and endurance, sleep quality, daytime oxygen and nighttime oxygen levels and daytime PCO_2 and PCO_2 levels at nighttime and these improvements are more marked with noninvasive positive pressure ventilation and now with supplemental oxygen probably because of a resetting and resting of chronically fatigued respiratory muscles that may rejuvenate and perform better in the daytime and reversal of micro atelectasis

by lung expansion, positive pressure ventilation and of course maintaining airway patency during sleep which also reduces work of breathing.

For this reason overlap syndrome patients benefit from nocturnal positive airway pressure and distinctions must be made as to what is best for the patient based on the coexisting sleep-disordered breathing, whether they need CPAP or bilevel positive airway pressure and still may still need some supplemental oxygen in addition after which hypnotics may also be required in low dose.

Bilevel positive airway pressure may have a particular role to allow reduction in expiratory pressures and make positive air pressure more comfortable in this patient population. Therapeutic goals for these patients are undefined. Most practitioners seek to eliminate sleep-disordered breathing both by objective criteria as well as by patient-defined outcomes of sleep satisfaction and improved quality of life much the same as we seek in other patient populations [16].

While patients with severe COPD may benefit from treatment with bilevel positive airway pressure due to improvement in nocturnal ventilation, for other patients conventional treatment with CPAP maybe adequate. Nonetheless despite these unknowns, it is important to recognize patterns of sleep and sleep disorders in this patient population which will be readily encountered in any sleep disorders medicine practice due to the widespread prevalence of both obstructive sleep apnea and COPD [17].

14.11 Sleep and Interstitial Lung Disease

Interstitial lung disease (ILD) includes a diverse array of lung disorders characterized by restrictive lung physiology. ILDs include idiopathic pulmonary fibrosis sarcoidosis autoimmune-related pulmonary disorders such as systemic sclerosis and hypersensitivity pneumonitis or restrictive lung disease following drug exposure such as amiodarone. Sleep has been most widely examined among these conditions in the setting of idiopathic pulmonary fibrosis (IPF) [18].

14.12 Sleep and IPF (Idiopathic Pulmonary Fibrosis)

IPF is, by definition, without known cause, characterized by a chronic and unremitting course with episodes of relapses—acute exacerbations and associated acute decline in lung function interspersed with periods of stability. It is the most common cause of Usual Interstitial Pneumonitis. Prognosis tends to be very poor, and physicians typically have focused on ameliorating only the most disabling symptoms. Histologically these patients are defined by findings of usual interstitial pneumonitis (UIP). Unlike COPD, IPF is relatively uncommon, rendering investigation of sleep and sleep disorders more difficult but recently there is an interest in examining sleep as a potential for modifying disease outcomes [19].

Patients with IPF report impaired sleep quality, excessive daytime sleepiness, increased sleep maintenance insomnia, reduced sleep efficiency, reduced total sleep

time and reduced REM sleep percentages. Worsening of hypoxemia is seen during sleep especially during REM sleep and there is evidence of an increased prevalence of obstructive sleep apnea syndrome in these patients. Sleep-disordered breathing is found to be extremely prevalent in the IPF patient population—reports range from more than two thirds of all patients to over 90% of patients studied.

Treatment of obstructive sleep apnea syndrome can certainly improve quality of life and perhaps disease outcome.

Nocturnal cough maybe a prime contributor to sleep disruption as well as the impact of medications including corticosteroids which are well known to cause insomnia. Comorbid depression and other affective disorders are commonly seen in the IPF patient which further impacts sleep and increases likelihood of insomnia.

Medications used to treat these comorbid affective disorders may further impact daytime function and increase daytime sleepiness.

Patients are noted to have nocturnal tachypnea in IPF compared to normal controls. Nocturnal desaturations during sleep can be more severe than the desaturations seen during exercise suggesting that sleep is a major stressor to the IPF patient.

If challenged with obstructive sleep apnea syndrome in addition, sleep in the IPF patient can become severely disrupted.

Treatment goals remain the same as treatment of other patients with obstructive sleep apnea and improving sleep quality in these patients offers a chance to reduce morbidity for patients with a poor long-term prognosis and escalating short term morbidities.

14.13 Critically Important the Pulmonologist *Does Not Overlook* Central Sleep Apnea Syndrome

Because of the societies where we practice in the developed world, our patients are very likely to have comorbid non communicable diseases in the setting of sleep disorders presenting to the pulmonologist sleep specialist.

Seventy percent of all cardiac patients will have a form of sleep-disordered breathing [20]. Increasingly we recognize the impact of sleep-disordered breathing on diseases our cardiology colleagues treat, including arrhythmias, coronary artery disease myocardial infarction and congestive heart failure. There is growing awareness of the sleep-disordered breathing in the congestive heart failure patient who remains unrecognized in the pulmonologist office even though they frequently come in for dyspnea, snoring and disrupted sleep. Among these patients, the central sleep apnea patient is the least recognized most often misdiagnosed and mistreated by sleep specialists.

Though the New England Journal editorialized [21] over 15 years ago that sleep medicine represented the "new cardiovascular frontier," recognition of sleep-disordered breathing in the cardiac patient remains lacking—patients often presenting to the sleep specialist years or decades after established heart disease and irreversible loss of cardiac function all too often caused in part by the detrimental

pathophysiology of decades of increased sympathetic nervous system tone caused by repetitive desaturations and reoxygenation during sleep which results in pro inflammatory stressors, arrhythmias, cardiovascular remodeling and long term morbidities. As their pulmonologists we can have an enormous impact on their cardiovascular outcomes.

Despite the high prevalence of chronic congestive heart failure patients with central sleep apnea syndromes, these patients in particular remain an under recognized, neglected patient population in terms of their sleep disorders, sleep dissatisfaction and the impact of their sleep on their global function.

A separate entity, central sleep apnea syndrome, is both highly prevalent and much neglected in the congestive heart failure patient. The heart failure patient may often demonstrate, obstructive sleep apnea syndrome with or without central sleep apnea syndrome in the setting of additional sleep-disordered breathing phenomena including Periodic Breathing also known as Hunter–Cheyne–Stokes respiration (CSR) [22] describing crescendo decrescendo changes in tidal volume is highly prevalent in patients with heart failure. Generally speaking, individual heart failure patients may demonstrate predominantly either obstructive sleep apnea syndrome or central sleep apnea syndrome, but it is not uncommon for the two forms to coexist. These patients are among the most complex sleep-disordered patients a sleep specialist will encounter. They are also the most difficult to treat which may be partly why they are less often successfully managed and remain poorly understood.

The identification of central sleep apnea is very important in patients with cardiac disease. Central sleep apnea can only be diagnosed on polysomnography by a sleep disorders specialist familiar with the distinctive events defined as absence of airflow in the setting of absent respiratory effort seen on chest and abdominal leads. Usually left as an exception instead of a rule, it has been a diagnosis typically made it is so pronounced it cannot be ignored. However, with new therapies which either can only treat central sleep apnea (phrenic nerve stimulation) or cannot treat CSA at all (hypoglossal neurostimulation and dental appliances), clarifying when each form of sleep-disordered breathing—separating obstructive sleep apnea from central sleep apnea—has now become crucial.

While AHI has been shown to be very reproducible between technicians at 88% [23], even central and obstructive apneas can be misclassified with central apneas misclassified 52% of the time. If the effort belts are not appropriately tightened, events may appear central when they are in fact obstructive in nature. Conversely, in severe heart failure, central apneas may look obstructive due to “cardiac noise” on the thoracic belt which may mimic respiratory effort. By increasing the amplitude of the channel, it becomes clear that the rate is much faster than a breath and the event can still be considered a central apnea.

Even more difficult than central apneas is the controversial area of central hypopnea classification. Whether 3% or 4% desaturation cutoff is used, distinguishing central apneas versus central hypopneas remains difficult [24]. Until now all hypopneas in my sleep center had been automatically classified as obstructive. I am now teaching my sleep center the distinctions. The gold standard is to place an

esophageal probe to determine negative inspiratory esophageal pressure changes measured in mmHg, but this is not practical in the clinical setting and used only in the research setting.

Currently, there are at least two different ways to classify obstructive versus central hypopneas [24], and the agreement with gold-standard studies is under 70% for both methods. The answer to this variability may come from a standardized approach in augmenting scoring. Artificial intelligence may be able to complement scoring of events with consistency, even though it is doubtful that the time would come when studies could be scored without oversight by technologists and clinicians skilled in sleep medicine [25].

Nonetheless, once the sleep specialist begins to become committed to evaluating sleep-disordered breathing in the cardiac population, central sleep apnea will inevitably present. Between 25% and 40% of patients with chronic HF have central sleep apnea (CSA) [26]. Moreover, although CSA syndrome is more common in patients with HF and reduced ejection fraction. CSA is also diagnosed in patients with HF and preserved ejection fraction. Patients with HF and CSA experience poor quality of life due to an array of troublesome symptoms including but not limited to sleep onset insomnia—often caused by sleep onset central apnea—sleep maintenance insomnia, nonrestorative sleep, nocturia which disrupts sleep, nocturnal enuresis particularly related to diuretic medication and tremendous daytime impact of the severe sleep fragmentation resulting from all the above.

These patients develop erratic sleep–wake patterns, profound daytime hypersomnolence, circadian rhythm disorders related to the impaired sleep hygiene from daytime sleepiness, additional insomnia resulting from daytime napping. Their sleep remains non refreshing so despite the daytime naps patients report sleep dissatisfaction, unremitting fatigue reduced energy and significant social isolation leading to depression.

Nocturnal sleep disruption can be so significant to become a precipitant for institutionalization due to the severe burden of the sleep disorder falling on the primary caregiver. The fragmented sleep drives increased sympathetic nervous system tone which spills over into wakefulness and leads to increased arrhythmias, cardiovascular morbidity including poorly controlled hypertension, ischemic events including unstable angina, worsening of congestive heart failure and eventually paroxysmal nocturnal dyspnea, nocturnal angina, and impaired cognitive function. These symptoms adversely impact quality of life, patient outcomes, and portend a poor prognosis.

While objective measures of an improved apnea hypopnea index, respiratory distress index or improved central sleep apnea index define outcomes and guide conventional treatment with CPAP, BiLevel PAP, or Adaptive ServoVentilation modes of PAP, truly successful management of sleep disorders focuses greatly on resolution of the daytime or waking impact of the underlying sleep disorder and restoration of function in activities of daily living as assessed by the patients subjective measures of sleepiness, sleep quality and functional quality of life. Resolution of insomnia is also critical to patient sleep satisfaction and well-being and additionally has a major impact on the primary caregiver.

Sleep specialists agree the clinical treatment of CSA primarily focuses on management of the underlying primary disease process—usually Congestive Heart Failure (CHF) but also underlying stroke, or opiate use, followed by the management of CSA-related symptoms, chiefly the sleep impact.

Symptoms may also be attributed to complications of medications—for instance diuretics causing nocturia and nighttime awakenings, or beta blockage causing insomnia and nightmares—rather than considering a primary sleep disorder driving the sleep fragmentation.

It is important to understand the complex pathophysiology underpinning central sleep apnea syndrome though mechanisms remain incompletely understood. A significant burden of data indicates that an exaggerated respiratory control response to changes in the arterial tension of carbon dioxide ($PaCO_2$) above and below a central sleep apnea threshold is central to the pathogenesis of CSA syndrome.

We discussed normal ventilatory responses and sleep above. In the heart failure patient significant respiratory instability results from change in three driving forces: hyperventilation; delayed circulation time; cerebrovascular reactivity. Normal breathing is thus destabilized leading to respiratory instability and wide swings of central sleep apneas and recovery hyperpneas. Both exert dramatic impact on sleep architecture and result in a distinctive oscillation pattern in respiration described as periodic breathing or Hunter–Cheyne–Stokes respiration.

Heart Failure patients chronically hyperventilate in wake and sleep thought to be related to pulmonary congestion worsened in supine position when excessive fluid is displaced rostrally from the lower extremities to the thorax activating pulmonary stretch receptors that stimulate ventilation raising respiratory rate. The underlying cardiac dysfunction causes an exaggerated response to the prevailing lower $PaCO_2$ (lowered by the increase in ventilation) and resets the apnea threshold driving central apneas which then eventually result in climbing $PaCO_2$ levels and then triggers an exaggerated respiratory drive to escalate ventilation and further lower the $PaCO_2$ and the cycle of central apnea and hyperventilation begins once again. Matters are worsened by the sluggish circulatory time in the heart failure patient delaying the detection of circulating arterial blood gas tensions and leading to delayed intervention by the peripheral and central chemoreceptors.

Finally changes in the $PaCO_2$ are critical to regulating cerebral blood flow otherwise known as cerebrovascular reactivity. In the heart failure patient's brain, the response to $PaCO_2$ changes is also diminished compounding the respiratory instability further. Because of an impaired buffering mechanism to absorb excess hydrogen ions centrally, $PaCO_2$ levels are more increased during hypercapnia and the central respiratory control center cannot dampen ventilatory overshoots resulting in severe hyperpnea or ventilatory undershoots leading to prolonged central apneas. The respiratory oscillation of the CSA cycle is therefore destined to be perpetuated; the patient permanently predisposed to have severe breathing instabilities during sleep.

As part of the respiratory control center seeking to control $PaCO_2$ levels regulated, central respiratory control centers send signals to the diaphragm via the right and left phrenic nerves each of which controls right and left hemidiaphragm

muscles. These signals control the contraction of the diaphragm, the largest and primary inspiratory muscle of respiration engaged in the work of breathing. Inspiratory muscle dysfunction is occurring during healthy ageing and this decline in function is heightened in the heart failure population.

Inspiratory muscle dysfunction contributes to several aspects of both heart failure and pulmonary pathophysiology which includes a reduced ability to clear the upper airway, a predisposition thus for pneumonia, reduced ability to sustain ventilation and gas exchange during exercise and thus reduced exercise tolerance, a propensity for alveolar hypoventilation due to shallow rapid breaths which again limits ventilation and profound sympathetic nervous system activation which causes cardiac arrhythmias and tissue.

The neuromuscular integrity of the prime muscle of respiration—the diaphragm-is the main determinant of the adequacy of respiration and being the prime muscle for respiration during sleep its function becomes even more critical when accessory muscles of respiration are quiescent, or in dream sleep, paralyzed. Changes with both age and heart failure alter phrenic nerve function and neuromuscular junctions consistent with neurodegeneration and denervation impacting the diaphragm as well as intrinsic myocyte dysfunction including changes in contractile proteins, accelerated muscle fiber atrophy and changes in muscle fiber distribution. Recent investigations show that the heart failure patient may have intrinsically weakened diaphragmatic muscles, and this may represent a marker for disease severity and reduced exercise tolerance. We also see similar atrophy of the diaphragm in advanced and chronic lung disease causing hyperinflation.

Many sleep specialists working in the pulmonary population do indeed recognize central sleep apnea syndrome [27] though I have found it depends very much on the sophistication of the sleep center and the education of sleep technicians and sleep physician scoring and interpreting sleep studies but assuming it is recognized the treatments thus far have not been particularly satisfying for either the central sleep apnea patient or the treating sleep specialist.

Limited indicated therapeutic options exist for patients with CSA, especially patients with HF with all therapeutic options leading to most often only partial control of central sleep apnea events significant challenges with compliance with an array of positive airway pressure devices including CPAP, Bilevel PAP, and ASV PAP devices—when they are not contraindicated by severity of lowered ejection fraction below 45%. Often the heart failure patient identified to have central sleep apnea syndrome has had numerous labor intensive and costly level I attended diagnostic polysomnography and numerous Level I attended in laboratory titration studies before treatment is commenced and numerous and protracted follow up subsequently often without yielding end point measures of success in terms of normalization of respiratory indices or subjective improvement in quality of life.

Transvenous phrenic nerve stimulation (TPNS) is a unique physiological approach to the treatment of CSA. The Remedē® System (ZOLL Respicardia, Inc., Minnetonka, MN, USA) [28] unilaterally stimulates one phrenic nerve to cause hemi-diaphragmatic contraction resulting in diaphragmatic movement similar to normal breathing, restoring inspiratory effort, terminating a central apnea and thus

stabilizes the carbon dioxide level. Often with the stimulation of one hemidiaphragm by the Remedē® System (ZOLL Respicardia, Inc., Minnetonka, MN, USA) the other hemidiaphragm becomes synchronously recruited into simultaneous contraction even though the phrenic nerve supply it is not stimulated by the device.

In this patient population namely their fatigue, daytime sleepiness, reduced daytime energy, nocturia, reduced exercise tolerance, isolation and social withdrawal and interrupted sleep are the hallmarks of living with heart failure across disease severity classification even when fully treated with tier one standard care in the first world (Figs. 14.1, 14.2, and 14.3).

While focus on measured outcomes in the heart failure patient is commonly followed, ejection fraction, control of arrhythmias, end organ function and its correlates (kidney function, cerebral function), quality of life, and, specifically, impacts on sleep and related sleep dissatisfaction are all too often overlooked. This neglect is often carried over into the sleep center where expertise in central sleep apnea is often deeply lacking both in the recognition of the patient candidate and the disease state but also the investigation, diagnosis, and treatment of this uniquely challenging sleep disorder patient population.

Today estimates project over 64.3 million people living with heart failure worldwide [29]. This number is growing amid younger age groups and there is a trend to earlier recognition leading to increasing prevalence of HF with preserved EF. Also worth noting is the devastating impact of the SARS COV-2 Covid 19 pandemic which is already resulting in increased cardiovascular morbidity including heart failure in survivors of the infection and the population at risk for CSAS in HF is increasing and the imperative to better recognize CSAS. Without such tools, impairments to quality of life could remain unacknowledged.

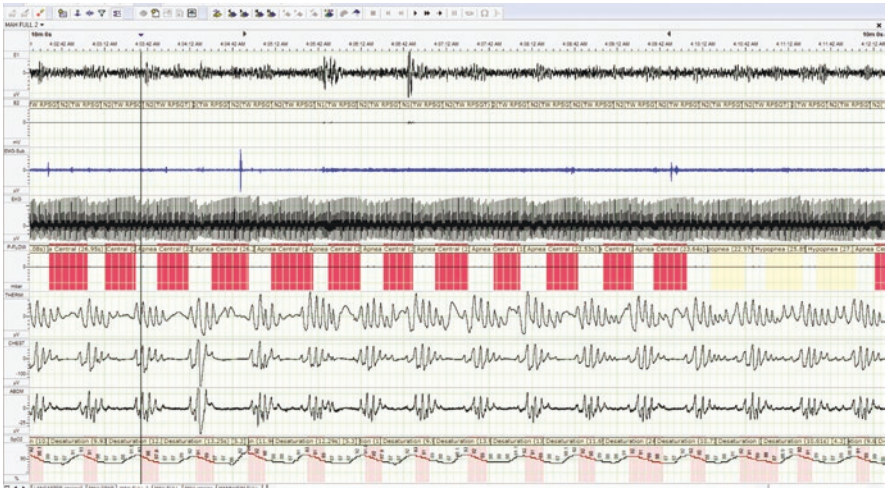

Fig. 14.1 Nocturnal Polysomnography of an 81 year old male with central sleep apnea syndrome seen—central apnea events are marked in red. Notice related desaturations lag due to circulation time

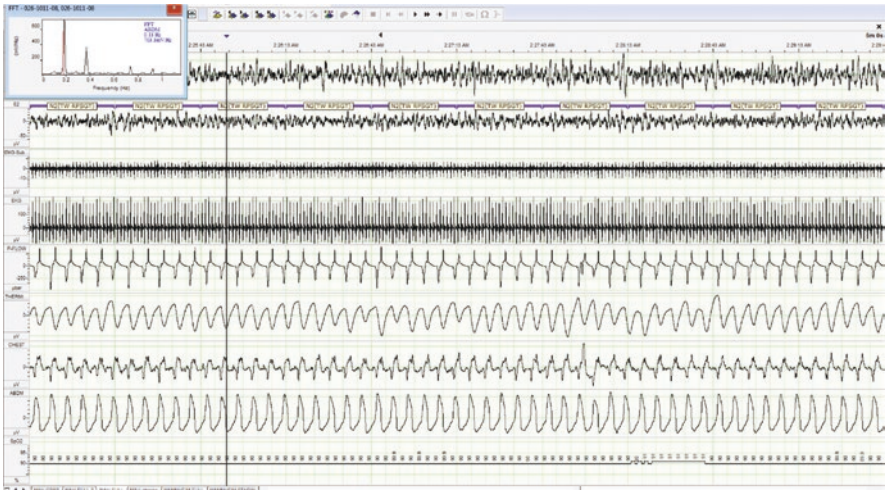

Fig. 14.2 Polysomnography of the same patient at 6 months following the Remede System implanted, activated, and optimized at a stimulation rate set at 11 breaths per minute (0.18 Hz). Central Apnea Index improved from 53.8 events per hour to 0.3 events per hour. Notice resolved desaturation

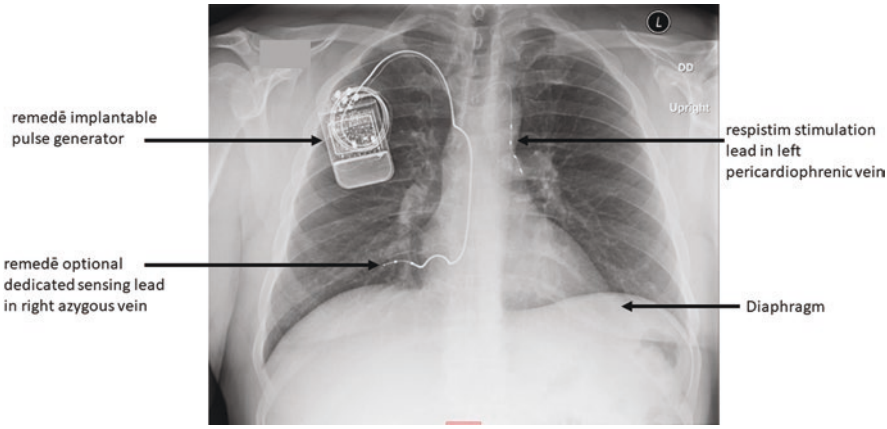

Fig. 14.3 Chest X Ray of patient with implanted transvenous phrenic nerve stimulator with the Zoll-Respicardia Remede System

TPNS therapy offers a chance to shed light on this much overlooked global patient population bringing their sleep disorders into sharp focus for the first time and likely driving an entirely new patient population to formal sleep evaluation for the first time.

14.14 Social Impacts of Sleep Loss

Sleep loss has been directly related to behavioral withdrawal, social isolation, and feelings of loneliness. Independently, loneliness contributes to greater mortality and loneliness is recognized to be a state distinct from either anxiety or mood disorders. Patients living with chronic pulmonary disorders often have social withdrawal as a function of their illness without the added impact of social isolation due to sleep loss [30].

Much of the world has experienced the social isolation of lockdowns during this global pandemic underlining our intense need for human connection. Investigations into social isolation and sleep are revealing clearly identified but little-known phenomena including sleep loss as a "social repellant" driving interpersonal separation of the sleep deprived patient from the social contact and vice versa. The asocial impact of sleep loss has been shown to propagate in carefully conducted studies looking at sleep deprivation, functional MRI data and human interaction. Those encountering a sleep deprived individual even in brief 1-min interactions come away feeling themselves lonelier and further averse to interacting with the sleep deprived subject suggesting a social contagion of isolation due to sleep loss.

14.15 Sleep Disorders Beyond Breathing

In my practice I take great interest in examining the upper airway and try to teach the patient and our fellows to take an interest in craniofacial development that may have contributed to the diagnosis recognition of the craniofacial respiratory complex is imperative particularly when looking for obstructive sleep apnea in patients of normal or below normal body mass and recognizing obstructive sleep apnea in the pediatric population [31–34].

14.16 Conclusion

Sleep disorders in the pulmonary population are common. Pulmonologists need to be well versed in the recognition of their diagnosis and treatment. Treatments are advancing and involve positive airway pressure, oral appliance therapy, multimodal surgical approaches on both the soft tissue and the craniofacial architecture, and lately both upper airway and transvenous nerve stimulation depending on the nature of the sleep-disordered breathing. Much more important is the role of the pulmonologist to empower both each patient and each referring physician and surgeon to become an ambassador to the field and a resource to the surrounding community that more of humanity begins to learn that sleep is a biological necessity and that disorders of sleep have wide-ranging impact on the health and well-being of the wider population and entire societies.

Take-Home Message

- Distinct clinical phenotypes of COPD influence the likelihood of coexistent OSA.
- Overlap COPD patients with obstructive sleep apnea carry more significant mortality, and obstructive sleep apnea syndrome patients with coexistent COPD are also at an increased risk of death.
- Interstitial lung disease (ILD) and Idiopathic pulmonary fibrosis should not be overlooked in association with OSA in patients who do not improve enough with CPAP therapy.
- The identification of central sleep apnea is crucial in patients with cardiac disease.

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OSA in Obstetrics and Gynecology

15

René De León Salazar and Cesar F. Saldaña Solorzano

15.1 Introduction

15.1.1 Definition and Epidemiology

Obstructive sleep apnea syndrome (OSAS) is a disease that constitutes a serious public health problem, due to the consequences it has on the people who suffer from it. The conditions that can occur are so varied and include, broadly speaking, the physical, psychological, and socioeconomic aspects. According to different studies, people who suffer from this syndrome have a higher risk of suffering traffic accidents, high blood pressure, problems with the perception of their quality of life, and an increase in cardiovascular morbidity [1].

Obstructive sleep apnea (OSAS) is characterized by a repetitive collapse of the upper airway during sleep, usually associated with oxygen desaturation and/or nocturnal awakenings. OSAS occurs in approximately 2% of women, and it is two to five times more prevalent in men. Hanser et al. have reported that the prevalence of OSAS in women is 23.4%, while in men, it is 49.7% [2, 3].

This incidence has increased notable in recent years, in parallel with aging and with the rise in obesity in the global population.

The symptoms commonly reported in women with OSAS are snoring (61%), difficulty falling asleep (32%), difficulty staying asleep (19%), daytime sleepiness (24%), sleep apnea observable (7%), body movements (60%), or restless legs syndrome (33%). It has been suggested that there may be a misdiagnosis or underdiagnosis of OSAS in women, since they tend not to report symptoms due to shame or even because they report nonspecific symptoms of disorders of the breathing in sleep, among which are: headache, fatigue, depression, anxiety, insomnia and

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nocturnal awakenings [4–6]. The presentation of atypical symptoms leads to fewer female patients being referred to sleep specialists, delaying diagnosis (and the registration of new cases).

15.1.2 Differences Between Men and Women

There are differences between genders that affect the caliber of the airways, causing recurrent pharyngeal obstruction during sleep. The pharynx is longer in man, regardless of height. When the throat relaxes and collapses during sleep, the airways close partially or totally restricting the passage of air to the lungs, producing microarousals due to lack of air, accompanied sometimes by a sensation of suffocation such an interruption of air causing a decrease in oxygen.

Magnetic resonance imaging (MRI) has shown that the length of the airway, tongue, soft palate, and total amount of tissue in the throat are less abundant in women. Therefore, a longer pharynx in the man is more susceptible and tends to collapse [7].

15.1.3 Terminology

Obstructive apnea is defined as a decrease of more than 80% of the airflow for 10 s (arrest of the respiratory signal) that can be of central or obstructive origin depending on diaphragmatic effort. A hypopnea is a decrease in airflow of at least 30% for 10 s, accompanied by a reduction in oxygen saturation of 4% or more. In the presence of thoracoabdominal effort, the apnea–hypopnea index (AHI) refers to the sum of apnea and hypopnea events per hour of sleep. When this index is greater than five events per hour, the diagnosis of OSAS is made.

When the symptoms of daytime dysfunction or other neurological alterations are directly attributed to sleep apneas/hypopneas, the obstructive sleep apnea is called obstructive sleep apnea syndrome.

The respiratory disturbance index (RDI) is defined as the frequency of decrease in saturation and/or nocturnal awakening per hour. The RDI can be mild when it is 5 to 15 events per hour; moderate when it is from 16 to 30 per hour and severe when it is more than 30 events per hour.

For snoring, Lugaresi et al. [8, 9] proposed a three stages of snoring, which only affects the companion.

- Stage 1: Snoring occupies long periods of sleep and daytime sleepiness.
- Stage 2: Snoring occupies long periods of sleep and daytime sleepiness and poses problems.
- Stage 3: Snoring is associated with a severe picture of OSAS (obvious).

Women report more difficulties sleeping; however, despite of recognizing such alterations, many remain without a specific diagnosis. Currently, medicine focuses

on the comprehensive treatment of patients, including all symptoms that can be reported.

Throughout life, women are continuously influenced by different hormonal levels (from menarche to menopause), that are dynamic and affected by the various reproductive stages. These hormonal changes put the female sex at a higher risk of sleep disturbances, and the circadian cycle.

Throughout this chapter, the different stages of a woman's life will be exposed, the hormonal changes that arise in each one of them, and how they are related to the diagnosis of OSAS.

15.1.4 OSA and Reproductive Age

In this second stage of life, a woman reaches sexual maturity physically and, therefore, can achieve a pregnancy.

15.1.5 Premenstrual Syndrome (PMS)

Women who have negative symptoms in the last days of their menstrual cycle have a decline in estrogen and progesterone levels [6]. Premenstrual syndrome (PMS) and premenstrual dysphoric syndrome (PMDS) are characterized by emotional, physical, and behavioral symptoms that occur in the days before menstruation and ends with the beginning of it [10–14].

Women with PMS and premenstrual dysphoric syndrome (PMDS) typically report sleep-related complaints such as insomnia, frequent awakenings, unrefreshing sleep, nightmares, poor sleep quality; and a repercussion on their productive life, which is accompanied by fatigue, decreased alertness, and lack of concentration.

Analyzing participants from the *Study of Women's Health Across the Nation* (SWAN), researchers found that women in the late reproductive stage had sleep efficiency that declined as the menstrual cycle progressed, with a pronounced decline in the week before menstruation [15].

15.1.6 Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, associated with an increased risk of metabolic disorders and the possibility of developing OSAS. Obstructive sleep apnea has been more prevalent in premenopausal women with PCOS than controls, even considering BMI. However, another study found a relationship between PCOS and OSA, but only in obese patients [16].

15.1.6.1 OSA and Pregnancy

Pregnancy produces a series of changes in the physiology and anatomy of the women; among which one can list the hormonal, psychological, metabolic, and

physical ones. These adjustments are necessary for maintaining the gestational state, but, in turn, affect the function of various systems. Sleep disturbances are an example of these repercussions.

The term sleep-disordered breathing (SDB) describes breathing disturbances that occur during sleep, ranging from simple snoring to OSAS. These disorders are defined by the AHI, which can be obtained through polysomnography. SDB can be of central origin, obstructive (the most frequent) or those associated with hypoventilation (Table 15.1).

Sex hormones (progesterone, androgens, and estrogens) and breathing are intimately related, it has not yet been determined which hormone is the most important in this relationship. During pregnancy, variations in the main hormones (estrogens and progesterone) generate respiratory and sleep physiology changes. Estrogens are related to the appearance of rhinitis and edema of the nasopharyngeal mucosa, conditioning a narrowing of the upper airways and, consequently, predisposing to OSAS. They are also related to the shortening of REM sleep periods, while progesterone has a sedative effect and can increase the duration of non-REM sleep [17].

Progesterone has a positive effect on the respiratory tract. Its relationship with hyperventilation due to decreased sensitivity to CO_2 has been described. This increase in the rate of respiration reduces the risk of OSAS [18].

Pregnancy has been associated with an increase in ventilatory sensitivity to hypoxia and hypercapnia; this increase is due to estrogen and progesterone in the carotid body [18]. However, pregnancy is a state with an increased risk of OSAS despite a higher level of sex hormones.

Fluctuations in hormone levels typical of pregnancy affect the sleep wake cycle. An increase in sex hormones leads to other risk factors such as increased neck circumference or nasopharyngeal edema. Poor quality and insufficient sleep in

Table 15.1 The origin of the SDB may cause different manifestations

Center origin SDB	Disorders of control of ventilation Periodic Cheyne–Stokes respiration (CSR) Periodic breathing triggered by height Central apneas not associated with CSR, triggered by other vascular, tumor, neurodegenerative, metabolic, or traumatic pathologies of the CNS Central apneas triggered by the use of certain drugs (opiates and CNS neurodepressants) Barely central newborn and preterm Central apneas triggered by the treatment of obstructive sleep apneas
SDB of obstructive origin	Obstructive sleep apnea in adults Obstructive sleep apnea in childhood
SDB associated with hypoventilation during sleep	Primary hypoventilation syndromes Congenital hypoventilation syndromes Hypoventilation syndromes secondary to obesity, neuromuscular disease with compromise of the respiratory muscles, mechanical alterations of the chest wall

pregnant women are associated with an increase in inflammatory markers that lead to poor health and pregnancy complications.

During the first trimester, pregnant women sleep more (total increase in hours of sleep) and experience greater daytime sleepiness, which improves in the second trimester. It has been shown that over 50% of pregnant women experience snoring during the second and third trimesters. In the third trimester there is an increase in sleep disturbances, with nocturnal awakenings (3–5 per night), the need for a more significant number of naps, decreased alertness, and insomnia [19, 20].

In global numbers, respiratory disorders can be found in the first trimester between 13% and 80% of women, which increases from 66% to 96% during the third trimester. The first trimester is of particular importance, because several factors affect the regular sleep in the first 12 weeks of gestation, such as nausea, dizziness, vomiting, nocturia, tension headaches, malaise, etc.

Upon reaching the second trimester, the gastrointestinal symptoms resolve; however, after week 24, sleep disturbances are generated by fetal movements, which cause nocturnal awakenings. Due to the increase in the uterus size, the diaphragm is displaced, reducing the residual lung capacity (promoting a collapse in the airway). There is also an increase in gastroesophageal reflux rate by these physical changes. As uterine size increases, there is a decrease in functional residual capacity and expiratory reserve volume. Therefore, pregnant patients with a pregnancy with more than 24 weeks should be advised to sleep in the left lateral decubitus position (to position the tongue laterally and allow better airflow).

OSAS affects between 9% and 15% of the general population; however, the exact percentage in pregnant patients is unknown. Some studies with nocturnal polysomnography have shown a high incidence of SDB in pregnant patients that suffer obesity after 30 weeks of gestation, even when they sleep in the lateral decubitus position as compared to normal weight pregnant patients. A maximum peak in OSA has been documented between weeks 28 and 29 of pregnancy.

Snoring is a common symptom present in OSAS. However, it is essential to study all pregnant patients to discard OSAS and have a higher risk of adverse outcomes and morbid processes during gestation such as preeclampsia, eclampsia, pulmonary embolism, and cardiomyopathy. It should be monitored in high-risk pregnancies if there are symptoms that suggest OSAS.

15.1.7 Factors Involved

15.1.7.1 Progesterone

Progesterone increases minute ventilation, ventilatory support, and tidal volumes to ensure increased blood oxygen levels (in response to maternal requirements for fetal development). It also increases daytime sleepiness and non-REM sleep time.

Its direct effect on the upper airways is an increase in the activity of the dilator muscles, causing them to be less collapsible. In association with the elevation of estrogen levels, it produces a decrease in REM sleep periods, being a protective factor against OSAS (Table 15.2).

Table 15.2 Effects of progesterone in breathing process

Protective mechanisms	Risk factors
Increased respiratory volume (progesterone)	Weight gain
Lateral decubitus during sleep _	Narrowing of the upper airways
Decreased duration of REM sleep _ _	Daytime sleepiness

The above can be summarized in the following table:

15.1.7.2 Hours of Sleep

Pregnant patients who sleep less than 6 hrs in the third trimester [21] have a greater predisposition to present prolonged labor (related to OSA) and therefore to a higher incidence in the number of cesarean sections (areas up to 4.5 times more than those who sleep more than 6 h).

The presence of apnea during sleep generates nocturnal awakenings, which range from small (barely perceptible) to a complete awakening due to the sensation of shortness of breath. They condition excessive tiredness and cause the pharyngeal muscles to relax when going back to sleep, causing a narrowing of the pharynx and, therefore, respiratory obstruction.

Usually, the person who first perceives sleep disorders is the patient's partner or some relative, so it is essential to ask questions addressed to the patient and her companions during prenatal care (Table 15.3).

1. **Obesity** is considered when body mass index (BMI) exceeds 30 kg/m^2. Weight gain occurs during pregnancy, so when added to the pre-existing weight, it can favor SDB. The overall weight gain in a pregnant patient should vary between 13 and 15 kg. Obese patients have a higher risk of snoring and desaturation during sleep.
2. **Increased Hormone Levels:** The variation of the hormonal levels constitutes the base of the sustenance and the development of the pregnancy. In the first trimester, the corpus luteum begins hormone production, which is later replaced by the placenta. Increased hormone levels are related to edema of the nasal mucosa and narrowing of the pharynx. Therefore, it is very common for pregnant patients to have nasal congestion and runny nose.
3. **Changes in the face and neck contour**: Changes in the face and neck contour are a consequence of the increase in the size of the tonsils and/or tongue; in patients who have hypognathia they have a greater predisposition to airway blockage.

Table 15.3 Factors and effects of the pregnancy in SBD

Summary of the factors involved in SDB during pregnancy	
Diaphragm elevation _	Restriction of the thoracic cage, reducing the pulmonary functional residual capacity
Increased estrogen _	They produce mucosal edema and hyperemia, increasing the resistance of the upper airway (especially in the third trimester)
Narrow oropharyngeal junction _ _	Narrowing of the oropharyngeal junction (mainly in the third trimester); reverses in the puerperium
	Finding found to a greater extent in preeclampsia
Weight gain	Obesity in pregnancy generates higher AHI, increases the incidence of snoring and nocturnal awakenings
Depression _ _	Present in 10%–25% of pregnant women, predisposes to SDB

15.2 Symptoms

The most common symptoms of sleep-disordered breathing (SDB) are the following:

- **Snoring:** Is the most apparent symptom. It affects 14%–41% of pregnant women (compared to nonpregnant women with 4%–17%). They can occur in any trimester of pregnancy and are predominantly nocturnal. Since this symptom is an indicator of OSAS, additional studies should be carried out on these patients if there is an increase in the amount of snoring, there is a decrease in snoring after giving birth. However, not all patients with snoring suffer from apnea.
- **Pauses in breathing:** During snoring, there may be pauses in breathing. An abrupt deep inspiration can accompany them due to lack of air or frequent microarousal. These pauses are more common when the pregnant woman sleeps in the decubitus–supine position.
- **Drowsiness and fatigue:** Can be associated with the hormonal changes typical of pregnancy; however, they are also a consequence of poor sleep quality.

Other symptoms associated with SDB (Table 15.4):

Poor sleep quality: patients with SDB (including OSA) have poor sleep quality, which produces metabolic, hormonal, and nervous system disorders, which can compromise the proper development of the pregnancy; They are also related to the onset of obstetric complications (maternal and fetal) such as: gestational hypertension, preeclampsia, eclampsia, gestational diabetes, depression, stillbirth, and accidents caused by fatigue.

It has been reported that during prenatal care, pregnant patients tell their obstetricians that sleep quality is affected in the first trimester, with an improvement during the second and a consequent deterioration in the third trimester. Objective information can be obtained by performing polysomnography (Table 15.5).

Table 15.4 Other symptoms associated with SDB

• Irritability	• Odynophagia
• Depression	• Headache
• Lack of concentration	• Cough
• Dry mouth	• Gastroesophageal reflux

Table 15.5 Symptoms and changes in sleep structure during pregnancy (Modified from Santiago et al., Sleep and sleep disorders in pregnancy: Ann Intern Med 2001;134: 396–408)

Period	Subjective symptoms _	Objective data (polysomnography)
First trimester	Increased SDB Increased daytime sleepiness Increase in naps Insomnia	Increased SDB Decreased stages 3 and 4 sleep (deep) Increased stages 1 and 2 sleep (superficial)
Second quarter	Regular SDB Heightened alert	Regular SDB
Third trimester	Decreased SDB Increased daytime sleepiness Insomnia Irregular sleep interrupted by awakenings	Decreased SDB Increase in awakenings Stage 1 boost Decrease in stages 3 and 4 Decreased REM sleep

15.3 Diagnostics

Objective measurements must confirm the clinical suspicion of sleep-disordered breathing (SDB) to define the best treatment strategy. If they former is positive, specialized studies should follow screening methods.

15.3.1 Diagnostic Tests

Diagnostic tests are recommended in patients with suspected OSAS (snoring, apneas observed by third parties and daytime sleepiness) and especially when there are comorbidities in pregnancy.

Screening tools to evaluate pregnant patients are:

- Berlin Questionnaire _.
- Questionnaire of the American Society of Anesthesiology (ASA).
- STOP Questionnaire.
- STOP BANG Questionnaire.
- Flemons Index.
- Epworth sleep scale.

Polysomnography (PSG) and respiratory polygraphy (RP) are used to confirm the diagnosis.

15.4 Complications in Pregnancy Due to OSAS

OSAS can cause hypoxia in the fetoplacental circulation, with possible consequences for the product: an increased risk of low birth weight, preterm delivery, small for gestational age (SFGA) product, restriction, or intrauterine growth retardation (IUGR); it also predisposes to maternal complications such as gestational diabetes, hypertension, preeclampsia, eclampsia, and prolonged labor (with a subsequent increase in the number of cesarean sections) [22, 23].

15.4.1 OSA and the End of Reproductive Life

Obstructive sleep apnea syndrome (OSAS) is characterized by complete (apneas) or partial collapse (hypopnea) or the upper airways during sleep, which are repetitive.

Sleep problems during menopause are a common complaint. However, several factors play a role in this problem, including vasomotor symptoms, changing hormone levels, abnormalities in the circadian cycle, exacerbation of primary insomnia, mood swings, coexisting medical conditions, and lifestyle.

15.4.2 Incidence and Prevalence in Menopause

The incidence of obstructive sleep apnea syndrome (OSAS) increases in women after 65 years of age. However, this increase begins from the transition to menopause. As previously mentioned, OSA is 2–5 times more prevalent in men than in women; this attributable gender difference is attenuated after menopause [3].

It has been documented that the differences between tender is attributable to the anatomy and physiology of the upper airways, to the craniofacial morphology, to the fat deposition pattern and respiratory stability [3]. Variations in physiological mechanisms that impact on the manifestation of symptoms related to sleep-disordered breathing are hormone-dependent. Considering the polysomnography parameters, women have less severe OSAS, with a lower apnea–hypopnea index (AHI) and shorter periods of apnea [24].

Approximately 20% of women develop obstructive sleep apnea syndrome at menopause. It has been recorded that in postmenopausal women, there is a prevalence of OSAS of 47%–67%. Age-related changes (in sleep architecture and sleep perception) may also contribute to sleep disturbances in women in the menopausal transition and post menopause [25].

15.4.3 Changes after Menopause

After menopause there is a tendency to gain weight (as part of aging); therefore, there is a higher body mass index (BMI), a larger neck circumference, and a more significant waist–hip ratio (WHR). Adipose tissue tends to have a peripheral

distribution in women of reproductive age, while in postmenopausal women the pattern of obesity tends to be central (upper body and trunk).

Weight gain alone is not the only factor responsible for this condition. For example, in magnetic resonance imaging (MRI) studies in obese men and women, it has been found that women there have less pharyngeal fat and soft tissue volume in the neck [26]. The distribution of fat in the upper airway, particularly in the posterior portion of the tongue, is crucial for the pathogenesis of OSAS.

15.4.4 Relationship of OSAS with Hormone Levels in Menopause

There is a theory that progesterone and estrogens produced in reproductive age protect against OSAS. The fact that most women with OSAS are morbidly obese and postmenopausal adds to this speculation.

Progesterone is a respiratory stimulant that increases the chemoreceptor response to hypercapnia and hypoxia and has increased upper airway tone. This stimulating effect of progesterone on ventilation is more important when it is associated with estrogens. Progesterone levels decrease after menopause.

Studies have shown that low estradiol levels are not as crucial as BMI and facial morphology [27]. There is no official study that shows the correlation between neuroendocrine hormonal changes, OSAS and the symptoms of menopause [28].

In postmenopausal women under estrogen therapy (ET), a lower incidence of sleep disturbances associated with breathing has been observed; even the results are better in patients who are on combined therapy of estrogens with progesterone [17].

We would like to emphasize that obstructive sleep apnea alters the homeostasis of hormones, and usually, the habits and quality of sleep are many times neglected in gynecological clinical practice. In recent years, it has been shown that OSAS negatively affects hormone concentrations (estrogens and progesterone) and sexual functioning [16].

In a published study, pre- and postmenopausal women with OSA suffered from sexual dysfunction and hormonal alterations [29]. A correlation was also found between OSA severity and sexual dysfunction, even after adjusting for body mass index (BMI).

Sleep disturbances possibly alter the levels of sex hormones and therefore sexual behavior. Testosterone has a cyclical secretion pattern, mainly associated with sleep patterns, not by the circadian cycle [30]. The maximum concentration in the blood occurs during sleep, in the first REM phase and reaches its nadir in the afternoon; it has been estimated that at least 3 h of sleep is necessary to maintain normal testosterone secretion.

Testosterone is driven by LH pulses (which occur every 90 min). Because of its relationship to sleep pattern, it stands to reason that sleep disruption is associated to a hormonal imbalance. Kalmabach et al. investigated the influence of night sleep duration on the quality of their sexual functioning, finding that sufficient night rest is essential to maintain sexual response and sexual desire [30]. Women with poor sleep duration have a lower sexual desire and are more likely to have some type of sexual dysfunction; therefore, sleep is vital for the reproductive process.

15.4.5 Impact of OSA on Quality of Life in Postmenopausal Women

The literature recognizes the increased incidence and prevalence of OSAS in women after menopause does not mean that all women suffering from this syndrome are treated. However, as mentioned in the introductory part of this chapter, OSA is underdiagnosed in females [31]. The presentation of atypical symptoms in women explains why a diagnosis is made at older ages, causing more significant changes in the quality of life.

Women, with untreated OSAS, report more mood changes as anxiety or depression. In addition, when applying questionnaires on quality of life, women report fatigue, daytime tiredness, reduced quality of sleep and worsening of neurobehavioral symptoms. Subjective measures such as self-administered questionnaires provide information on sleep disturbances and how the patient perceives them. However, there is no correlation between subjective and objective measurements of menopause-related sleep disturbances.

One of the main symptoms in post menopause is precisely the disturbance of sleep. Sleep quality is crucial determinant of health status and quality of life in general.

15.4.6 OSA in Postmenopausal Women

In the *Wisconsin Sleep Cohort Study,* menopause was found to be a risk factor for OSAS. Regardless of age, alcohol consumption, smoking, hypertension, exercise, cardiovascular disease, and physical condition, postmenopausal women experience mild OSAS 2–6 times more than premenopausal women. If severe OSAS found, postmenopausal women present it 3.5 times more than premenopausal women [32].

Although a lower severity of OSAS has been observed in women, the consequences are similar or even worse, especially in women with a higher risk of suffering from arterial hypertension, endothelial dysfunction, anxiety, or depression (common in post menopause). OSAS tends to be less severe in premenopausal and postmenopausal women under hormonal treatment [4].

Changes in cerebral white matter have been observed in women with OSAS compared to men, which may reflect of the poor quality of life that these women have [33]. Such effect in the quality of life is quantified with a negative impact woman's social life, physical and psychological health, as well as on labor productivity.

Women, who suffer from sleep-disordered breathing (SDB), have lower levels of estrogen and/or progesterone, hence the higher prevalence in postmenopausal patients. Rowley et al. reported that estrogen/progesterone decrease the CO2 apnea threshold and sensitivity to hypercapnia or hypoxia, causing less respiratory stability, which explains why sleep apnea is less frequent in premenopausal women [18].

The risk of OSAS is more significant with increasing age and body mass index (BMI). As they age, they have an increase in BMI, with a predominance of central

fat deposition [34]. A greater severity of OSAS has been reported in obese women. Sleep apnea is an independent risk factor for coronary heart disease, regardless of obesity.

Greenberg-Dotan et al. found that women with OSAS are more likely to have comorbidities such as cardiovascular disease and diabetes, and greater propensity to develop dementia and cognitive decline. OSAS involves oxidative stress, inflammatory processes, endothelial damage, sympathetic activation, and metabolic alterations predisposing to atherosclerosis, making it a common cause of systemic arterial hypertension. Hypoxia causes oxidative stress that causes an overproduction of reactive oxygen species, which generate endothelial dysfunction and, therefore, atherosclerosis [35].

15.4.7 Determination of Sleep Disturbances in Post Menopause

The determination of sleep disturbances in menopausal patients includes subjective and objective measurements. A sleep history and sleep–wake diary help identify sleep hygiene problems, sleep duration, circadian rhythm abnormalities, insomnia, and primary sleep disorders. The techniques that *provide* objective information are polysomnography and wrist actigraphy. Polysomnography assesses sleep and is particularly useful in evaluating sleep disorders related to breathing, narcolepsy, sleep-related movement disorders, sleep disturbances, and the circadian cycle [36].

The continuous electroencephalogram allows the determination of the sleep architecture, including the distribution in the different stages of sleep. Respiratory monitoring and electromyogram of the legs allow the determination of intrinsic sleep abnormalities.

Take-Home Message

- Throughout life, women are continuously influenced by different hormonal levels (from menarche to menopause) that are dynamic and affected by the various reproductive stages. These hormonal changes put the female sex at a higher risk of sleep disturbances and the circadian cycle.
- Obstructive sleep apnea has been more prevalent in premenopausal women with Polycystic Ovary Syndrome especially in obese patients.
- Pregnancy is a state with an increased risk of OSA despite a higher level of sex hormones.
- Approximately 20% of women develop obstructive sleep apnea syndrome at menopause.
- Women, with untreated OSA, report more mood changes as anxiety or depression.

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Urological Issues Related to Obstructive Sleep Apnea

16

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There has been a long-time controversy on the relationship between urological issues and obstructive sleep apnea (OSA) due to all the comorbidities that are commonly related to this pathology (cardiovascular, neurological, psychiatric, endocrine, and metabolic) [1, 2]. Some urological conditions associated with OSA include erectile dysfunction, hormonal changes during puberty, irritative urinary tract symptoms, benign prostatic hyperplasia, neurogenic bladder, nocturia, lithiasis, etc. We will do a short review of the more relevant topics.

Based on the studies made by Master and Johnson, complemented by Helen Kaplan, the phases of sexual function have been defined as desire, arousal, and orgasm. Therefore, sexual dysfunction is the disturbance of any phases of human sexual response that causes dissatisfaction, and damages to sexual health and quality of life [2]. Erectile dysfunction (ED) is defined as the persistent disability to achieving and maintaining an adequate erection that can lead to an unsatisfactory sexual performance [3].

Synchronization of different components is required to achieve an appropriate erection. The first one is an adequate arterial filling that needs a competitive endothelial function at the same time. Almost 70% of erectile dysfunctions are caused by damage at this level. At the same time, the occlusive vein system impairs the blood outlet from the penis during erection. This implies that the relaxing process from the cavernous tissue and the endothelium dilatation mediated by nitric oxide might function is adequate [4]. It is clear that testosterone plays a fundamental role not only in sexual desire but in both erotic and nocturnal erections. In addition, there are

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testosterone receptors in the cavernous tissue and in obtaining nitric oxide synthetase, which is essential to produce nitric oxide.

Diseases such as diabetes, high blood pressure, metabolic syndrome, chronic kidney failure, chronic liver disorders, hyperuricemia, rheumatic disease, and chronic obstructive pulmonary tend to cause erectile dysfunction, that is classified by pathophysiology as mixed origin [2, 3].

In the context of a patient diagnosed with OSA, erectile dysfunction is generated secondary to hypoxemia, hypercapnia, and acid–base decompensation [3]. Likewise, the reduction of testosterone and prolactin levels is related to the severity of OSAS. Changes in values of sex hormones are considered the most critical factor in ED [5].

Hypogonadism in OSA must be diagnosed by measuring baseline testosterone on two separate moments, performed early in the morning [6]. However, there is controversy in defining the cutoff point. The American Urologic Association (AUA) guidelines are below 300 ng/dL [6], and the European Urologic Association (EUA) guidelines is 350 ng/dL [3]. We prefer the AUA cutoff point. However, the absolute contraindications to starting hormone replacement therapy according to the EUA guidelines are prostate and breast cancer, poorly controlled or uncontrolled congestive heart failure, and hematocrit >/= 54%. A hematocrit of 48%–50% is a relative contraindication, which would make hormone replacement therapy difficult in patients with OSAS and hypogonadism [3]. Therefore, bleeding therapy has been proposed for treatment in some cases.

Patients with OSAS during the night present intermittent hypoxia, which generates lesions in the axons of the peripheral nerves and in the myelin sheath and blocks or delays the transmission of neural signals, which will result in a prolonged reaction time for the corpus cavernosum reflex [4]. In addition, there may be endothelial injury and reduced nitric oxide synthesis, resulting in decreased conversion of guanosine monophosphate (GMP) to cyclic GMP (cGMP) in the smooth muscle, which increases smooth muscle contraction and reduces blood flow to the penis [4].

The treatment of erectile dysfunction can be carried out with first-, second-, and third-line treatments. In the first line, in addition to modifying reversible factors, such as controlling diabetes, losing weight, changing treatments that cause erectile dysfunction, controlling alcohol intake, and quitting smoking, among others, treatment should be started with phosphodiesterase five inhibitors (sildenafil, tadalafil, vardenafil, and avanafil) [3, 7]. The use of vacuum devices is an alternative for these patients.

Recent studies have found benefits in using CPAP in erectile dysfunction since CPAP therapy increases the levels of nitric oxide and nitric oxide synthetase [4]. Additionally, management with CPAP and sildenafil was superior to treatment with CPAP alone [8, 9].

If there is no response or the response is insufficient for the first-line treatment, in that case, intracavernous self-injection therapy can be given with alprostadil or mixtures (papaverine, phentolamine, alprostadil, etc.) [3, 7]. If these do not work or the patient cannot inject, the placement of penile prostheses is the treatment of choice. These prostheses can be semirigid or inflatable, depending on the

characteristics of the patients, with excellent results and high satisfaction rates for both patients and their partners [3, 7].

Additionally, a relationship has been established between sleep disorders, such as OSA and insomnia, and depression with hormonal changes during the pubertal period, which are more frequent in women than men [9–13]. Puberty begins with the release of gonadotropin-releasing hormone by the hypothalamus and the consequent activation of the pituitary–gonadal axis [14]. The hypothalamus regulates the sleep–wake and feeding circuits. These circuits establish a connection through the hormone hypocretin-1, which, through the nucleus accumbens, regulates feeding and locomotor activity and the transduction of signals in the cycle of light and darkness in the central nervous system [14]. However, the controversy persists.

A series of urological pathologies related to aging are probably aggravated in patients with OSAS since they are directly associated with sleep disorders. Although benign prostatic hyperplasia is responsible for most of these symptoms in men over 50 years of age, some studies show that OSAS patients have a higher prevalence of this pathology [15]. Others show that patients with OSAS present an increase in both obstructive and irritative urinary symptoms assessed in the international index of prostate symptoms (IPSS) [8] and an increase in nocturia and urinary incontinence, altering the quality of life of these patients [9, 15, 16]. On the other hand, it has been shown that patients with urinary symptoms, especially nocturia, alter sleep patterns [17], and their treatment improves these patterns [18].

Various studies show that urinary symptoms improve with the use of CPAP [8, 19], especially in patients with moderate to severe breathing sleep disorders that have high blood pressure and increased B-type natriuretic peptide, that is related to a higher cardiovascular risk. The use of CPAP decreases nocturia and these risks [19].

The origin of urological problems is multifactorial. A plausible theory, which is increasingly accepted, refers to the fact that the increase in oxidative stress resulting from an abnormal inflammatory response contributes to the development of urological diseases [20, 21]. The increase in these pathologies in patients with OSAS is because the pathophysiological mechanisms are similar [15].

A study carried out in Taiwan in 6180 patients with an average age of 47.8 years with a standard deviation of ±13.8, of which 1236 patients had OSAS, found an increase in benign prostatic hyperplasia (15.13 vs. 7.28%) OR: 2.54 (CI: 2.05–3.15), chronic prostatitis (4.37 vs. 2.16%) OR: 1.95 (CI: 1.38–2.74), erectile dysfunction (2.91 vs. 0.97%), 2.95 (CI 1.89–4.61), urinary incontinence (3.32 vs. 0.87%), OR: 4.13 (CI: 2.63–6.50), urinary stones (12.06 vs. 6.80%), OR: 1.89 (CI: 1.53–2.33), and prostate cancer (0.97 vs. 0.40%) OR: 2.14 (CI: 1.03–4.43) [15] (Table 16.1).

These findings have been consistent in other studies [1, 9, 15, 16].

There is a potential bidirectional relationship between chronic kidney failure and OSAS, supported by epidemiological and experimental studies. End-stage renal failure likely contributes to OSA due to fluid accumulation, uremic toxins, metabolic acidosis, and changes in chemoreceptor sensitivity, which will produce a narrowing of the pharynx. OSA contributes to chronic renal failure through increased blood pressure, renal hypoxia, and oxidative stress. However, these studies are

Table 16.1 Relationship between urological pathology and OSA [15]

Benign prostatic hyperplasia: (15.13 vs. 7.28%)	OR: 2.54 (CI: 2.05–3.15)
Chronic prostatitis: (4.37 vs. 2.16%)	OR: 1.95 (CI: 1.38–2.74)
Erectile dysfunction: (2.91 vs. 0.97%)	OR: 2.95 (CI 1.89–4.61)
Urinary incontinence: (3.32 vs. 0.87%)	OR: 4.13 (CI 2.63–6.50)
Urinary stones: (12.06 vs. 6.80%)	OR: 1.89 (CI: 1.53–2.33)
Prostate cancer: (0.97 vs. 0.40%)	OR: 2.14 (CI: 1.03–4.43)

performed in patients with renal replacement therapy, so the controversy persists [22]. Mao H's group has carried out a systematic review with 18 studies, including 4568 patients. They found that the levels of cysteine and proteinuria are elevated in patients with OSAS. In addition, the glomerular filtration rate was decreased, independent of factors such as arterial hypertension and diabetes, concluding that OSAS was associated with a higher risk of early kidney failure [23].

Patients with clear cell cancer of the kidney who have undergone nephrectomy with OSAS have a worse histological Fuhrman grade (57% vs. 31%). The pathophysiological mechanism of this behavior is still not understood [24].

Take-Home Message

- There is a close relationship between OSAS and urological diseases, either due to common pathophysiological processes or associated comorbidities. In some cases, due to mechanisms not yet understood.
- The alteration of sexual function, in different phases such as desire due to hormonal alterations and erectile dysfunction due to mixed factors, including endothelial alterations may improve by controlling reversible factors. Early treatment consists of the use of phosphodiesterase five inhibitors (sildenafil, tadalafil, vardenafil, avanafil) or use of vacuum devices. Second-line therapies include self-injection program, and third-line therapies include the use of penile prostheses.
- Urinary tract symptoms alter sleep patterns, and treatment improves these patterns. There is increasing evidence that patients with OSAS have a higher risk of increasing urinary symptoms, especially nocturia and a higher risk of benign prostatic hyperplasia, chronic prostatitis, urinary incontinence, lithiasis, prostate cancer, and renal failure. Treatment, including the use of CPAP, greatly improves the symptoms of these entities.

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Dangerous Liaisons: Obstructive Sleep Apnea, Dysbiosis, and Chronic Inflammation

17

Silvia Sánchez-Ramón and María Guzmán-Fulgencio

17.1 Introduction

Sleep represents approximately one-third of the human life span that is essential for maintaining and repairing various physiological functions of the body, including immune homeostasis [1]. Sleep is a reversible physiological process ultimately controlled by dynamic changes of neuropeptides in the brain. It has been well documented that diverse neurotransmitters, such as serotonin (5-hydroxytryptamine, 5-HT), γ-aminobutyric acid (GABA), norepinephrine, dopamine, and glutamate, have waking-promoting functions [2, 3].

Besides diverse regulatory mechanisms (nervous, endocrine, and immunological), it exerts reciprocal regulatory effects in what has been considered a metasystem. Indeed, some factors, such as inflammatory cytokines and the hypothalamic–pituitary–adrenal (HPA) axis are also found to be associated with sleep physiology [4–6].

Obstructive sleep apnea (OSA) refers to apneic episodes during sleep resulting from restricted airflow through the upper airways [7]. There are three types of obstructive breathing events: apnea, hypopnea, and respiratory effort-related arousal. OSA is the most prevalent (yet underdiagnosed) chronic sleep-related breathing disorder in children and adults, with an estimated prevalence of almost one billion people worldwide, exceeding 50% in some countries [8]. OSA affects 9%–37% of men and 4%–50% of women, with men being more severely affected than women [9, 10]. Known risk factors for OSA include obesity, middle age, male

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sex, increased neck circumference, enlarged tongue or tonsils, and retro/micrognathia [7]. OSA causes sleep fragmentation, increased daytime sleepiness, impaired concentration, and fatigue, among other manifestations. The repetitive collapse of the upper airway during obstructive sleep apnea/hypopnea induces frequent, transient, brain hypoxic episodes. In addition, the loss of cerebrovascular reactivity in sleep, particularly in OSA, means that physiologic compensatory mechanisms may not ensure adequate brain oxygen levels [11].

Sleep disturbances like OSA have a bidirectional relationship with inflammation. OSA is more prevalent in patients with immune-based diseases than in the healthy population. Disrupted sleep can result in decreased quality of life and chronic fatigue; it might also worsen other symptoms, such as pain and discomfort, which, in turn, further affects sleep quality [12, 13]. Sleep disorders are very diverse and common in chronic autoimmune and inflammatory diseases. For instance, joint erosive degeneration in patients with rheumatoid arthritis (RA) is frequently associated with a high risk of OSA [14]. In other cases, such as demyelinating diseases or multiple sclerosis (MS), lesions affecting white matter at the cervical cord or neuron degeneration might contribute to OSA or restless leg syndrome [15]. In addition, OSA independently contributes to the risk of developing inflammatory disorders and major depressive disorder.

Genetic predisposing factors associated with OSA relate to Human Leukocyte Antigens (HLA) in humans. HLA molecules present peptide antigens to T lymphocytes: HLA class I molecules present antigens to $CD8^+$ T lymphocytes, while HLA class II to $CD4^+$ T lymphocytes. HLA-DRB1 allele frequencies of HLA-DRB1*03 alleles have been described as significantly associated with OSA in some populations [16, 17]. There is an urgent need to better understand the complex relationship between microbiome, inflammation, and OSA converging to a vicious cycle of chronic inflammation, cardiovascular, neuropsychiatric, and neurodegenerative manifestations, as well as cancer through omic approaches. A deeper analysis of the immune signatures of OSA might help to approach the OSA conundrum in a more personalized way, more aligned with the pathophysiology in the individual patient.

17.2 Immune Response and OSA

Sleep is crucial for developing the proper functioning of innate and adaptive immune responses and adequate immune homeostasis [18]. In addition, disruption of normal sleep, in OSA can weaken immunity, increasing susceptibility to infection and inflammatory diseases.

Sleep consists of two main phases that take place in the form of repeated cycles: the nonrapid eye movement (NREM) phase followed by the rapid eye movement (REM) phase (successive NREM-REM cycles). NREM sleep phase is further subdivided into three “stages”: N1, N2, and N3, which parallel a continuum of sleep depth. Stage 3 sleep is also referred to as slow-wave sleep (SWS). SWS predominates in the night’s first half, while the REM phase predominates in the night’s second half [19].

On one hand, a recent study shows that sleep might facilitate the homing of the T helper lymphocytes (Th cells) to lymph nodes, where they can get into contact with an antigen, differentiate, proliferate and produce proinflammatory cytokines [20]. Sleep NREM and REM phases correlate with changes in innate immunity, involving the production and release of systemic cytokines, such as IL-6, TNF, and IL-1β. On the other hand, the specific effects of immune circadian oscillators and sleep-dependent processes are complicated to determine. On the other hand, the influence of cytokines on sleep brain control is complex and challenging to approach, and study results are heterogeneous. Also, sleep disturbances increase the production of reactive oxygen species, the number of circulating monocytes, and monocyte trafficking [21]. In this review, we focus on the relationship between major proinflammatory cytokines TNFα, IL-6, IL-1β, and the role of sleep in the nocturnal regulation of the inflammatory biology dynamics and the setting of OSA (Fig. 17.1).

IL-6 is a proinflammatory and pyrogenic cytokine [22]. IL-6 is a main promoting factor of Th17 cell differentiation, affecting the regulatory T cells (T_{Reg})/Th17 equilibrium, enhancing proinflammatory response [23]. Accompanied by other cytokines, it might also impair the regulatory function of T_{Reg}, advancing inflammation [23]. Some authors report increased levels of IL-6 in both short and extremely long sleep. There are two circulating peaks of IL-6 driven by circadian control (Vgontzas, 1999). Chronic disruption of normal sleep and the circadian rhythms amplify the secretion of IL-6, as occurs in autoimmune diseases, such as RA, celiac disease (CD), or psoriasis [22, 24, 25]. According to these authors, when IL-6 is administered to humans, it decreases SWS during the first half of the night and increases in the second half [22]. This might be because of short-term stimulation of cortisol production (physiological peak of which occurs around the sleep offset) by this cytokine [22]. However, increased IL-6 in general correlates with decreased SWS [26]. Sleep deprivation (SD) during night's early period alters the cytokine's pattern

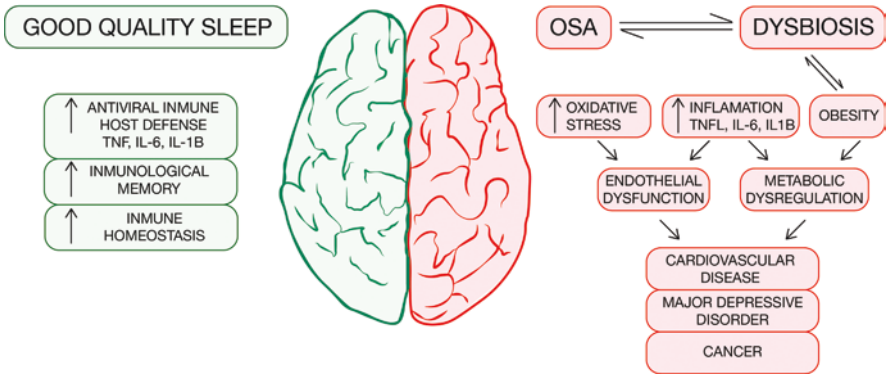

Fig. 17.1 Adapted from [91]. The "cross-talk" among immune system, adipose tissue and intestine and mechanistic actors and mediators associated with main components in the pathogenesis of the relationship OSA and sleep. Abbreviations: *IL* interleukin, *IFN* interferon, *TNF* tumor necrosis factor

of secretion: the IL-6 peak occurs later, and serum cytokine levels stay relatively low [19]. IL-6 increase has been associated with restless leg syndrome (RLS). This cytokine induces hepcidin production by hepatocytes, which decreases iron absorption in the intestines and inhibits iron release from the macrophage, leading to hypoferremia, which is associated with fatigue, irritability, and RLS [27].

IL-1β is a pyrogenic proinflammatory cytokine. Increased IL-1 β has been involved in the pathophysiology of systemic autoimmune diseases, such as RA, systemic lupus erythematosus (SLE), immune-mediated thyroid diseases [28] and autoinflammatory syndromes. IL-1β might enhance NREM sleep and sleep intensity [29]. This effect is thought to be mediated by the IL-1 receptor [29]. SD was reported to increase IL-1β serum levels, which could potentially promote processes such as the production of plasmocytes, dendritic cells, and M1 macrophages, as well as the production of Th cells and cytotoxic T lymphocytes [30, 31]. An increase in IL-1β serum levels after SD suggests the activation of the inflammasome. The inflammasome is a multimeric complex formed in response to a variety of physiological and pathogenic stimuli, as an essential component of the innate immune response. It consists of caspase-1, an adaptor protein, and the NLR family pyrin domain containing 3 (NLRP3), which cleaves IL-1, forming IL-1β and α. Excessive inflammasome activation is also a significant driver of autoimmune and autoinflammatory diseases. Several lines of evidence suggest that the inflammasome is involved in shaping the sleep architecture during inflammation. Interestingly, NLRP3 knock-out (KO) mice, showed a different response to SD than wild-type (WT) mice: their NREM intensity (as measured by delta power) did not differ significantly from the baseline, whereas in WT mice this parameter was increased [32]. Also the REM phase, usually not associated with IL-1β: REM phase duration and frequency, was also altered only in WT mice [32]. Inflammasome also partakes in the process of IL-18 formation, which stimulates the production of INFɣ by T and natural killer cells. INFɣ is associated with immune-mediated diseases, such as SLE or CD [31].

TNFα is another systemic proinflammatory cytokine whose primary origin is microglia. Diverse brain regions involved in sleep control, such as the hypothalamus, hippocampus, and brainstem harbor immunoreactive neurons for IL-1β and TNFα and their receptors. Increased levels of TNFα have been described in sleep disorders, for instance, in OSA, and autoimmune diseases, such as RA, CD, and psoriasis [33, 34]. It, in turn, stimulates the production of proinflammatory mediators, inducing the recruitment of immune cells. It suppresses T_{Reg}, enhances nociception in the central and peripheral nervous system, and might stimulate enzymes contributing to tissue degeneration [35]. TNFα shows a bimodal action: it appears to promote the NREM phase while, in higher doses, it suppresses REM in animal models [36]. According to human study, higher levels of TNF after intravenous endotoxin administration were associated with increased sleep propensity [37]. According to another study, after central administration, TNFα enhanced sleep intensity in NREM [29]. It appears that serum levels of TNFα are not affected by SD or sleep disturbances, although the results of the studies are controversial [19]. Some studies have suggested that such alterations in sleep architecture (REM

suppression and NREM increase) might facilitate fever: energy is spared through long NREM, whereas shorter time spent in REM allows for shivering [38].

17.3 Inflammation and OSA: Two Bad Companions

There is recent consensus that OSA is a low-grade chronic inflammatory disease by itself [39]. Several pathophysiologic mechanisms upregulated in OSA, including elevated sympathetic nervous system activity, renin-angiotensin aldosterone system activation, endothelial dysfunction, inflammation, and metabolic dysregulation, dysbiosis and obesity, as well as associated immune-based disorders impact negatively the course of OSA (Fig. 17.1).

Attenuation of inflammation is mediated through the hypothalamic–pituitary–adrenal (HPA) axis, a highly complex network of endocrine interactions between the hypothalamus, the pituitary gland, and the adrenal gland, through cortisol production. Sleep disorders can disrupt HPA function and its delicate equilibrium. Shift work, a factor associated with sleep disorders, can also influence the daily secretion of cortisol (HPA activity marker) [40]. One longitudinal study on young (mean age, 30 years old) subjects showed that waking levels of cortisol were higher in shift workers, total secretion was increased, and the fall-off occurred faster [41]. Other studies have shown opposite results, with waking cortisol levels being decreased and slope flatter (which might also be a sign of HPA dysfunction) [42]. HPA dysfunction appears to be associated with OSA and its comorbidities [43]. In studies both in nonobese males and obese females with OSA, cortisol levels are increased compared to controls [44]. Interestingly an increase in adrenal gland size was associated with sleep fragmentation in OSA patients [45], thus further supporting the association between the HPA axis and OSA [45]. Continuous positive airway pressure (CPAP) treatment, a standard therapy for OSA, also appears to lower cortisol levels [43]. The role of the HPA axis in OSA patients requires further studies, as its understanding might help to alleviate comorbidities, such as hypertension.

In addition, patients with OSA have high circulating levels of inflammatory markers, including high sensitivity C-reactive protein (CRP), IL-6, IL-8, TNFα, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 [46, 47]. In the inflammatory disease context, the coexistence of OSA with asthma is common, partly due to the high prevalence of both diseases in the general population and the shared risk factors and genetic background. A bidirectional link has been described between the two diseases with mutual adverse consequences for each other: On one hand, OSA modifies asthmatic airway inflammation and is associated with poor asthma control. On the other hand, asthma and its medications increase the collapsibility of the upper airways contributing to the development and worsening of OSA. Apart from common risk factors, such as obesity, gastroesophageal reflux disease, and allergic rhinitis, emerging evidence suggests that the two disorders may complicate the clinical course of each other [48].

To summarize, inflammation and sleep have a complex and reciprocal relationship. Acute and chronic SD might lead to an increase in proinflammatory mediators,

disrupting various immune functions and the neuroendocrine control through HPA axis, which might be a significant risk factor for immune-mediated diseases.

17.3.1 Chronic Inflammatory Diseases and OSA

Sleep-disordered breathing appears to make people more susceptible to immune-mediated disorders [18]. Indeed, OSA patients are at greater risk of autoimmune or inflammatory diseases, such as psoriasis (prevalence 8.7% versus 2% in the general population), RA (adjusted hazard ratio (aHR) 1.33), Sjögren syndrome (SS)-aHR 3.45), and Behçet disease (BD)-aHR 5.33) [49–51]. The interaction between OSA and the autoimmune disease, as in many such cases, might be bidirectional (the influence of immune-mediated diseases on the OSA development has already been discussed above). Another aspect of this relationship is the influence of OSA on the immune system. Intermittent hypoxia, which might increase hypoxia-inducible factor 1 (HIF-1), is proposed to influence the Th17 cells/T_{Reg} cells balance, an important factor in the development of immune-mediated diseases, such as psoriasis, RA, inflammatory bowel disease (IBD), and MS [52, 53]. HIF-1 might inhibit T_{Reg} differentiation, as well as promote the formation of proinflammatory T_{Reg}, which produce interferon (INF)-ɣ) [52]. HIF-1 also stimulates the production of Th17 (and subsequently IL-17), shifting the balance in favor of effector immune response instead of tolerance [52].

It has also been suggested that hypoxia causes the deposition of uric acid in cells, which has been linked to cell-mediated autoimmune reactions [54]. Individuals with OSA were also shown to have elevated levels of proinflammatory cytokines, indicating dysregulation of the immune system [54].

According to one study, treatment with CPAP decreases the hazard ratio (HR) to 0.22 for RA and 0.51 for other autoimmune diseases, which were not specified by the authors [50].

Changes in the immune system caused by sleep disorders are still a subject for research. Sleep disorders might not only negatively affect the risk of disease development (e.g., OSA increases the aHR for BD, SS, and psoriasis) but also the disease course (e.g., causing more frequent relapses). As studies show, drugs used in treating of chronic inflammatory diseases, such as steroids or monoclonal antibodies, also influence sleep in more complex ways than those resulting from attenuation of the disease symptoms. Such discrepancies might be a result of treatment effects (e.g., steroids are known to worsen sleep quality), psychiatric disorders (e.g., depression, which is known to cause insomnia disorder, is more prevalent in individuals with autoimmune diseases), comorbidities, or socioeconomic factors [55]. Data on the prevalence of OSA in IBD patients are scarce. However, it seems to be similar to that of the general population, and lower in comparison with other immune-mediated diseases. A possible explanation for this finding is that obesity, a strong risk factor for OSA, tends to be less prevalent in IBD (18%) as compared to the general population (28%) and other diseases (32%–50% in fibromyalgia, 20%–31.6% in RA, 28.3% in MS) [18, 55]. There has been no research on the

differences in OSA prevalence between ulcerative colitis (UC) and Crohn's disease (CrD) patients. The risk for OSA in psoriasis appears to be associated with disease severity, and psoriatic arthritis, with incidence ratios rising for mild, severe, and rheumatologic forms. One factor contributing to this finding might be that the degeneration of joints (e.g., cricoarytenoid and temporomandibular) can obstruct the airflow in patients with psoriasis. Moreover, as the study shows, psoriasis increases the risk of obesity within 10 years, further exacerbating the risk of apneas/hypopneas [56]. Sjögren syndrome and Behçet disease patients have an increased risk for OSA, with males' risk being more than two times as high as females' [49].

17.4 The Immune–Gut Microbiome Axis: The Third Wheel to Inflammation and OSA

Exploration of the gut microbiome has added new medical advances since dysbiosis has been linked to many comorbid illnesses, including OSA. Besides, the current evidence suggests that gut microbiota plays a significant role in the emergence and progression of some metabolic disorders like obesity [57].

With the increasing comprehension of the brain–gut–microbiome (BGMA) axis, a bidirectional communication channel linking the brain and gut, the roles of gut microbiota (GM) in sleep much attention is being paid. Evidence has shown that GM is essential for maintaining normal sleep physiology. In turn, it has also been demonstrated that abnormal sleep patterns and duration affect the GM's composition, diversity, and function through the BGMA [58]. A balanced homeostasis of GM is critical for maintaining physiological sleep, and certain genera have been proved to be directly associated with good sleep quality. In turn, disturbed sleep also affects the composition, diversity, and function of the GM. Overall, current evidence supports the relationship between OSA and increased *Firmicutes:Bacteroidetes* ratio, lower diversity of GM, and elevated low-grade system inflammation [58]. Therefore, it is generally accepted that GM may serve a crucial role in the development of OSA. Studies of OSA and GM in children have shown a decreased microbial diversity concerning healthy subjects in terms of the number of observed species and *Chao1 index* ($p = 0.01$). *Firmicutes/Bacteroidetes* ratio was directly correlated to Sleep Clinical Record ($p = 0.03$). The abundance of several inflammation-related strains (*Proteobacteria, Clostridiaceae, Oscillospiraceae, Klebsiella*) significantly modified concerning sleep parameters. Bacteria implied in the gut barrier integrity (*Desulfovibrionaceae, Bacteroides fragilis,* and *Faecalibacterium prausnitzii*) were significantly different in the two study groups and correlated with sleep parameters [59].

Evidence has shown that exposure to chronic intermittent hypoxia results in significant changes in GM, manifesting as increased *Firmicutes* richness and decreased *Bacteroidetes* richness, as well as a decline of α-diversity in GM [60].

17.5 Organ Interactions in the Pathogenesis of OSA and Dysbiosis

OSA adversely affects multiple organs, systems and conditions such as oxidative stress, systemic inflammation and obesity. Interestingly, some authors suggest that altered sleep and oxygenation patterns, as seen in OSA, will promote specific alterations in the gut microbiota that in turn, will elicit the immunologic alterations that lead to OSA-induced end-organ morbidities [61]. These close interactions between dysbiosis and OSA share the common pathophysiologic feature of metabolic and endothelial dysregulation (Fig. 17.1).

There is widespread consensus that OSA is an oxidative stress disorder. Apnea in OSA produces a decline in oxygen levels, followed by reoxygenation when breathing resumes. Intermittent hypoxemia causes anoxia and reoxygenation in OSA patients, which contributes to the production of oxygen radicals and elicits local and systemic inflammation [62]. Also, fat accumulation in obesity increases endoplasmic reticulum (ER) stress in adipocytes lead to increased production of ROS which contributes to chronic inflammation, tissue dysfunction, and oxidative stress, directly relating it to obesity-associated neoplastic transformation and DM2 in breast cancer cells [63].

It is widely accepted that the role of OSA in the progression of endothelial damage is mediated by inflammation. Indeed, both obesity and OSA are associated with vascular endothelial inflammation and increased risk for cardiovascular diseases. In OSA, normal ventilation is affected during sleep due to upper airway narrowing. In addition, several studies directly related hypoxia from OSA with endothelial dysfunction [64], and nocturnal endothelin levels correlated with OSA severity and increased ambulatory blood pressure [65]. Several studies have also shown an improvement in the endothelium function with successful treatment of OSA [66–68].

The relationship between metabolic disorders and OSA is multidirectional. Moreover, OSA alters glucose metabolism, promotes insulin resistance (IR), and is associated with the development of metabolic syndrome, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) [69]. OSA or sleep deprivation would elevate the risk of developing IR, while diabetes would worsen sleep quality [70]. Among the most important are glucose intolerance and IR, which are risk factors developing diabetes and cardiovascular disease [71], liver disease, cancer, and neurodegeneration [72].

The association between OSA and impaired fasting glucose, glucose tolerance and diabetes is widely demonstrated, with no differences between obese and non-obese patients [73]. A metaregression analysis of 107 datasets with 18,116 pooled patients, found that patients with OSA appear to have increased dyslipidemia (high total cholesterol, LDL, triglycerides (TG), and low HDL) [74]. However, recent studies have also shown a relationship between OSA and hepatic steatosis, fibrosis, and NAFLD [75], as well as chronic kidney disease [76, 77].

17.6 Immunomodulatory Therapy of OAS

17.6.1 Monoclonal Antibodies

Therapy with monoclonal antibodies targets specific relevant mediators for treating immune-mediated conditions. In a study on patients with spondyloarthritis, treatment with an anti-TNF antibody (golimumab) was shown to improve sleep quality measured by using *Jenkins Sleep Evaluation Questionnaire* [78]. Improvement was seen only in patients whose clinical parameters (i.e., pain, overall functionality, and signs of inflammation) were better than the baseline. Thus, this increase in sleep quality might be attributed to pain amelioration [78].

A study on the influence of adalimumab on sleep quality in patients with ankylosing spondylitis (AS) brought similar results: treatment improved sleep adequacy and reduced somnolence (reported subjectively by the patients, the assessment was performed by using *Medical Outcomes Study Sleep Scale*) [79]. Sleep quality improvement was also associated with improvement in other parameters: back pain, C-reactive protein concentration, etc. [79].

In another study conducted on RA patients treated with infliximab (IFX), it was observed that IFX administration improved sleep structure by decreasing the number of arousals and sleep latency time of phases I and II NREM and increasing sleep efficiency, duration of REM, and SWS in the night following the drug administration. Psychomotor tests were performed within 15–18 h after IFX infusion [80]. Vigilance was enhanced; however, daytime sleepiness remained the same. However, there was no improvement in clinical parameters, such as the number of swollen/tender joints and morning stiffness, so the mentioned changes cannot be attributed to disease amelioration [80].

Other therapies with monoclonal antibodies also yield promising results. Subjective sleep quality and daytime sleepiness (measured using *Pittsburgh Sleep Quality Index* (PSQI) and Epworth Sleepiness Scale (ESS)) improved in RA patients after the therapy with IL-6 antibody tocilizumab (TCZ) [81]. As another study shows, treatment with TCZ reduced fatigue, as measured by The Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT Fatigue Scale) [82]. Disease activity was not significantly associated with daytime sleepiness or sleep quality, thus suggesting that blocking of this cytokine alone can improve sleep.

Therapy with ixekizumab, an anti-IL-17A antibody, improved fatigue and sleep quality in patients with AS. Those effects were most evident in subjects whose clinical status has improved; thus, the changes mentioned earlier can result in disease amelioration [83].

Therapy with monoclonal antibodies might decrease inflammation, thus alleviating pain, which can account for better sleep quality. However, since proinflammatory cytokines can influence the sleep structure, changes in their levels following the therapy might affect sleep independently of clinical outcomes.

17.6.2 Probiotics

Modulation of the microbiota composition through probiotics administration was shown to have a beneficial effects on immune-mediated diseases. In SLE mice administrated with probiotics, IL-10 was increased, IL-6 diminished, and the intestinal barrier permeability also improved [84]. According to the *European Crohn's and Colitis Organisation*, probiotics might be effective in inducing remission in UC; however, they do not have better effects than mesalamine in terms of remission maintenance [85]. Probiotic treatment was also ineffective in CD [85]. Alterations in the serum levels of cytokines, such as an increase in IL-10 and a decrease of IL-6, without changes to TNFα, in MS patients have been reported [86]. RA patients experienced a reduction in IL-6, IL-1β, and TNFα and an increase in IL-10 [87]. Changes in cytokine levels might cause pain and inflammation alleviation, which could contribute to the improvement of sleep quality; however, more studies on the subject would be desirable. Probiotic administration might also directly influence sleep quality and structure. VSL3, a probiotic drug, can elevate butyrate levels, which increases the NREM phase while reducing the number of REM episodes in rats [88, 89]. Similarly, prebiotics increasing *L. rhamnosus* administered to mice in their early life increased time spent in NREM (this effect was not long-lasting) [90]. Those prebiotics also increased REM sleep duration after a stressful situation [90].

Probiotic therapy might find application as an adjuvant treatment in immune-mediated diseases. However, it can yield clinically significant benefits and has negligible side effects.

Therapy of patients with chronic inflammatory diseases requires addressing sleep problems, as they may affect the course of the underlying disease.

17.7 Concluding Remarks and Future Challenges

A better understanding of the complex relationship between microbiome, inflammation, metabolic syndrome, and OSA converging to a vicious cycle of chronic inflammation, cardiovascular, neuropsychiatric, and neurodegenerative manifestations, as well as cancer, through omic approaches, is crucial. Therefore, a deeper analysis of the immune signatures of OSA is needed to approach the OSA conundrum in a more personalized way, more aligned with precision medicine.

Take-Home Messages

- The connection between OSA and the immune response is complex, multifactorial, and modulated by genetic predisposition and biological and lifestyle factors.
- Inflammation and gut microbiome dysregulation are critical actors in the pathogenesis of OSA.
- OSA, dysbiosis, and chronic inflammation conform a dangerous triangle predisposing to cardiovascular, neurodegenerative, psychiatric, inflammatory diseases, and cancer.

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General Practitioner, Sleep Disorder Breathing, and Public Health

18

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Most patients first discuss their sleep problems with their family physicians. So, this doctor must be trained to identify the main sleep disorders and guide their management. The family doctor has the best technology to evaluate the patient with complaints of sleep disorders and it is not polysomnography but the clinical history. A good clinical history should draw the details of the symptoms during sleep and wakefulness in a kind of "24-h drawing" that gives an idea of the subject's performance and mood during sleep and during their work activities, leisure, and social relations (see Chap. 3). Ideally, the clinical history must be accompanied by information from the bed partner who can report on details of the patient's sleep, when he gets out of bed, or his mood during the day. In this chapter, we describe the current role of the PCP in the management of patients with OSA and the improvements that should be implemented for their care.

18.1 Burden of Sleep Disorders in Primary Care

The primary care physician (PCP) is the gateway to the health system and has, among other things, the responsibility of early detection of various acute and chronic diseases based on the symptoms that patients present. Of course, health disorders that are not associated with specific symptoms (hypertension, dyslipidemia,

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diabetes) and which, given their prevalence and importance for health, must be diagnosed by carrying out the corresponding screening (blood pressure measurement, blood tests). Other clinical entities are not perceived by patients as "important enough" to discuss with the physician (insomnia or sleep apnea). PCPs rarely ask about their patients' sleep problems [1] and consequently, many patients remain undiagnosed for many years. This is especially serious for patients with OSA for two reasons: its high prevalence ranging from 5% to 50% of adults depending on age and sex [2], and because OSA has been associated with neuropsychological impairment, metabolic syndrome, motor vehicle accidents, decreased quality of life, and increased mortality [3–6]. Treatment of OSA improves clinical outcomes and is cost-effective [7]. Despite these facts, the United States Preventive Services Task Forces, the American Academy of Family Physicians, and the Center for Disease Control have not recommended routine screening for sleep disorders [8].

In a recent survey in a primary care clinic, high risk for OSA was found in 33%, insomnia in 30%, and restless legs syndrome in 22% [9]. Interestingly, validated questionnaires such as the Berlin and de STOP questionnaires can efficiently identify those patients at risk for these common sleep disorders. Most PCP lack confidence in managing OSA and have objective knowledge gaps [10]. However, several recent studies have demonstrated that primary care physicians can effectively manage sleep disorders with appropriate training [11].

18.2 Roll of Primary Care Physicians (PCP) in Obstructive Sleep Apnea

As stated by the recent International Consensus Document on Obstructive Sleep Apnea [12], the role of the primary care physician (PCP) in OSA includes:

1. Improving the underdiagnosis of OSA.
2. Identifying the most severe cases and bringing these patients to referral centers as soon as possible.
3. Coordinate with reference centers of sleep disorders to work as a network.
4. Collaborate in the initiation and follow-up of ventilatory support therapies, including treatment with continuous positive airway pressure (CPAP).
5. Evaluation, follow-up, and management of comorbidities in patients with OSA.

Barriers have been identified for PCPs to meet the above goals. The factors that have been identified in most primary medicine centers were the lack of knowledge, skills, and attitude. Therefore, the patients were underdiagnosed, undertreated, and with a low level of prioritization [13, 14]. In the following sections, we propose the theoretical bases of a minimum of knowledge about OSA that every PCP should have.

18.3 Diagnosed Suspicion of OSA in Primary Care

The general practitioner should complete any clinical history asking about symptoms related to sleep quality. Clinical suspicion, and therefore the diagnostic process, should be initiated in all those patients who complains of at least two of the three main symptoms of OSA: snoring, witnessed apneas, and/or excessive daytime hypersomnolence. However, these symptoms are not exclusive to OSA and are common in the general population. Therefore, there isn't a need to refer simple snorers, obese or hypertensive patients without other accompanying symptoms or hypersomnolence justified by other causes to sleep clinics. However, sometimes OSA presents with other symptoms and/or may be less symptomatic. There are groups of patients with specific symptomatic presentations. For example, unjustified intense daytime tiredness is a predominant symptom in patients with heart failure or metabolic diseases,. In patients with COPD or heart failure, snoring and daytime hypersomnia are usually less striking. The PCP should suspect OSA in subjects with (a) type II obesity or greater (BMI > 35), (b) short and wide neck (greater than 43 cm in men and 41 cm in women), (c) refractory hypertension, (d) tonsillar hypertrophy or soft tissue of the upper airway, and (e) other anomalies of the structure of the upper airway such as retrognathia.

OSA remains underdiagnosed in women. Physicians have a lower suspicion of OSA in females. On the other hand, they are more reluctant than males to complain of snoring. Finally, women reported more sleep and medical comorbidities such as depression, fibromyalgia, hypothyroidism, or chronic fatigue syndrome that ultimately can be attributed as responsible for daytime sleepiness. Hence, clinicians need to include OSA in their differential diagnoses when evaluating female patients.

To improve the suspicion of OSA, it is essential to consider conducting self-reported questionnaires in primary care since they have been shown to be as predictive as when they are used in a Sleep Unit. The STOP-BANG questionnaire substantially increases OSA diagnosis, mainly moderate and severe, so it would help improve underdiagnosis if used routinely [15]. STOP-BANG questionnaire is a concise, compelling, and reliable OSA screening tool. The probability of moderate to severe OSA increases directly to the STOP-BANG score. Patients with a STOP-BANG score of 0–2 can be classified as at low risk for moderate to severe OSA. Those with a STOP-BANG score of 5–8 can be classified as at high risk for moderate to severe OSA (Table 18.1). The latter must have a quick diagnostic procedure to confirm the presence and severity of OSA.

18.4 Referral Criteria to a Sleep Unit

Physicians in primary care usually use instruments and protocols for referral to the corresponding specialists. However, the same should happen with sleep disorders. In the case of OSA, an algorithm accepted in our health system appears in Fig. 18.1.

Patients who do not meet the criteria for preferential referral, but meet the criteria for clinical suspicion, should be referred by the usual route [12]. Simple snorers

Table 18.1 List of questions of the STOP-BANG questionnaire

STOP-Bang Questionnaire Please answer the following questions below to determine if you might be at risk of obstructive sleep apnea		
Yes	No	**S**noring? Do you **Snore Loudly** (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
Yes	No	**T**ired? Do you often feel tired, fatigued, or sleepy during the daytime (such as falling asleep during driving or talking to someone)?
Yes	No	**O**bserved? Has anyone observed you stop breathing or choking/gasping during your sleep?
Yes	No	**P**ressure? Do you have or are being treated for High Blood Pressure?
Yes	No	**B**ody mass index more than 35 kg/m^2?
Yes	No	**A**ge older than 50?
Yes	No	**N**eck size large? (Measured around Adams apple) Is your shirt collar 40 cm or larger?
Yes	No	**G**ender = Male?
OSA—Low Risk: Yes to 0 – 2 questions; OSA—Intermediate Risk: Yes to 3 – 4 questions; OSA—High Risk: Yes to 5 – 8 questions		

Modified from: Chung F et al J Clin Sleep Med Sept 2014

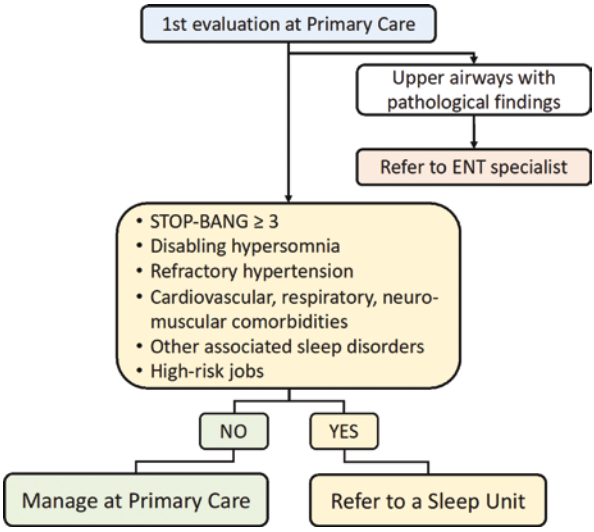

Fig. 18.1 Diagram for referral a patient with suspected OSA

or those patients with obesity or cardiovascular risk who do not present symptoms compatible with OSA or whose excessive daytime hypersomnolence could be justified by other causes should not be referred. However, if upper airway abnormalities are found on physical examination of any subject with or without OSA, he/she should be referred to the appropriate specialist (e.g., ENT surgeon).

18.5 Diagnostic Procedures in Primary Care

When the PCP is faced with a patient with suspected OSA, it is essential to collect a detailed and structured clinical history in the partner's presence. The following should be obtained: personal and family history of sleep disorders, sleep habits, psychological profile, alcohol intake, tobacco use, illegal drugs, and medicines. The STOP-BANG questionnaire should be grouped around daytime and nighttime symptoms related to suspected OSAS. Sleepiness should ideally be quantified using the Epworth scale [15]. Therefore, it is vital to assess the type and intensity of the clinical picture, with the repercussions on social and work life, and the comorbidities that the patient may present, such as hypertension, diabetes, heart failure, coronary artery disease, respiratory diseases, neurological diseases, etc. (Fig. 18.1).

After a complete history has been obtained, a systematic examination should be performed. Common physical findings can be observed in the craniofacial, nasal, pharyngeal, and dental areas. The oropharynx must be examined, and the degree of oropharyngeal crowding can be scored using the Friedman Tongue Position or the Mallampati scores. The patient should be weighed, measured, and his body mass index obtained. The circumference of the neck and abdomen should also be measured. Peripheral edema should be sought as a sign of possible coexisting heart failure. Blood pressure, heart rate, and basal SaO_2 obtained.

Randomized controlled studies have shown that outpatient management of OSA by sleep specialists, using home respiratory polygraphy (HRP) and auto-CPAP for titration studies, have the same results as those in sleep units using polysomnography [16]. However, few studies that have demonstrated the efficiency of the use of HRP by PCPs for the identification of patients with OSA. Validated HRP devices are now available that can be used with minimal training (Fig. 18.2). These polygraphs must record at least: (1) airflow detected by pressure sensors, (2) respiratory effort measured by thoracicabdominal bands, and (3) arterial oxygen saturation measured by pulse oximetry. As indicated in other chapters of this book, this type of record is sufficient to manage more than 80% of cases of suspected sleep-disordered breathing.

A recent International Consensus Document on Obstructive Sleep Apnea proposed that primary care use simplified studies with single- or double-channel devices based on oximetry and/or nasal pressure [12]. Nevertheless, this approach is

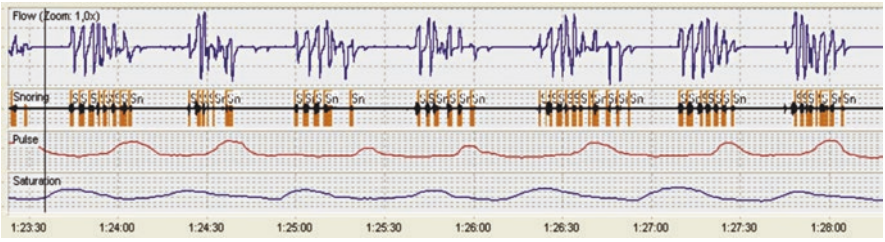

Fig. 18.2 Home respiratory polygraphy

only recommended for patients with a high probability of disease due to excessive daytime symptoms (Epworth ≥ 12) [17].

18.6 Role of the PCP in the Treatment of Patients with OSA

A primary role of the PCP is to encourage sleep hygiene measures and promote appropriate management of comorbidities for all OSA patients.

Can PCPs initiate CPAP treatment in patients with uncomplicated OSA? Some controlled studies have shown that management of OSA by sleep specialists, using HRP and auto-CPAP for titration studies, had similar outcomes to standard laboratory methods [16]. However, data is limited on the transferability of these results to a primary care setting.

Regarding the application of CPAP treatment by PCPs, a study from the Spanish Sleep Network showed non-inferiority in managing patients with an intermediate-high probability of sleep apnea from primary care compared to specialized care [18]. Another multicenter randomized study to assess whether initiation of CPAP treatment in a primary or specialized care setting affected adherence showed that the primary care setting was cost-effective and did not affect adherence. However, the improvement in ESS and patient satisfaction was superior in the hospital setting [19]. These studies are performed with PCPs previously instructed and trained in all aspects of OSA, so these results lack generalization. Therefore, at present time, the diagnosis of OSA must be made definitively, and a reference sleep unit must be initiated treatment with CPAP. Therefore, a primary role of the PCP is to encourage sleep hygiene measures and promote appropriate management of comorbidities for all OSA patients.

18.7 Follow-Up of Patients with OSA by PCPs

A patient with OSA does not suffer from a stable clinical entity over time; on the contrary, aggravating or "relieving" factors can modify the clinic of subjects suffering from OSA. Then the PCP must once again re-evaluate the patient according. Once a sleep unit has evaluated a patient with OSA and it has been decided not to start a certain medical or surgical intervention, the general practitioner should review the patient with some regularity to insist on hygienic-dietetic measures. Patients that refuse treatments or cannot tolerate them may need to be referred to the appropriate specialized units if the patient wishes to receive treatment again. Finally, many patients with OSA who have been successfully treated surgically or who receive CPAP appropriately, that is, with daily use of more than 4–5 h and without side effects. In these cases. The role of the PCP will be to insist on the patient's hygienic-dietetic measures (reduce weight, not drink alcohol or smoke), periodically reassess daytime/nighttime symptoms and monitor side effects of CPAP (facial lesions, tooth mobility). In short, a patient with OSA is a person who suffers from a chronic disease that must be monitored over time, regardless of the treatment he/she

receives. This is a job that must be done by both the general practitioner and the specialist.

Take-Home Message

- The primary care physician (PCP) has a primary role in diagnosing, treating, and following up patients with obstructive sleep apnea (OSA).
- The suspicion, identification, and grading of OSA severity should be done through a good, structured sleep history and with specific questionnaires such as the STOP-BANG and the Epworth scale.
- Home sleep polygraphs can do confirmation of OSA through a sleep study as an alternative to polysomnographic studies.
- PCPs should refer the patient at the appropriate time and to the appropriate specialist to design a specific treatment, either upper airway surgery or mandibular advancement devices.

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Ophthalmology: Neuro-Ophthalmological

19

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19.1 Introduction

Obstructive sleep apnea (OSA) does have an impact on ocular health. McNab [1, 2], Waller et al. [3], and Nieto Enriquez et al. [4] summarized the different ocular pathology that can be found in OSA patients more than a decade ago. Since then, several extensive studies and novel findings on this issue have been reported. These findings have been recently reviewed in several systematic reviews and meta-analysis [5–9].

Several pathways have been proposed to explain the association between OSA and different ocular diseases, including damage to the vessels and optic nerve that may cause glaucoma progression or retinal deterioration, but also having hypoxia, endothelial proliferation, angiogenesis and oxidative stress, promoting the development of keratoconus and proliferative diabetic retinopathy (Fig. 19.1).

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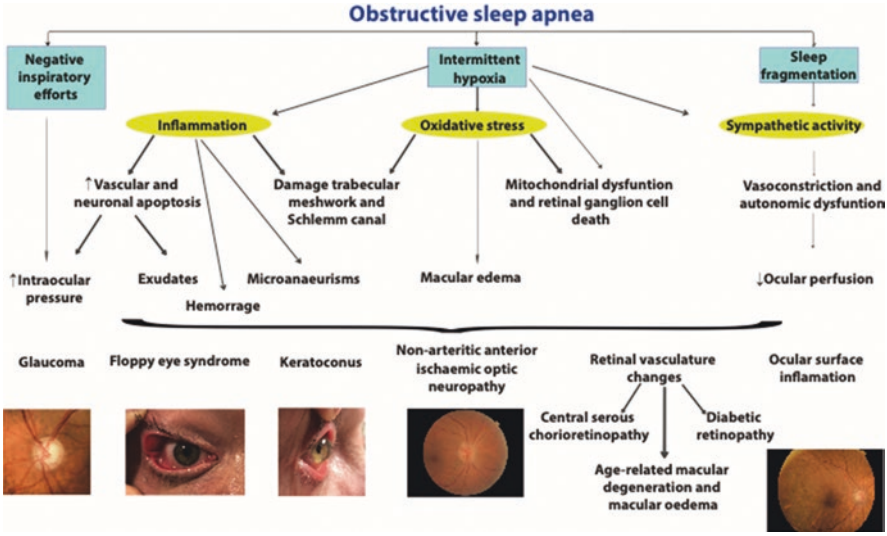

Fig. 19.1 Obstructive sleep apnea-related ocular pathology

19.2 Floppy Eye Syndrome

In 1981, two ophthalmologists, Culbertson and Ostler [10], described for the first time an unusual entity characterized by "floppy" and redundant upper eyelids with marked papillary conjunctivitis in obese middle-aged and older men (Fig. 19.2). They coined the term "floppy eyelid syndrome." The affected eye corresponded to the side the patient preferentially slept on and if both eyes were affected, the patient alternated sides they slept on, or they slept face down. Some were noted to sleep with the affected upper eyelid spontaneously everted and rubbing on the pillow. The patients typically complained of symptoms of watering, stickiness, discomfort, and blurred vision in the affected eye(s), and these symptoms were typically worse on waking.

Since the first description of floppy eye syndrome in an OSA patient by Woog [11], several series and reviews [12–29] have been reported including, many patients with floppy eye syndrome related to OSA. It affects primarily middle-aged obese men with a diagnosis of OSA. However, only a small minority of patients (2%–5%) with OSA have floppy eye syndrome, although two series have reported higher incidence, up to 50% of OSA patients [22–24, 29].

Two recent meta-analyses showed that floppy eyelid syndrome is more common in OSA patients. Huon et al. [6]. found it in 312 of 690 patients with OSA and in 25 of 212 patients without OSA. The overall pooled (odds ratio) OR for floppy eyelid syndrome was 3.126 ($P < 0.001$) in the OSA group versus the non-OSA group. Wang et al. [30] found pooled OR for floppy eye syndrome in OSA of 4.12 in a total of 767 participants (Fig. 19.3), and such OR increased up to 7.64 in severe cases.

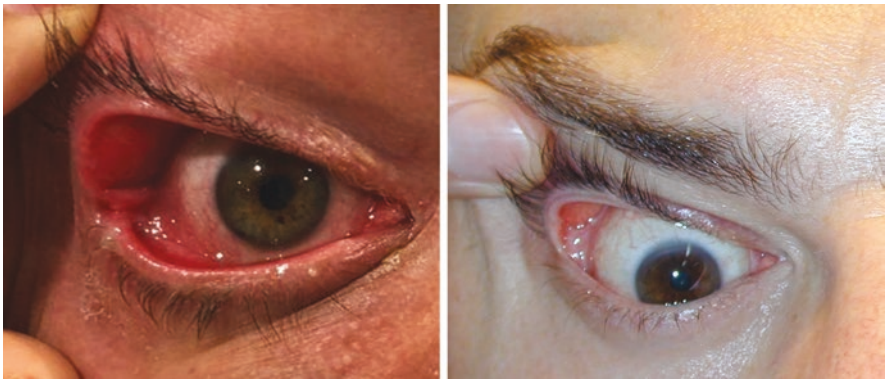

Fig. 19.2 Floppy eyelid, showing increased upper eyelid laxity with easy eversion of the eyelid

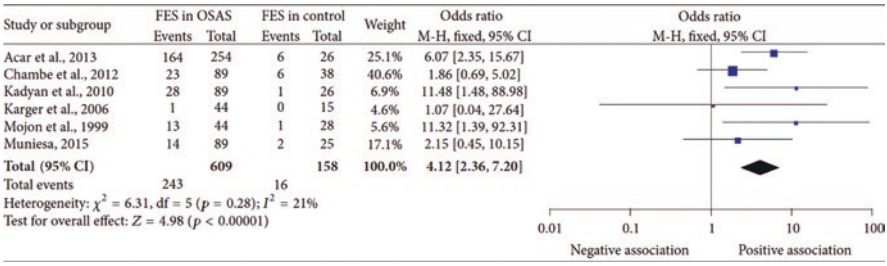

Fig. 19.3 Forest plot of floppy eyelid syndrome (FES) prevalence in OSA. CI, confidence interval. From Wang et al. [30]

Mild ptosis, downward-pointing eyelashes, or inversion may also be present. Papillary conjunctivitis is apparent in the involved eye. Corneal involvement is common and may include punctuate keratopathy, gross surface scarring, ulceration, or increased vascularization.

Patients with suspected floppy eyelid syndrome should be referred for a full ophthalmologic evaluation. If floppy eyelid syndrome is confirmed, patients should strongly be considered in OSA assessment. Treatment of floppy eyelid syndrome can consist of conservative measures, including weight loss, eye shields or other protective devices, lubricants, and occasionally corticosteroids or antibiotics based on ophthalmologic findings. Resolution after treatment of OSA has been well documented.

Viera et al. [31] observed that floppy eye syndrome reversed in about half of 34 patients after 6 months of CPAP therapy. However, Kadyan et al. [17] failed to find any significant difference in upper or lower lid laxity between CPAP-treated and untreated patients. Bayir et al. [32] have shown how surgical treatment of OSA through anterior palatoplasty improved floppy eyelid in 50%–60% of the patients. Surgical tightening of the eyelids can be performed in medically refractory cases,

but high recurrence rates after surgery have been documented in patients with untreated OSA. This observation further stresses the importance of managing OSA in these patients.

19.3 Keratoconus

Corneal changes occurring with floppy eye syndrome, such as reduced corneal hysteresis and increased tendency to eye rubbing, have been suggested to predispose to keratoconus [9, 33, 34]. Keratoconus is a noninflammatory thinning and bulging of the cornea, causing a distortion of the normal shape of the cornea and resulting in extreme myopia and/or astigmatism. It has been described in OSA patients (Fig. 19.4).

A case–control study further reported that patients with OSA had thinner corneas by 20 μm compared to controls, with increased severity of OSA associated with thinner corneas [35].

Several studies have also reported that patients with keratoconus have a high prevalence of OSA (18%–20%) or are at high risk of OSA (12%–53%) as assessed by the Berlin Questionnaire [36–40]. A meta-analysis estimated that patients with OSA have an OR of 1.84 (95% confidence interval, 1.163–2.914; $P = 0.009$) for keratoconus compared to controls (Fig. 19.5) [41]. Thus, there is significant evidence that OSA is associated with keratoconus. Therefore, proper screening for OSA is warned for keratoconus patients to prevent various cardiovascular comorbidities.

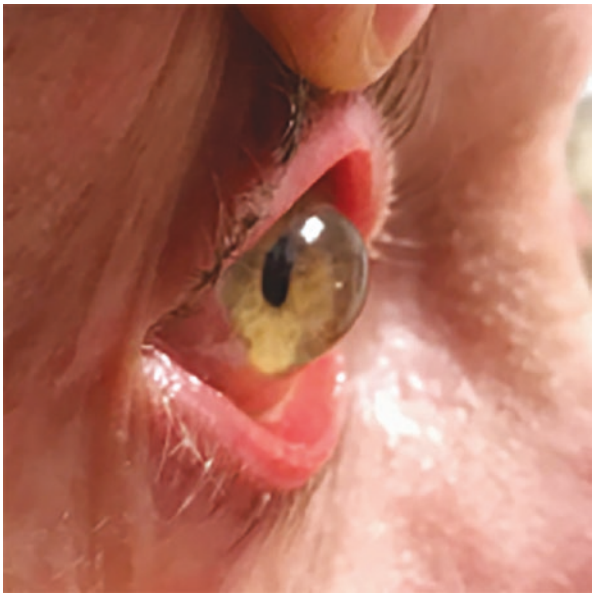

Fig. 19.4 Keratoconus

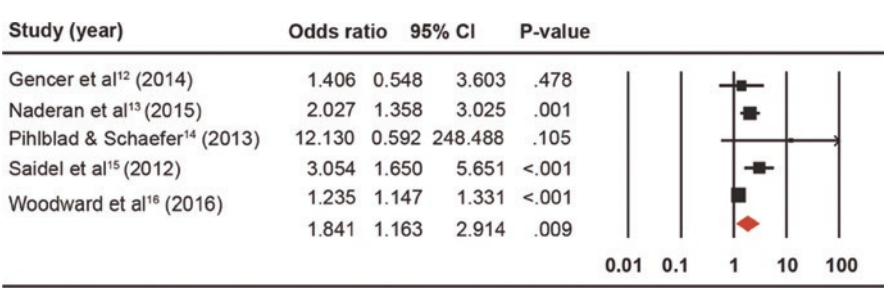

Fig. 19.5 Forest plot of the association between obstructive sleep apnea and keratoconus. Squares represent study-specific odds ratio (size of the square reflects the study weight), horizontal lines represent 95% confidence intervals (CIs), and the diamond represents the pooled odds ratio, which was computed by using random-effects model. From Pellegrini et al. [41]

19.4 Ocular Surface Inflammation

The first line of treatment for OSA is CPAP because of both its efficacy and its safety. However, common complications of CPAP treatment are nasal irritation and dryness, skin irritation, skin breakdown, and ulceration secondary to pressure from the mask. Ophthalmologic problems or complications after CPAP are also occasionally seen [3, 4]. In 1984, Stauffer et al. [42] described a patient with bacterial conjunctivitis after CPAP use. In 2006, Ely and Khorfan [43] reported a case of a woman with OSA who developed unilateral periorbital swelling with CPAP treatment that resolved when she stopped CPAP treatment. Harrison et al. [44] reported three patients with eye complications while undergoing CPAP treatment.

Eye complications from CPAP treatment may arise from two possible mechanisms. The first, and probably most common, is from an air leak around the superior portion of the mask, resulting in the air blowing into the eye. The second may be retrograde movement of air and mucus from the nasal passage through the nasolacrimal duct and into the eye. Furthermore, CPAP increases ocular irritation, tear evaporation, and squamous metaplasia in the conjunctiva of the patients' right and left eyes [45].

Nocturnal lubrication or artificial tears relieve to patients who develop morning eye dryness while receiving CPAP treatment. Proper mask fit should be verified to prevent air leaks. Switching from a nasal mask to an intranasal interface may alleviate areas of pressure and air leakage near the eyes Early ophthalmologic consultation is required to exclude corneal disease if a patient develops substantial eye irritation that persists into the day or has signs of infection. However, given the possibility of increased risk of eye infections, it is reasonable to advise against extended-wear contacts. In patients who develop recurrent eye infections or depend on contact lenses and cannot tolerate CPAP treatment secondary to eye irritation, alternative therapy to CPAP treatment may need to be considered.

19.5 Glaucoma

Glaucoma is a progressive optic neurodegenerative disease characterized by progressive loss of optic nerve fibers with corresponding visual field defects (Fig. 19.6).

Since the first description by Mojon et al. [46] in 1999, a possible link between OSA and glaucoma, mainly primary open-angle glaucoma, has been established in the last two decades [7–9], with four meta-analyses published that confirmed this association [6, 47–49] finding a pooled OR for glaucoma in patients with OSA ranging from 1.4 to 2.5. However, more recent and larger, well-designed cohort or population-based studies have failed to find significant associations between OSA and glaucoma, especially after accounting for comorbidities [9, 50–53]. A very recent meta-analysis including 16 case–control studies (233,273 patients with OSA and 4802,386 subjects without OSA) has confirmed that OSA is associated with a significantly increased risk of glaucoma (Fig. 19.7), with a pooled OR of 1.50 (CI: 1.25–1.80; $p < 0.001$) [8].

Instead of relying on the presence of glaucoma, some studies explored associations of OSA with measures of glaucoma-related endophenotypes, such as the peripapillary retinal nerve fiber layer (pRNFL) thickness measured through optical coherence tomography (OCT) (Fig. 19.8), intraocular pressure (IOP), and visual field defects. Findings from most of these studies supported a link between OSA and thinner pRNFL, higher IOP, or poorer visual fields morbidities [54–59].

However, these studies have failed to find a relationship between IOP and apnea-hypopnea index (AHI) [8]. Five meta-analyses [60–64] further noted thinner global pRNFL by 2–4 μm in patients with OSA compared to controls. These results are less significant when adjusted for potential confounders [9].

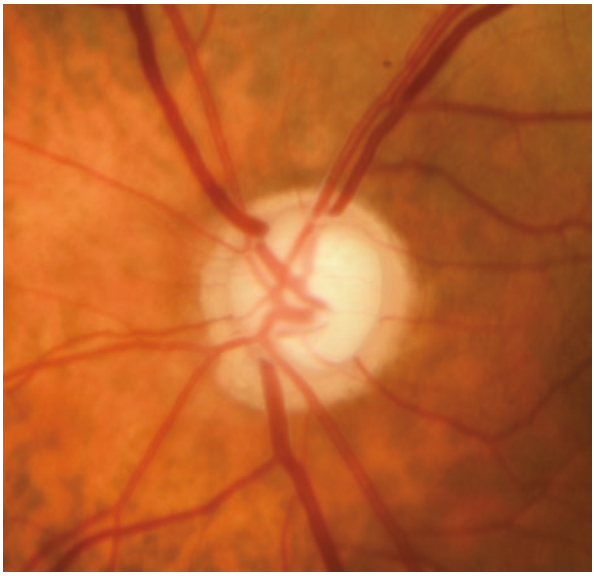

Fig. 19.6 Optic nerve showing glaucomatous cupping

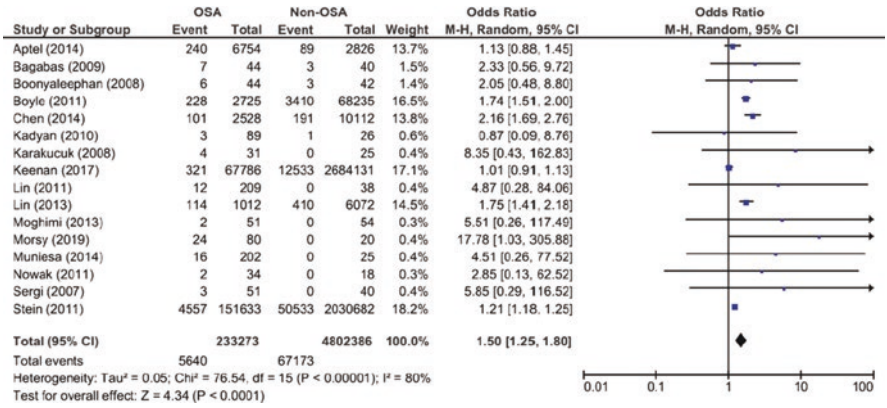

Fig. 19.7 Forest plot of cross-sectional studies showing the odds ratios (OR) with 95% confidence intervals (95% CI) of glaucoma for participants with and without OSA. The squares and horizontal lines represent the study-specific OR and 95% CI. The sizes of the squares reflect the statistical weights of the studies. The pooled OR is indicated by a diamond (random-effect model). From Garcia-Sanchez et al. [8]

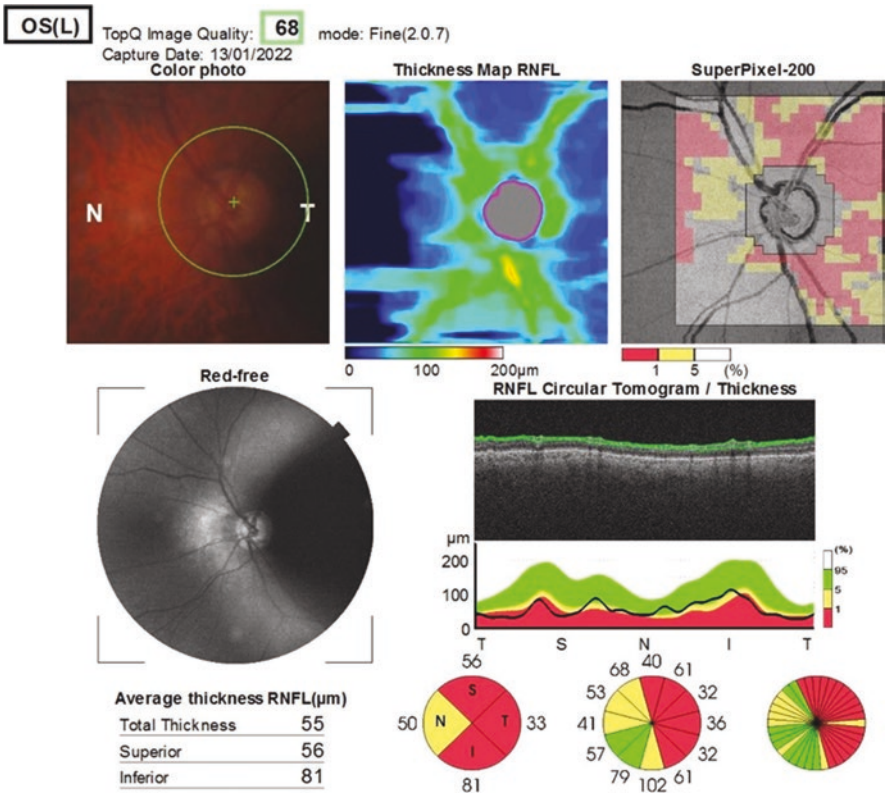

Fig. 19.8 OCT showing thinning of the retinal nerve fiber layer around the optic nerve

Given the presumptive ischemia of the optic disc induced by OSA, we may expect glaucoma progression to be faster in patients with OSA than in those without respiratory disease. Indeed, studies have reported that patients with OSA tend to have more rapid glaucoma progression than those without OSA. In a retrospective study comprising 32 patients with glaucoma, Fan et al. [65] reported that those with moderate or severe had an eight-fold increase in the risk of pRNFL thinning than those with no or mild OSA, after adjusting for age, sex, body mass index (BMI), and co-morbidities. Over 3-years, Wozniak et al. [66] similarly reported that the rate of global pRNFL loss in glaucoma patients with OSA was almost double the rate in those without OSA (−1.1 vs. −0.6 μm/year), after adjustments for potential confounders.

OSA treatment has a great potential indeed to slow glaucoma progression [67–74]. CPAP therapy is highly effective in alleviating upper airway collapse and improves optic nerve perfusion and reduces glaucoma risk. Himori et al. [68] reported that patients with OSA and glaucoma had slower rates of visual field loss after undergoing an initial CPAP therapy. Other studies [69–73] also reported increases in pRNFL thickness, macular thickness, or visual field sensitivity after 3–6 months of CPAP therapy. However, these studies lacked control groups, and the improved measures, especially in visual fields, could be due to a learning effect.

Zengin et al. [70] studied 44 OSA patients treated with CPAP, who were followed for a whole year with OCT examinations every 3 months, and compared those results to healthy subjects. Baseline OCT data showed no differences between both samples; however, following 1 year of CPAP therapy, a lower average peripapillary RNFL, and nasal, inferior, and superior quadrant thicknesses were described in the patients with OSAS group as compared to the control group. They also studied the correlation between the AHI and the RNFL thickness, observing a weak negative correlation. Similarly, Lin et al. [71] presented a prospective study on 32 OSA patients treated with CPAP who underwent an OCT 3 months after treatment. They found that the inferior quadrant and nasal-inferior sector of the RNFL thickness significantly improved after treatment. In addition, the macula layer thickness in the superior-inner sector, inferior-outer sector, nasal-outer sector, superior hemisphere, and inferior hemisphere was also significantly improved after treatment. The improvement of macular layer thickness in the superior-inner sector positively correlated with the AHI and desaturation index correction. Naranjo-Bonilla et al. [72] have recently reported a prospective study including 28 patients treated with CPAP and 12 untreated, again showing normalization of the choroidal thickness measured by OCT in treated patients.

While CPAP therapy potentially improves optic disc perfusion, its use is known to elevate IOP [74–76], which may paradoxically increase the risk of glaucoma or worsen existing disease. As a result, some authors have suggested that patients with glaucoma or those at high risk of glaucoma using CPAP therapy should be closely monitored.

Surgical treatment of OSA has also shown to improve glaucoma in OSA patients [77–81]. In a retrospective study involving over 12,000 patients, Chen et al. [81] reported that CPAP-treated and untreated patients with OSA had similar levels of increased glaucoma risk relative to a comparison cohort (HR = 1.65 and 2.15,

respectively). However, those who had undergone surgical treatment did not have an elevated risk of glaucoma compared to the controls, suggesting that surgical treatment for OSA may be more beneficial than CPAP therapy regarding glaucoma risk. In 108 patients with OSA, Lin et al. [77] noted improvements in visual fields measures and thickening of the macula 6 months after surgical treatment for OSA. However, this study lacked a control group like the CPAP studies above. On the contrary, Kaya et al. [78] presented a prospective study on 34 OSAS patients treated with expansion sphincter pharyngoplasty. After 6 months, the preoperative and postoperative AHI scores and average oxygen saturation values were significantly different, but there was no significant disparity between the preoperative and postoperative RNFL thicknesses.

Jayakumar et al. [79] published a prospective study including 36 patients, comparing CPAP, uvulopalatopharyngoplasty, and no treatment. They showed that choroidal thickness and vascularity improved after surgery and CPAP for 6 months. Tejero-Garcés et al. [80] also found an improvement in OCT findings in severe OSA patients after CPAP or surgical treatment. However, they did not obtain any correlation between changes in the AHI and changes in the OCT after surgical treatment. The most relevant finding in their study was that the foveal thickness and retinal nerve fibers' (RNFL) average thickness improved after 6 months of treatment in severe cases.

19.6 Nonarteritic Anterior Ischemic Optic Neuropathy

Nonarteritic anterior ischemic optic neuropathy (NAION) is an ischemic disorder of the anterior portion of the optic nerve (Fig. 19.9), characterized by sudden, and painless unilateral visual loss, altitudinal visual field defects and optic disc swelling

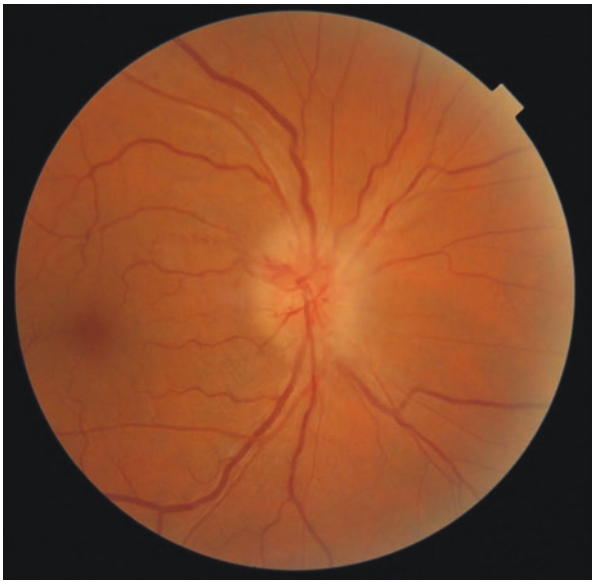

Fig. 19.9 Nonarteritic anterior ischemic optic neuropathy (NAION) showing edema of optic nerve fibers and splinter hemorrhages

[82]. It is the most frequent acute optical neuropathy after the age of 50, with an incidence of 2–10 per 100,000 people per year. It is classically associated with several risk factors, particularly cardiovascular, such as hypertension, diabetes, dyslipidemia, ischemic heart disease, or cerebrovascular disease. Moreover, NAION patients have a 15% risk for contralateral eye involvement within 5 years [8, 83].

The presumed optic nerve vascular dysregulation, including hypercapnia, induced by OSA has also been suggested to increase the risk of NAION, with a meta-analysis estimating that the odds of NAION are increased six-fold in those with OSA, compared to controls [84]. In addition, two recent large studies, which reported HRs of 1.7–3.8 for NAION in patients with OSA have reinforced such association [85, 86].

Evidence that treatment for OSA using CPAP therapy may reduce the risk of incident NAION is promising. In a retrospective review of over two million clinical records, Stein et al. [52] reported that untreated patients with OSA had a 16% increased risk of developing NAION relative to those without OSA, after adjusting for potential confounders, including age and co-morbidities. Those treated with CPAP therapy, on the other hand, did not have elevated NAION risk relative to controls. In another small study of 67 patients with unilateral NAION and OSA, Aptel et al. [87] reported that those with poor compliance to CPAP therapy had a significantly higher risk of second eye involvement, with an HR of 5.5. A recent meta-analysis evaluating seven studies (Fig. 19.10), including 9571 patients with OSA and 43,296 subjects without OSA, showed that patients with OSA are more at risk of NAION than nonapneic subjects, with a pooled OR of 3.62 (CI 1.94–6.76; $p < 0.001$) [8].

Given the importance of preserving the fellow eye in patients with NAION, it may be prudent to consider addressing any undiagnosed or untreated OSA in all patients with NAION.

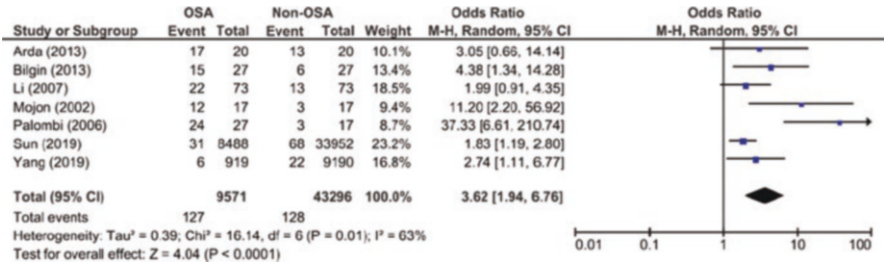

Fig. 19.10 Forest plot of cross-sectional studies showing the odds ratios (OR) with 95% confidence intervals (95% CI) of nonarteritic anterior ischemic optic neuropathy (NAION) for participants with and without OSA. The squares and horizontal lines represent the study-specific OR and 95% CI. The sizes of the squares reflect the statistical weights of the studies. The pooled OR is indicated by a diamond (random-effect model). From Garcia-Sanchez et al. [8]

19.7 Retinal Vasculature Changes

19.7.1 Central Serous Chorioretinopathy

Central serous retinopathy or chorioretinopathy (CSC) is characterized by an idiopathic serous detachment of the neurosensory retina secondary to serous fluid collection beneath the retina. CSC and OSA have been suggested to share underlying pathophysiological mechanisms, such as increased sympathetic activity and elevated serum cortisol concentrations via activation of the hypothalamic-pituitary-adrenal axis [88]. Moreover, both conditions share risk factors such as male sex and hypertension.

A meta-analysis found an OR of 2.02 (CI: 1.08–3.78) in patients with CSC relative to controls [6], and a second more recent one found an OR for OSA of OR of 1.56 (CI: 1.16–2.1) in patients with CSC, relative to controls [89]. However, half of the studies [90–92] included in those meta-analyses only defined OSA cases as those having a "high risk" of OSA. Recent population-based studies [93] reported that participants with OSA had a slightly higher incidence of CSC by 11%–20% than controls.

Additionally, CPAP-treated patients with OSA had about half the risk of CSC as untreated patients [94, 95].

19.7.2 Diabetic Retinopathy

Diabetic retinopathy (DR), the most frequent microvascular complication of diabetes and a major cause of vision loss, can be nonproliferative, with dilated retinal veins and microaneurysms causing hemorrhage or edema, or proliferative diabetic retinopathy (PDR), with new vessels forming near the optic disc (Fig. 19.11). A rise in inflammation and oxidative stress in OSA has been suggested to affect energy

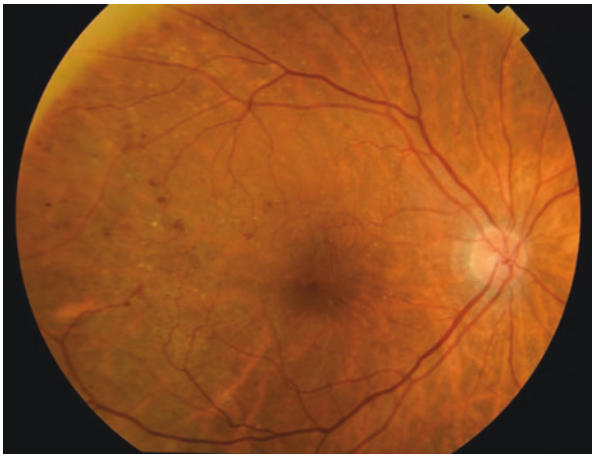

Fig. 19.11 Moderate diabetic retinopathy showing hemorrhages and retinal exudates through the posterior pole

metabolism, increasing insulin resistance and dysglycemia, and thus increase the risk of type II diabetes and DR [8, 9, 96].

Even among nondiabetic individuals, Steiropoulos et al. [97] noted that lower oxygen saturation during sleep was associated with higher insulin levels. While some of the link between the two conditions may be mediated by common risk factors, most notably obesity, even lean or nonobese individuals with OSA exhibit higher levels of insulin than age-, sex-, and BMI matched controls, suggesting that OSA could be an independent risk factor for diabetes [98–100]. Adherent use of CPAP therapy has reduced glycemic levels and insulin resistance [96].

While there has been consistent evidence supporting a link between OSA and diabetes, findings on an independent association between OSA and DR have been inconsistent, with meta-analyses arriving at different conclusions [4, 8, 101, 102]. A meta-analysis by Leong et al., [101], including three studies, failed to detect a significant association, although OSA was associated with a more advanced stage of DR and the lower oxygen saturation was associated with diabetic macular edema (adjusted OR: 0.79; CI: 0.65–0.95) and retinopathy (OR: 0.91; CI: 0.87–0.95). The authors highlighted that many previous studies that have reported a significant association between OSA and the prevalence of DR did not adjust for potential confounders. In contrast, a later meta-analysis by Zhu et al. [102], including six eligible studies, found that OSA was significantly associated with an increased risk of DR (2.01; CI: 1.49–2.72). Finally, a very recent one by García-Sánchez [8], this time evaluating ten studies and including 1387 patients with OSA and 1307 subjects without OSA (Fig. 19.12), shows that patients with OSA are more at risk of DR than nonapneic subjects, with a pooled OR of 1.57 (CI: 1.09–2.27; $p = 0.02$). Furthermore, adjusted studies have found that the presence of OSA is associated with more severe DR [103] or progression in DR [104, 105]. However, other recent studies have not shown a significant association between OSA and DR [106–109].

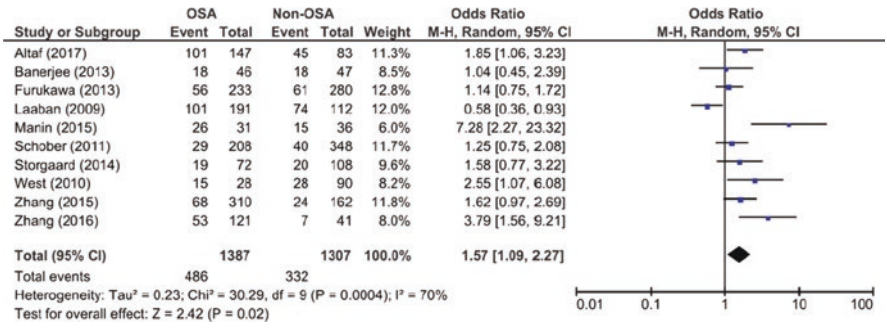

Fig. 19.12 Forest plot of cross-sectional studies showing the odds ratios (OR) with 95% confidence intervals (95% CI) of diabetic retinopathy for participants with and without OSA. The squares and horizontal lines represent the study-specific OR and 95% CI. The sizes of the squares reflect the statistical weights of the studies. The pooled OR is indicated by a diamond (random-effect model). From Garcia-Sanchez et al. [8]

Another way to assess the association between OSA and DR is to analyze the effect of apnea-hypopnea suppression by specific treatment. Cross-sectional studies [110, 111] have reported that CPAP therapy use may reduce DR rates or progression of DR. In an observational nonrandomized study, good adherence to CPAP treatment was associated with a higher improvement of the visual field within 6 months [111]. However, a randomized clinical trial performed by West et al. [112] in 131 severe OSA patients with diabetes and diabetic macular edema causing visual impairment did not detect a significant difference in visual acuity after 12 months between the CPAP and the control groups. CPAP use time was unable to detect differences, so the authors concluded that CPAP therapy for OSA did not improve visual acuity in diabetic patients with diabetic macular edema compared to standard care alone over 12 months. Similarly, Turnbull et al. [113] conducted a multicenter, double-blind, randomized, parallel, controlled trial in patients with OSA on CPAP. Participants were randomized to 14 nights of either continued CPAP or sham CPAP to generate a return of OSA. Nineteen patients were randomized to sham CPAP, and 18 patients were randomized to continued CPAP. CPAP withdrawal and OSA return had no significant effect on retinal microvascular responses. This contrasts with the effect of CPAP withdrawal on macrovascular endothelial function and suggests that OSA has different effects on macrovascular and microvascular endothelial function.

Therefore, more randomized trials are still needed to assess the CPAP effect on variables related to the severity or progression of DR. Given that CPAP therapy use for OSA treatment may be beneficial for controlling systemic glycemic and insulin levels, it is plausible that it could also improve ocular outcomes in patients with diabetes.

19.7.3 Age-Related Macular Degeneration and Macular Edema

Schaal et al. [114] in 2014 noted that patients with age-related macular degeneration (AMD) or diabetic macular edema (DMO) were more likely to have poor response to antivascular endothelial growth factor (VEGF) therapy if they had symptoms of OSA or untreated OSA, a relation between AMD and OSA has been suspected. Later, in 2016 [115]. the same group reported 38 patients with OSA and anti-VEGF injections for exudative AMD. Patients with untreated OSA required double the number of injections compared to those treated with CPAP (mean of 16 vs. 8 injections) to reduce the macular edema. Moreover, after completing the anti-VEGF injection regimens, the untreated OSA group had poorer final visual acuity and thinner maculas than the CPAP-treated group (visual acuity: 0.7 vs. 0.3 logMAR; macular thickness: 322 vs. 254 μm), despite having similar baseline measures prior to anti-VEGF therapy.

The mechanism underlying the poorer treatment response is unclear. However, there was a suggestion in an editorial article that upregulation of VEGF levels due to the hypoxia induced by OSA may offset the effects of the anti-VEGF therapy [116]. This, by extension, could mean that the presence of OSA does not merely

reduce anti-VEGF treatment response, but may also increase the risk of exudative AMD or DMO. Indeed, a link between OSA and DMO has been reported [117, 118]. In patients with Type II diabetes, Chiang et al. [117] found a higher incidence rate of DMO in those with OSA than those without OSA (HR = 3.0), while Vie et al. [118] reported that those with DMO were more likely to have higher AHI and lower oxygen saturation levels. In the United Kingdom, Keenan et al. [119] reported a sizeable data-linkage study that found an elevated risk of AMD by 44% in patients with OSA relative to controls. Recently, the hazard of AMD has been raised by 33%–39% in two large-scale cohorts after accounting for potential confounders, including co-morbidities [120].

Given the relative novelty of the reported associations between OSA and AMD and the importance of AMD as the leading cause of blindness and visual impairment, further studies on the link between these conditions are warranted. The benefits of OSA treatment on AMD risk and visual outcome is particularly worthy of exploration [9].

19.8 Conclusions

Obstructive sleep apnea (OSA) affects ocular health in many patients due to hypoxia and oxidative processes usually involved. There is consistent evidence of an increased risk of floppy eyelid syndrome, keratoconus, glaucoma, nonarteritic anterior ischemic optic neuropathy, central serous chorioretinopathy, diabetic retinopathy, and diabetic macular edema. Furthermore, OSA treatment with CPAP or upper airway surgery may reduce the risk of these eye diseases. Moreover, it may also help to monitor OSA evolution after treatment. Finally, ocular surface complications secondary to leaking masks commonly used in OSA reinforce the need for a good mask fit during CPAP.

Take-Home Message

- OSA affects ocular health in many patients and therefore should be investigated.
- There is consistent evidence of an increased risk of floppy eyelid syndrome, nonarteritic anterior ischaemic optic neuropathy, diabetic macular oedema, and other retinal vasculature changes in individuals with OSA.
- Other ocular diseases have also recently been associated to OSA, such as keratoconus, glaucoma, central serous chorioretinopathy, and diabetic retinopathy.
- Moreover, OSA treatment may reduce risk of these eye diseases, and some recent works have shown how ocular findings may help to monitor OSA evolution after treatment.

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Anesthesia Considerations in Obstructive Sleep Apnea

20

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20.1 Introduction

Obstructive sleep apnea (OSA) is a condition in which the upper airway is periodically, partially, or completely obstructed during sleep, causing hypoxia, hypercarbia, sleep disorders, and various medical complications, including daytime sleepiness and an increased risk of hypertension, diabetes, and cardiovascular disease [1, 2].

The name obstructive sleep apnea–hypopnea syndrome was adopted by consensus using the acronym OSA. OSA is characterized by recurrent episodes of apnea or hypopnea that generate desaturations and microarousals due to upper airway collapse during sleep. These events produce inflammatory, cardiovascular, neurocognitive, and metabolic responses that increase the patient's morbidity and mortality [1, 3, 4].

The prevalence of OSA in the general population varies from 3% to 7% for adult men and 2% to 5% for adult women, depending on the population studied and the diagnostic criteria used [1]. The prevalence is greater in surgical patients, between 24% and 41% [5]. The main risk factors associated with the development of OSAHS are obesity, male sex, and increased age [2, 3].

Senaratna et al. in 2017 published a systematic review that reported patients with an apnea–hypopnea index (AHI) ≥5 events/hour with a prevalence in the general

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population of 9% to 38%, a predominance in men, and a proportional increase with age. This factor was found in some groups of elderly adults, reaching 90% in men and 78% in women. The prevalence of OSA was also greater in obese men and women [6].

These studies demonstrate that OSA is associated with increased perioperative morbidity and mortality. These patients have a greater risk of cardiovascular and respiratory compromise and a possible transfer to intermediate or intensive care in the immediate postoperative period.

20.2 Physiopathology

Upper airway obstruction that leads to obstructive apnea occurs when negative pressure generated by the inspiratory muscles exceeds the pressure of the dilator muscles of the pharynx [2, 7]. These muscles have tone and are driven by mechanoreceptors and chemoreceptors. OSA occurs when the muscles of the soft tissues of the pharynx, such as the tongue, palate, uvula, or lateral walls, relax, causing airway narrowing, vibration, tremor of the soft tissues, and/or partial or total closure that causes breathing to stop momentarily [8, 9].

The shape of the mandible, adipose tissue, the area of the palate, the uvula, and the size of the tongue form the upper airway (Fig. 20.1) [10]. In addition to the anatomical structures, the central nervous system coordinates airway opening; for

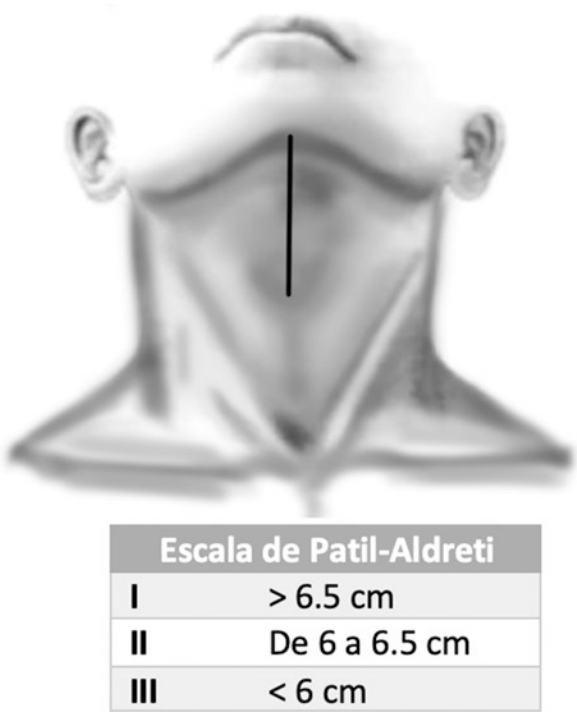


Fig. 20.1 Patil-Aldreti test

example, when we talk or swallow during the day. At night, pharyngeal muscle tone decreases and, therefore, favors collapse. The diaphragm, which continues to be active, must work harder to overcome the increased upper airway pressure [1, 9, 11]. This effort can cause microarousals that coincide with airway opening and normalization of breathing. The succession of microarousals during the night disrupts the sleep cycle causing nonrestorative sleep [9].

20.2.1 The Cardiovascular Mechanism in Patients with OSA

Patients with apnea–hypopnea syndrome suffer intermittent hypoxia with periods of decreased oxygen saturation and increased CO_2. These changes increase sympathetic tone, which causes vasoconstriction and raises arterial pressure [12]. Hypoxia releases vasoactive substances such as endothelin, which increases blood pressure. When intermittent hypoxia occurs with sleep disruption, inflammatory mediators related to cardiovascular diseases, such as C-reactive protein, cytokines 6 and 8, and tumor necrosis factor, are released. Therefore, systemic inflammation, sympathetic activation, and oxidative stress produce endothelial damage and, as a result, cardiovascular disease [13]. It is frequent to see patients with OSA and hypertension. It is estimated that 35% to 80% of patients with OSA have hypertension, and approximately 40% of individuals with hypertension have OSA [14].

20.3 Clinical Presentation

OSA is a common problem that has been detected more frequently. However, patients and doctors are not aware of this problem. Physicians do not routinely ask their patients about sleep symptoms to reach a precise diagnosis, especially before a surgical procedure [15, 16].

This syndrome is linked to daytime sleepiness, cognitive dysfunction, cardiovascular problems such as hypertension, ischemic heart disease, arrhythmias, pulmonary hypertension, congestive heart failure, metabolic dysfunction, and reduced quality of life [12].

Risk factors for OSA include obesity, a body mass index greater than 35 kg/m^2, male gender, excess alcohol intake, smoking, a neck circumference greater than 40 cm, and low physical activity [2, 17].

20.4 Diagnostic and Severity Criteria

20.4.1 Apnea–Hypopnea Index (AHI)

The apnea–hypopnea index represents the number of respiratory events (apneas, hypopneas, and microarousals) per hour of sleep. It is used to identify cases, quantify disease severity, and determine disease prevalence in normal and clinical populations. Apnea is when an individual stops breathing for 10 s or more during a

polysomnogram. Hypopnea is defined when there is a ≥3% oxygen desaturation from baseline and/or when the event is associated with an arousal. A score greater than 5 events is diagnostic of OSA [18, 19].

- An AHI ≥ 5 per hour is mild.
- An AHI ≥ 15 but <30 per hour is moderate.
- An AHI ≥ 30 per hour is severe.

20.4.2 Heart Failure and OSA

The apnea–hypopnea index is useful for evaluating patients with heart failure. Patients with moderate or severe OSA have twice the mortality compared to those with heart failure without apnea or with mild apnea [20]. For example, a patient with an AHI greater than 30 per hour has a probability of 58% of developing heart failure compared to those with 5 events per hour [21]. These patients are also more likely to have arrhythmias such as atrial fibrillation and ventricular arrhythmias, which can cause sudden death.

20.4.3 Arrhythmias and OSA

A series of events such as increased diastolic ventricular pressure plus dilatation with increased atrial wall pressure plus hypoxemia, hypercapnia, and autonomic stimulation cause arrhythmias in patients with OSA [22, 23].

The most frequent arrhythmias are atrial fibrillation in up to 49%. Atrial and ventricular tachycardia and ventricular extrasystoles are also seen in approximately 40%. Arrhythmia episodes are more frequent at night and increase with the severity of OSA [22, 23].

Sinus pauses or bradycardias are common, most often during rapid eye movement (REM) sleep when apneas tend to be prolonged. Bradycardias depend on the number of episodes of apnea and hypoxia, which are more frequent with severe OSA.

The QTc interval is prolonged during apnea and shortens in the postapnea period. This prolonged QT interval favors ventricular arrhythmias and is directly related to OSA severity [22].

20.4.4 Pulmonary Hypertension and OSA

This common anomaly in OSA is more marked during REM sleep. It occurs due to activation of the autonomic nervous system, hypoxic alveolar vasoconstriction, and increased intrathoracic negative pressure. The latter because of the inspiratory effort caused by the obstructed airway [20].

Pulmonary hypertension is more common in obese individuals or when chronic obstructive pulmonary disease is present and is not directly related to the

apnea–hypopnea index as in cardiovascular disease. OSA is associated with repetitive nocturnal arterial oxygen desaturation and hypercapnia, large changes in negative intrathoracic pressure, and acute increases in pulmonary artery pressure. Rodents exposed to several hours of brief, intermittent hypoxia to mimic OSA develop pulmonary vascular remodeling, pulmonary hypertension, and right ventricular hypertrophy. However, it was unclear whether OSA-associated episodic nocturnal hypoxemia is sufficient to cause similar changes in humans [24].

Recent studies have shown that pulmonary hypertension occurs in 20% of patients with OSA in the absence of other cardiopulmonary disorders and with pulmonary artery pressure reductions in patients with OSA after nocturnal continuous positive airway pressure treatment. OSA-associated pulmonary hypertension is mild and may be due to a combination of precapillary and postcapillary factors, including pulmonary arteriolar remodeling, hyperreactivity to hypoxia, left ventricular diastolic dysfunction and left atrial enlargement [24, 25].

The development of pulmonary hypertension is a poor prognostic sign in patients with OSA and affects mortality and quality of life. Although pulmonary hypertension in OSA is traditionally viewed as a result of apneas and intermittent hypoxia during sleep, recent studies indicate that neither of these factors correlates very well with pulmonary artery pressure. Human data show that pulmonary hypertension in the setting of OSA is largely due to left heart dysfunction with either preserved or diminished ejection fraction. Longstanding increased left heart filling pressures eventually lead to pulmonary venous hypertension. The combination of hypoxic pulmonary vasoconstriction and pulmonary venous hypertension with abnormal production of mediators will result in vascular cell proliferation and aberrant vascular remodeling leading to pulmonary hypertension. These changes are similar to those seen in other forms of pulmonary hypertension and suggest shared mechanisms. Most patients with OSA are not diagnosed and undertreated. Appreciating the high prevalence and understanding the mechanisms of pulmonary hypertension in OSA would lead to better recognition and management of the condition [25].

Changes have been reported in the structure and function of the right ventricle in patients with OSA; however, their clinical significance has not been demonstrated. Right ventricular failure in OSA seems uncommon and is more likely if there is coexisting left-sided heart disease or chronic hypoxic respiratory disease [24].

Obstructive sleep apnea affects up to 4% of middle-aged adults. The most common complaints are loud snoring, restless sleep, nocturia, and excessive daytime sleepiness, which can reduce the quality of life. Patients may develop cardiovascular abnormalities because of repetitive snoring, airway collapse, and arousal. Most patients are overweight and have a short, thick neck. Some are of normal weight but have retrognathia. Patients with obstructive sleep apnea may go undiagnosed because they are unaware of their heavy snoring and nocturnal arousals; therefore, it is helpful to question the bedroom partner or a family member about chronic sleepiness and fatigue [1, 17, 26].

Polysomnography in a sleep laboratory is the gold standard for confirming the diagnosis of obstructive sleep apnea; however, the test is expensive and not widely available. Home sleep studies are less costly but not as diagnostically accurate.

Treatments include weight loss, nasal continuous positive airway pressure, dental devices that modify the tongue or jaw position, and upper airway and jaw surgical procedures in selected patients; however, surgery is restricted because of its invasiveness and expense [26].

20.5 Diagnosis

20.5.1 The Berlin Questionnaire

This questionnaire is frequently used for OSA in primary care. It includes 11 questions organized into three categories. The predictive yield of the Berlin questionnaire for OSA varies according to the diversity of the populations. Sensitivity ranges from 54% to 86% and specificity from 43% to 87% in primary care patients. The questionnaire has not been validated in surgical patients (Table 20.1) [17, 27].

20.5.2 The ASA STOP Questionnaire

A checklist—the ASA STOP questionnaire—has been recommended as a routine tool for OSA in the perioperative management of patients with obstructive sleep apnea. The STOP questionnaire was developed and validated for surgical patients as a useful tool in individuals with OSA or suspicion of OSA. Some studies have validated the Berlin and ASA-STOP questionnaire as diagnostic tools for OSA in surgical patients [27].

Patients with undiagnosed OSA have increased perioperative morbidity and mortality. Anesthesiologists require a sensitive instrument to identify patients with a high risk of OSA. Although several predictive questionnaires have been developed to identify patients with OSA, none have been validated for surgical patients. The STOP-BANG questionnaire has been studied the most (Table 20.2) [28, 29].

20.5.3 Epworth Sleepiness Scale

Several scales assess excessive daytime sleepiness in patients with OSA. Among these is the Epworth Sleepiness Scale (ESS), which is frequently used [30]. It is a self-administered questionnaire with 8 questions that measure daytime sleepiness. It is based on a 4-point scale (0–3) that measures the subject's propensity to doze off or fall asleep in different situations that occur in common daily activities. The ESS score ranges from 0 to 24. The higher the score, the higher the person's propensity in daily life [31].

Table 20.1 The Berlin questionnaire

Name: _____ Date. _____ Age: _____ Gender: _____ Weight: _____ kg Height: _____ cm		
1. Has your weight changed in the last 5 years? A. Increased B. Decreased C. Has not changed	7. Do you feel tired or fatigued in the morning after your sleep? A. Almost every day B. 3–4 times a week C. 1–2 times a week D. 1–2 times a month E. Never or rarely	10. Do you have high blood pressure? A Yes B. No
2. Do you snore? A. Yes B. No C. Don't know	8. Do you feel tired or fatigued during the day? A. Almost every day B. 3–4 times a week C. 1–2 times a week D. 1–2 times a month E. Never or rarely	
3. Is your snoring…? A. Slightly louder than breathing B. As loud as talking C. Louder than talking D. Very loud that it can be heard in the next room	9. Have you ever felt sleepy or fallen asleep as a passenger or while driving a vehicle? A. Yes B. No	
4. How often do you snore? A. Every night B. 3–4 times a week C. 1–2 times a week D. 1–2 times a month E. Never or rarely	9.1 If the answer is yes, how often does this happen? A. Almost every day B. 3–4 times a week C. 1–2 times a week D. 1–2 times a month E. Never or rarely	
5. Has your snoring ever bothered other people? A. Yes B. No C. Don't know		
6. Has anyone noticed that you stop breathing during your sleep? A. Almost every night B. 3–4 times a week C. 1–2 times a week D. 1–2 times a month E. Rarely or never		

Category 1. Questions 2–6: High risk: 2 or more of the underlined answers
Category 2. Questions 7–9: High risk: 2 or more of the underlined answers
Category 3. Question 10: High risk: One yes and/or body mass index greater than 30

Table 20.2 The STOP-BANG questionnaire

STOP-BANG questionnaire		
S	Snoring	Do you snore loudly (loud enough to be heard through a closed door?
T	Tired	Do you often feel tired, fatigued, or sleepy during the daytime?
O	Observed apnea	Has anyone observed you stop breathing during sleep?
P	Pressure	Do you have or are you being treated for high blood pressure?
B	Body mass index	Is your body mass index more than 35 kg/m^2?
A	Age	Are you older than 50?
N	Neck circumference	Is your shirt collar 40 cm or greater?
G	Gender	Are you male?

High risk of obstructive sleep apnea syndrome: Yes to 5–8 questions
Intermediate risk of obstructive sleep apnea syndrome: Yes to 3–4 questions
Low risk of obstructive sleep apnea syndrome: Yes to 0–2 questions

20.6 Polysomnography, Home Sleep Apnea Testing, and Drug-Induced Sleep Endoscopy

20.6.1 Polysomnography

Conventional polysomnography (PSG) is a simultaneous recording of neurophysiological and cardiorespiratory variables that assesses the quantity and quality of sleep [32] and identifies different cardiac, respiratory, and motor events and their impact on sleep [33].

PSG can be performed at night, or during the subject's habitual sleep schedule, with at least 6.5 h of recordings and 180 min of sleep [4].

There are common parameters recorded in almost all PSG studies, such as electroencephalography (EEG), electrooculography (EOG), surface electromyography (EMG), and electrocardiogram (ECG) channels, nasobuccal flow, and/or respiratory bands. Sleep apnea protocols focus on recording respiratory and cardiac parameters, which include oxygen saturation (SaO_2) by pulse oximetry, respiratory effort recordings with thoracic or abdominal bands, snoring sensors, and nasobuccal flow using pneumotachographs or thermistors [4, 8, 26].

Ambulatory monitoring for simplified diagnosis of sleep apnea (Home PSG).

Home PSG consists of a compact and simple device for home sleep with up to five information channels: respiratory effort, pulse, oxygen saturation, nasal flow, and snoring. This device also provides a longer recording time and storage space [34, 35].

Parameters

- Central, obstructive, and mixed apnea index.
- Hypopnea index.
- Apnea–hypopnea index.
- Flow limitation with and without snoring.

- Oxygen desaturation index.
- Probability screening for Cheyne–Stokes respiration to help determine when to refer patients for further laboratory diagnosis.
- Differentiation between obstructive apnea and central apnea.

20.6.2 Drug-Induced Sleep Endoscopy

Although nocturnal PSG is the study of choice or the "gold standard" for this syndrome, it does not exactly locate the upper airway obstruction [8, 26]. Drug-induced sleep endoscopy (DISE) is a fibroendoscopic examination in which sleep is induced. Airway videoendoscopy is performed to determine where the greatest obstruction occurs during sleep [36].

DISE is an invasive study that dynamically assesses the anatomical structures of the upper airway. It is performed with a 4-mm fiberscope while the patient is sedated with anesthetic drugs. It must be carried out in the operating or endoscopy room with essential monitoring (electrocardiogram, pulse oximetry, and noninvasive blood pressure measurement). It is convenient to measure sedation depth with the bispectral index (BIS), maintaining adequate sedation with a BIS value between 60 and 70 [37, 38].

The patient is evaluated in three positions, supine, right lateral decubitus, and left lateral decubitus, with mandibular advancement in the same positions [39]. The study is used for diagnosis and as a tool in case of planned surgery and when surgery is indicated for the patient. The soft palate, and the lateral walls of the oropharynx, including the palatine tonsils, tongue, and epiglottis, are observed as part of the protocol [38]. The most frequently used anesthetic drugs for this procedure are propofol and dexmedetomidine (Table 20.3) [36, 40].

Table 20.3 Differences and effects of anesthetic drugs used for drug-induced sleep endoscopy

Agent	Propofol	Dexmedetomidine
Drug characteristics	Alkylphenol	Alpha-2 adrenergic
Site of action or receptors	Gamma-aminobutyric acid (GABA)	Alpha-2 receptors in the locus ceruleus
Use in anesthesia	Inductor of anesthesia Total intravenous anesthesia (TIVA) Sedation	Antihypertensive Sedative Analgesic Maintenance of anesthesia
Cardiac effect	Reduces systemic vascular resistance Reduces blood pressure	Reduces blood pressure Reduces heart rate
Respiratory effect	Dose-dependent depression	Minimal respiratory depression
Cerebral effect	Neuroprotector Anticonvulsant	Neuroprotector Induces physiological sleep
Start of anesthetic effect	2–8 min	After 10 min
Drug elimination	7–10 min	More than 20 min

20.7 Preoperative Evaluation

The main objective of the preoperative evaluation is to develop an adequate anesthesia plan to reduce transoperative morbidity and mortality and prevent immediate and late postoperative complications. The patient must be informed of the planned procedure, and informed consent must be obtained. All components of the preanesthesia evaluation should be assessed in an orderly manner and classified considering the surgical procedure and its indication.

A history of previous surgeries and anesthesia should be obtained, emphasizing a personal and family interview. A comprehensive review of systems and physical examination must include a correct and complete assessment of the upper airway to avoid difficult intubation and identify the presence of OSA [15].

Aspects to consider in the preoperative assessment should be those described for a conventional clinical assessment, but a comprehensive examination of all parameters that can identify if a patient has a difficult airway or not should be considered [41].

Although obesity has been associated with OSA, it is important not to forget that not all patients suffer this syndrome. It frequently occurs in patients with average weight; therefore, it is necessary to start from a basic interview where the parameter "snoring" is positive [12, 15].

As previously mentioned in physiopathology, the anatomical characteristics of the airway in these patients influence the tendency for OSA. Examination of patients with suspicion or diagnosis of OSA should be thorough [17].

In several reviews on this topic, the characteristics of the mandible and soft tissues of the oral cavity and neck are relevant for the presence of OSA. There are parameters in airway exploration that should not be overlooked, such as macroglossia, dentition, the Mallampati test, thyromental distance, neck circumference, and the sternomental distance [42–44] (Figs. 20.1, 20.2, 20.3, and 20.4).

The review of systems should emphasize and specifically focus on the cardiovascular and respiratory systems to detect or rule out heart rhythm disorders, hypertension, chest pain (angina), or a history of previous myocardial infarction, which are strongly associated with OSA.

The main risk factors that develop or increase OSA symptoms are age greater than 50 years, male gender, obesity, and menopause, among others. A history of smoking and alcohol and sedative use increases the severity of OSA. In cases of chronic tobacco use, the risk of difficult extubation should be evaluated since bronchospasm can occur [3].

Patients' drug history gives us an idea of their metabolic status and if they need a specific drug intraoperatively. A history of previous surgeries or anesthesia helps us prevent problems if the patient had difficult intubation or an adverse event [15].

Patients with a history of an ischemic or hemorrhagic cerebrovascular disease should be evaluated since they usually have OSA. Also, patients with a history of domestic, work, or traffic accidents regularly suffer from OSA [45, 46].

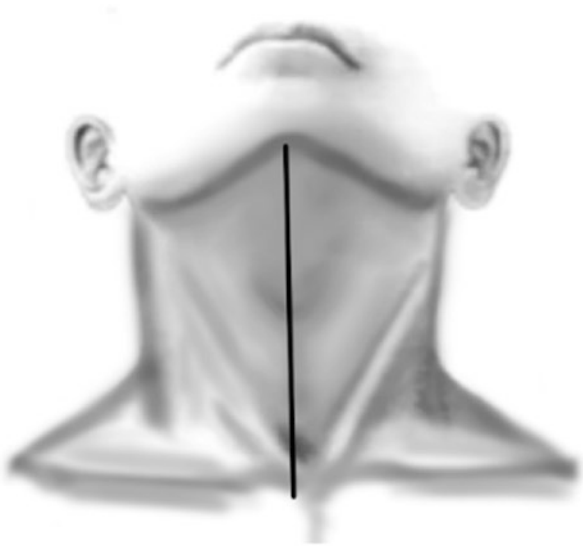


Fig. 20.2 Sternomentonian distance

Distancia Esterno-Mentoniana	
I	> 13 cm
II	De 12 a 13 cm
III	De 11 a 12 cm
IV	< 11 cm

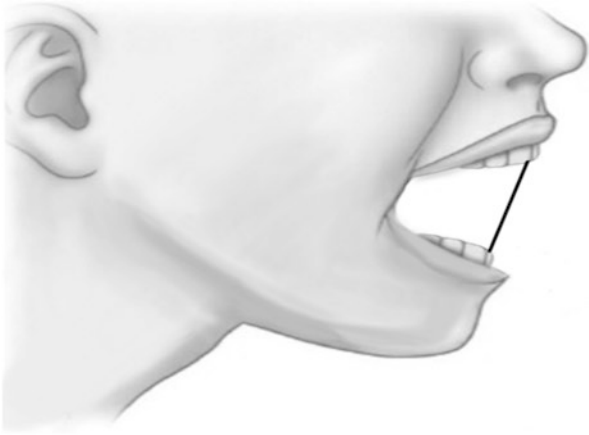
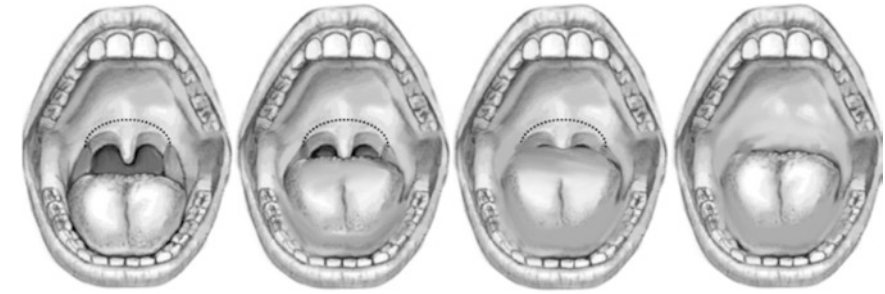


Fig. 20.3 Interincisor distance

Distancia interincisivos	
I	> 3 cm
II	De 2.6 a 3 cm
III	De 2 a 2.5 cm
IV	< 2 cm



Escala de Mallampati			
I	II	III	IV
Paladar blando, úvula, fauces y pilares visibles	Paladar blando, úvula y fauces visibles	Paladar blando y base de la úvula visibles	Únicamente paladar duro visible

Fig. 20.4 Mallampati score

Finally, the laboratory and special tests that ideally should be carried out with OSA patients include polysomnography and DISE, which provide specific OSA data and its severity. The Berlin questionnaire, The Stop-Bang questionnaire, laboratory studies, X-rays, and an electrocardiogram should also be used.

20.8 Intraoperative

OSA is a risk factor for postoperative complications. The most common are respiratory, such as oxygen desaturation. Other factors that can increase this risk are upper airway resistance syndrome, which occurs in young, nonobese patients who snore and have interrupted sleep with an AHI of less than 5 events per hour, and obesity hypoventilation syndrome, which is demonstrated by daytime hypercapnia ($CO_2 > 45$ mmHg) and obesity (BMI >30 kg/m^2). The latter syndrome is present in 0.3% of the general population, with a prevalence of up to 8% in bariatric surgery patients [47].

The main concerns in the intraoperative anesthetic management of patients with OSA are choosing the most convenient anesthetic technique for the surgical procedure, airway management, and the type of monitoring the patient will need [15].

Patient management should be individualized according to the surgery and type of anesthesia. It is also relevant to define if postoperative opioids and in-hospital or ambulatory care are necessary. Patients with OSA have an increased anesthetic risk of difficult intubation, mask ventilation, and maintaining a patent airway after extubation.

These patients are susceptible to respiratory depression and airway effects such as relaxation of pharyngeal structures and airway collapse when sedatives (benzodiazepines), opioids, and inhaled anesthetics are used. Therefore, potential postoperative respiratory compromise should be considered when choosing transoperative

drugs [15]. Sedation as premedication should be avoided unless the patient is monitored and there is adequate equipment for airway management.

The American Society of Anesthesiologists considers regional or local anesthesia preferable for superficial procedures.

If sedation or general anesthesia is necessary for OSA patients, noninvasive blood pressure monitoring, pulsometry, electrocardiography, capnography, permeable venous access, and equipment for difficult intubation should be used. If there are findings (right heart failure, pulmonary hypertension) during the assessment of an OSA patient, intraoperative cardiovascular monitoring should be considered [10].

In procedures that require sedation, anesthetic drugs and short-acting opioids should be used. Combining fentanyl and propofol causes depression of laryngeal reflexes, with the cough reflex being the most affected (protective reflex of the airway) [48].

In several studies, alpha-2 agonists, such as dexmedetomidine, caused less respiratory depression than other sedatives; however, its combination with other sedatives can cause additive effects [49]. The only disadvantage is that a bolus over 10 min is required to begin its effect, followed by a continuous infusion. The dose will depend on the procedure and the time necessary to carry it out. Also, different authors recommend regional or neuraxial anesthesia that complements general anesthesia. This option will always be good if the patient's condition allows it. This way, opioids, muscle relaxants, and various intravenous infusions are reduced as much as possible.

Ketamine does not produce respiratory depression or airway obstruction; however, it relaxes bronchial muscle. This drug must be administered with a benzodiazepine to counteract its dissociative effects [48].

If the patient requires general anesthesia, it is important to be prepared for the risk of difficult intubation. In OSA patients, general anesthesia with a secure airway is preferable to deep sedation with an unsecured airway [50].

Adequate preoxygenation must be carried out with ventilation equipment adapted to the patient (face mask, oral and nasopharyngeal cannulas). Nasopharyngeal cannulas are more appropriate in these patients for adequate airway management since the main area of obstruction is at the nasotracheal level, according to various imaging studies such as MRI. Adequate preoxygenation can be achieved in several ways: (1) Spontaneous breathing with an FIO2 of 100% for 2–5 min; (2) with the four vital capacities method; (3) with deep breaths. After 3 min of preoxygenation, obese patients tolerate a 3-min apnea, maintaining an SPO_2 greater than 90%. The time needed to increase oxygen saturation above 96% after a desaturation is 37 s compared to 22 s in healthy individuals [51].

The size of the pharyngeal airway is increased, so anesthetized patients with OSA may benefit from being placed in the sniffing position, which reduces the risk of pharyngeal collapse [50]. Laryngoscopy in obese patients with OSA can be facilitated by placing a ramp under the patient's head and shoulders to align the ear and sternal notch [52].

Awake intubation and/or the use of fibroscopy or video laryngoscopy is recommended for tracheal intubation due to the high risk of airway management

difficulties [41]. A laryngeal mask is inappropriate in these patients because of the possibility of airway collapse and gastroesophageal reflux disease [12].

Patients with OSA present hypotonia of the lower esophageal sphincter; therefore, gastroesophageal reflux disease must be considered. Proton pump inhibitors, antacids, a rapid induction sequence, and pressure on the thyroid or cricoid cartilage (the BURP maneuver) are recommended to reduce the risk of aspiration [52]. CPAP or an oral airway management device should be considered during deep sedation in patients treated with these devices [15].

Opioids should be used with caution in patients with OSA due to the risk of respiratory depression. For maintenance of anesthesia, short-acting anesthetic agents or mixtures of propofol, remifentanil (a short-acting opioid), or poorly lipid-soluble inhaled agents, such as desflurane, are recommended [48].

However, we must consider desflurane's tendency to trigger sympathetic responses described during its use [53]. These responses can represent a risk of cardiac complications previously described in these patients, such as arrhythmias caused by severe hypoxia or hypercapnia [22, 41].

Extubation is recommended with a fully awake patient (spontaneous eye opening, responding to commands) unless there is a medical or surgical contraindication and a confirmed patent airway to avoid ventilation failures and subsequent desaturation [15].

Neuromuscular blockade with complete reversal should be mandatory in these surgical patients due to the increased risk of pulmonary complications regardless of the degree of OSA. Excessive administration of intravenous infusions of 0.9% saline solution increases the neck circumference causing an increase in the severity of apnea–hypopnea events in the postoperative period [47].

Multimodal analgesia is recommended in patients with OSA to reduce the use of opioids. If intense analgesia is required, buprenorphine is recommended because its mu receptor agonist effect is less potent, and atypical opioids such as tramadol (a weak mu agonist that causes less respiratory depression) [47]. Alternative medications such as NSAIDs, COX-2 inhibitors, acetaminophen, ketamine, pregabalin, and gabapentin, with or without dexamethasone, should be used to help reduce the use of opioids and avoid respiratory depression. In regional anesthesia, postoperative use of catheters in epidural or nerve blocks with local anesthetics reduces opioid requirements [52].

20.9 Postoperative

As mentioned at the beginning, an apnea–hypopnea index (AHI) ≥5 events/h with a range between 9% and 38% has been reported. This range was higher in men, increased with age, and in some older adults, reached 90% in men and 78% in women [6].

The postoperative period is a time of high risk for patients with OSA due to the residual effects of narcotic anesthetics and sedatives, which promote the described complications. Several studies have found that patients with OSA undergoing non-cardiac surgery have a higher incidence of postoperative hypoxia, respiratory

failure, cardiac events, and the need for intensive care than those without OSA. Unfortunately, 90% of patients with OSA are not recognized before surgery, leading to an increased risk of complications during the perioperative period [54].

Obstructive sleep apnea is a syndrome associated with difficult airway management, due to the morbid obesity of most of these patients or to the anatomical–physiological alterations that they may present (a thick, short neck, large tongue) [12]. These alterations require close monitoring in the postoperative period, considering they are susceptible to obstruction, hypoxia, hypercapnia, and total respiratory depression. The use of nonopioid analgesics is recommended; if these are required, they should be used in minimal doses [48].

Anesthetic and analgesic agents used in the perioperative period can decrease pharyngeal tone and depress the ventilatory response to hypoxia and hypercapnia. These effects may exacerbate the underlying anatomical and physiological abnormalities associated with OSA [55].

A recent study shows that 24% of patients with OSA have significant postoperative complications compared to only 7% of patients in a control group [56].

Short-acting blockers or antagonists with minimal adverse effects are recommended, such as sugammadex, which can reverse neuromuscular blockade caused by aminosteroids with fewer postoperative respiratory complications compared to neostigmine [50].

After extubation, the patient should preferably recover in a semi-Fowler position (head elevation of 30°) in lateral or any other position other than full supine, with an inspired fraction of oxygen of 100% and with positive pressure support during the next 2 min before transfer to the recovery room [48].

20.10 OSA and Outpatient Surgery

The term outpatient can be defined as any medical, organizational, and administratively permissible practice to leave the clinic or a medical stay on the same day of the intervention in less than or equal to 12 h.

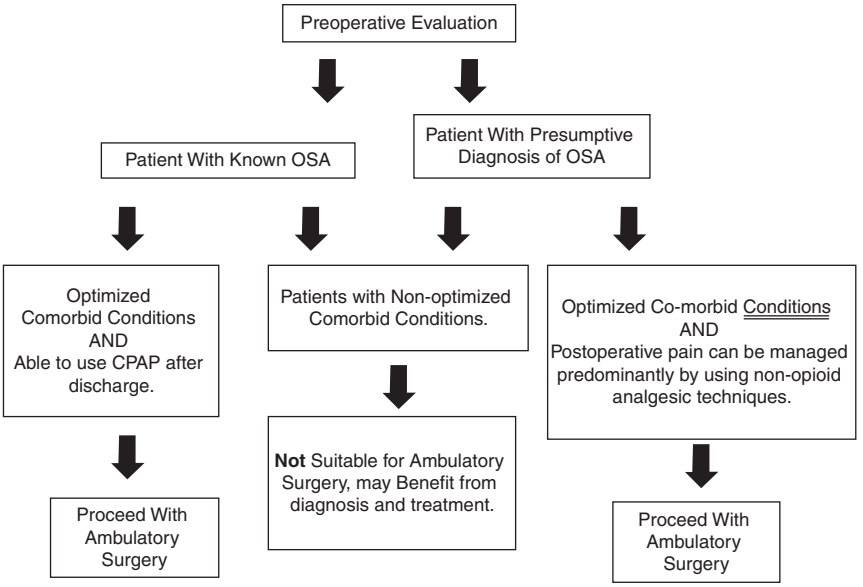
According to the NOM-026-SSA3-2012 of Mexico for the practice of major ambulatory surgery, article 4.2 establishes that discharge of the patient from Major Outpatient Surgery will be performed in a period no longer than 12 h, counted from the time of admission, during which the surgical act was performed, and postanesthetic recovery was completed [57]. Around 40% of surgeries are of this type, with a considerable progress margin. The objective is to reach the rates of first-world countries, which are near 80%.

The anesthesiologist and the attending physician are responsible for selecting the patient, the operation, or the outpatient medical procedure. The competence of the physician administering anesthesia should be tailored to the procedure and the patient's condition and comorbidities.

The International Association for Ambulatory Surgery (IAAS) and the Association Francaise de Chirurgie Ambulatoire (AFCA) agree that the suitability of ambulatory surgery in OSA patients is controversial. The decision to indicate a treatment of this type is the responsibility of the surgeon and the anesthesiologist

according to the patient's physical condition, the type of surgery, and the conditions of the healthcare environment [15]. However, it would be convenient to have a clear consensus among the physicians with previously established rules and procedures, especially regarding behaviors related to duration and follow-up.

The Society for Ambulatory Anesthesia reached a consensus for the development of an algorithm for the selection of adult patients with OSA scheduled for ambulatory surgery (Fig. 20.5). This algorithm is oriented according to the comorbidities



Preoperative Considerations:

- Comorbid conditions include hypertension, arrhythmia, heart failure, cerebrovascular disease, and metabolic syndrome.
- If OSA is suspected during the preoperative evaluation, one could proceed with a presumptive diagnosis of OSA albeit with caution.
- Educate surgeon, patient, and family.

Intraoperative Considerations:

- Non-opioid analgesic techniques, when possible.

Postoperative Considerations:

- Exercise caution in OSA patients who develop prolonged and frequent severe respiratory events (e.g., sedation analgesic mismatch, desaturation, and apneic episodes) in the postoperative period.

Fig. 20.5 Flowchart of suitable patient for surgery to take place in an ambulatory setting according to anesthesia evaluation

and the use of CPAP and other factors, facilitating the specialist's decision to proceed or not with ambulatory surgery in this type of patient [58].

Take-Home Message

- In the preoperative period, the characteristics of the mandible and soft tissues of the oral cavity and neck are relevant for the presence of OSA.
- OSA patients are susceptible to respiratory depression and airway effects such as relaxation of pharyngeal structures and airway collapse when sedatives (benzodiazepines), opioids, and inhaled anesthetics are used.
- Patients with OSA present hypotonia of the lower esophageal sphincter; therefore, gastroesophageal reflux disease must be considered. Proton pump inhibitors, antacids, a rapid induction sequence, and pressure on the thyroid or cricoid cartilage (the BURP maneuver) are recommended to reduce the risk of aspiration.
- Patient extubation is recommended with a fully awake patient (spontaneous eye opening, responding to commands) unless there is a medical or surgical contraindication and a confirmed patent airway to avoid ventilation failures and subsequent desaturation.

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Radiological Diagnosis in OSA

21

Vijaya Krishnan Paramasivan, Srinivas Kishore, Vikas Agrawal, and Mohan Kameswaran

21.1 Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent partial or complete upper airway obstruction occurring at the level of the pharynx during sleep [1]. OSA is diagnosed by polysomnography, and the level of obstruction is identified by radiological imaging and sleep endoscopy. Both the investigations are essential in evaluating and managing patients with OSAS.

Multiple soft-tissue structures surround the pharynx, and these are encased by the maxillofacial skeleton and the cervical spine. An increase in bulk of the soft tissues and decrease in size of the maxillofacial skeleton are the anatomical causes of constriction of the upper airway which can be evaluated radiologically.

Lateral cephalometry and sleep MRI are investigations to diagnose the level and pattern of obstruction that are commonly done. Lateral cephalometry and computed tomography of the airway are static airway evaluations, whereas Cine MRI will give pathophysiological changes that happen to the airway during sleep. However, ultrasonogram of the airway is still not a commonly used method as it is a little difficult to assess during sleep. Both CT and MRI can provide an excellent evaluation of the

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various anatomical planes of the site of obstruction, which helps better clinical assessment and better planning for a possible surgical approach.

These procedures have established themselves as an essential supporting assessment tools in the clinical diagnosis, preoperative evaluation, and posttreatment follow-up of patients who do not respond well to initial therapy. However, each technique has limitations, and no gold-standard method has been established until now. Therefore, a validated investigation capable of identifying the obstruction site accurately during sleep enables appropriate patient selection for surgery and other treatment modalities with an improvement in treatment outcomes.

21.2 X-ray Nasopharynx

X-ray nasopharynx or lateral radiograph of the neck is a basic commonly done investigation to evaluate adenoidal enlargement in children. It gives a measure of the absolute size of the adenoids and an assessment of its relation to the size of the airway. The size of the adenoids is graded according to the palatal airway measured from the most convex point of the adenoid tissue (A1) to the soft palate (A2) (Fig. 21.1). The narrowest distance between the nasopharyngeal soft tissues and the soft palate was taken [2].

In Fig. 21.1, we have marked the skull base as a line connecting b1 and b2. The line connecting A and A1 is the most convex point of adenoidal tissue. The distance between A1 and A2 is the posterior airway space. Accordingly, it has been graded from 1 to 3. Grade 1: >6 mm, Grade 2: 4–6 mm, Grade 3: 0–3 mm (Fig. 21.2). Grade 0 is considered as post adenoidectomy. Lateral skull radiograph is a noninvasive procedure that is well tolerated by children, unlike a flexible fiberoptic scope. It is still a useful tool in practice.

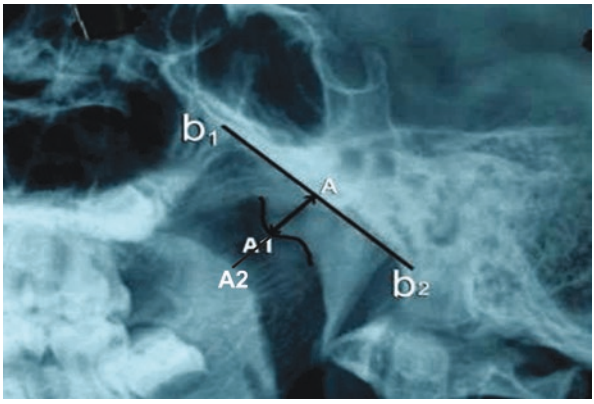

Fig. 21.1 X-ray nasopharynx showing the distance between A1 and A2, which is the posterior airway space between adenoid and soft palate

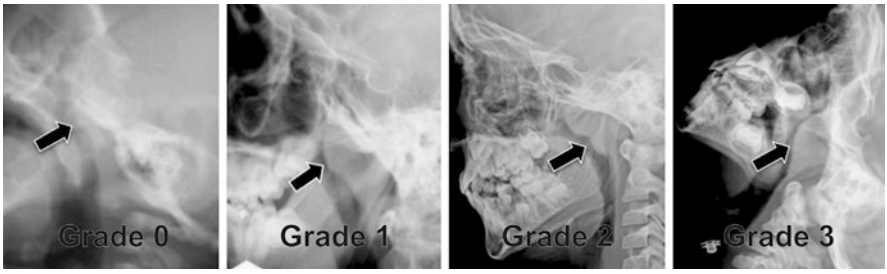

Fig. 21.2 X-ray nasopharynx showing 0–3 grades of adenoidal hypertrophy causing airway obstruction

21.3 Lateral Cephalometry

The standard method of assessment of the skeletal relationship is defined from measurements derived from a lateral cephalometric radiograph. Similar information is given by a midline reconstruction from cone-beam computed tomography (CBCT) or Multi-Detector Computed Tomography (MDCT). A small maxilla and mandible are associated with oropharyngeal crowding and predisposition to OSA, as is a high arched palate. Skeletal factors are a more significant factor in children and non-obese adults.

Lateral cephalography helps analyze skeletal and soft-tissue characteristics of patients with OSA and is available in most dental clinics, easy to perform, and less expensive [3, 4]. Moreover, a tendency toward a shorter dimension of the cranial base and maxillary length, maxillomandibular retrognathia, and increased anterior lower facial height and mandibular plane angle have been reported [5–7]. Figure 21.3 shows various bony landmarks and measurements.

The position of the hyoid bone with reference to the inferior mandibular border (mandibular plane: MP) can be obtained from the same radiograph or reconstruction; multiple studies have confirmed that an inferiorly situated hyoid bone correlates closely with an increased length of the oropharynx and both measurements are proportional to the severity of OSA [8, 9].

It provides information for anteroposterior but not lateral pharyngeal structures implicated in the pharyngeal narrowing which is considered one of the major disadvantages. It doesn't show the dynamic airway collapse during sleep.

Lateral cephalometry serves as an important tool in the clinical diagnosis of OSA patients demonstrating distinct craniofacial morphological changes. Thereby gives a clue to the site of obstruction, based on specific skeletal and soft-tissue components and helping in skeletal framework surgical planning.

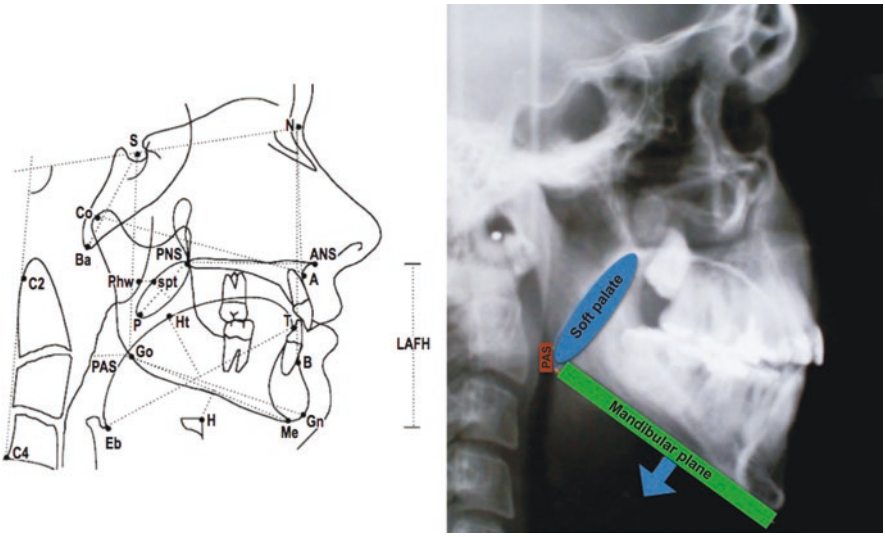

Fig. 21.3 Lateral cephalometry

21.4 Cone-Beam CT Analysis

Cone-beam computed tomography (CBCT) is a commonly used three-dimensional imaging technique introduced to dentistry in 1998 [10]. The most significant advantage is that CBCT can acquire quality images at a radiation dose equivalent to approximately one-half of the dose associated with conventional two-dimensional imaging.

Although 2-dimensional imaging is of great value, the complex shape of the airway is not evaluated except with 3-dimensional (3D) imaging techniques [11].

Computerized tomography (CT) and magnetic resonance imaging are powerful 3D imaging tools. However, radiation is an issue with CT scans and the limitations with MRI in terms of availability and compliance dictate the search for more alternatives.

Cone-beam CT fits this gap perfectly due to its advantage in short scanning time (10–70 s), and there is a relatively low dose of radiation compared with conventional CT [12]. When utilizing a large field of view (FOV) protocol, the upper airway is visible within the CBCT volume and, thus, CBCT is a useful diagnostic tool for the evaluation of the airway. Using CBCT, Enciso and colleagues, found that the presence and severity of OSA are associated with a narrow lateral dimension of the airway [13]. Mayer and colleagues reported a decrease in the transverse width of the oropharynx in OSA subjects [14]. Despite the low soft-tissue resolution, CBCT shows high contrast between bone, empty spaces, and soft tissues, allowing the airway to be visualized ideally in relation to the hard-tissue structures of the skull.

21.5 Radiographic Analysis

The CBCT images were exported as DICOM (.dcm) files and then imported into the software program for analyzing. The upper airway affected by OSA is frequently defined as the soft-tissue region bounded by the nasopharynx superiorly and the epiglottis inferiorly. Therefore, the images of the oropharynx from the hard palate to epiglottis were isolated from the data for analysis by using manual segmentation of each axial slice from the surrounding soft tissue with thresholding or setting the upper and lower gray level values of the area of interest (upper airway). Once the airway was isolated, the software computed the area (mm^2) and volume (mm^3) of each axial slice for the entire isolated portion of the airway (Fig. 21.4). These area and volume measurements were used to identify the smallest axial slice, and width and anterior–posterior (A–P) dimension measurements were then carried out on the smallest axial slice in each CBCT study. The average of multiple measurements was recorded as the value representing the width and AP dimension. All linear measurements were acquired by the same individual. The total number of axial slices segmented from the hard palate to the epiglottis was used to calculate the airway length. The A–P distance and the width of the minimum surface area of the oropharynx are commonly used to evaluate the upper airway [15].

The volumetric analysis of the airway can also be done while asking the patient to perform Muller's maneuver (Fig. 21.5). A recent systematic review revealed that the most common measurements of the airway used to evaluate OSA subjects with CBCT included total volume and minimum cross-sectional area, followed by area and lateral and anterior–posterior linear measurements [16]. A study conducted by Camacho and colleagues was the first to compare airway morphology between upright and supine patient positions using CBCT. They found that the minimum

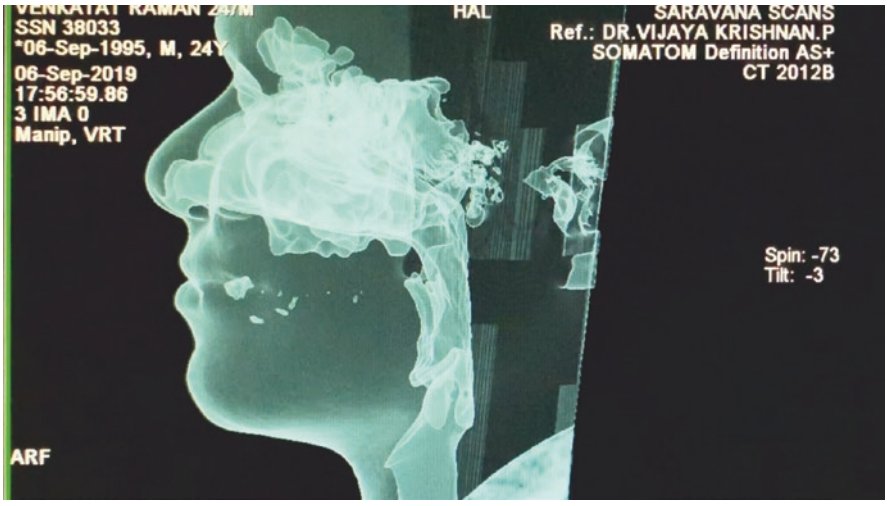

Fig. 21.4 CT airway volumetric analysis from nasal cavity to hypopharynx

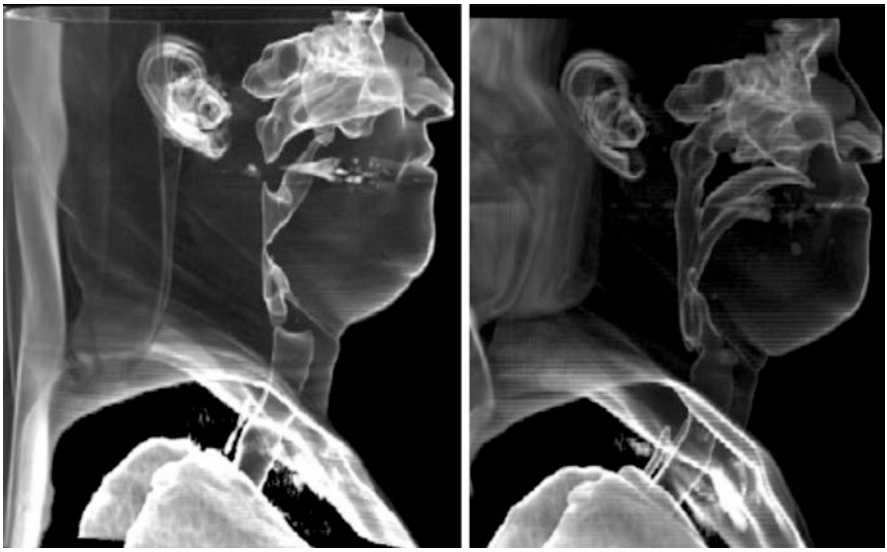

Fig. 21.5 CT airway volumetric analysis during Muller's maneuver

cross-sectional area decreased from 124 ± 29 to 30 ± 5 mm^2 when the patient was scanned in the supine position [17]. Finally, the average area and volume assessment of the total mean airway volume is made.

21.6 Role of CBCT in Surgical Planning

Specific software analyzed raw DICOM data from CBCT scanning including linear and volume and the smallest cross-sectional area where assessments are made. CBCT was performed at both ends of expiration and inspiration, which helped in the accurate determination of the level of collapse. Subsequently, this could change the surgical decision, especially in retroglossal collapse patients. CBCT is considered a low dose, a highly efficient diagnostic tool essential in conjunction with a clinical assessment to evaluate OSA, especially in severe cases properly [18].

21.6.1 Dynamic MRI

Magnetic resonance imaging of the upper airway during sleep is also termed sleep MRI, Cine MRI, or Dynamic MRI. It can detect the level, degree, and cause of obstruction in the upper airway, which helps the clinical diagnosis and treatment. This noninvasive imaging is used to identify the site of upper airway obstruction for the prediction of treatment outcomes and monitoring and follow-up of patients with OSAS after therapy. In addition, MRI of the airway with cine sequence is

considered an excellent alternative method to examine dynamic upper airway conditions during sleep [19–21]. MRI sleep studies are noninvasive and allow dynamic abnormalities of the entire airway to be assessed at once.

21.6.2 Anatomical Subdivision of Upper Airway

The upper airway is divided into nasopharynx, velopharynx, oropharynx, and hypopharynx. The nasopharynx is the region between the skull base, and the horizontal imaginary line from the tip of the post nasal spine of the hard palate. Velopharynx is the region between the postnasal spine and the tip of the soft palate. The oropharynx is the region between the tip of the soft palate and the tip of the epiglottis. Hypopharynx is the region between the tip of the epiglottis and the level of the glottis.

21.6.3 Dynamic Sleep MRI Technique

In this dynamic sleep MRI, midsagittal and axial sequential T1-weighted (repetition time, 650 milliseconds; echo time, 14 milliseconds) and T2-weighted (repetition time, 6000 milliseconds; echo time, 90 milliseconds) images with 3-mm slice thickness will be taken. The sagittal planes are obtained from the midline laterally, and the axial planes are obtained from the skull base to the larynx. Patients will be in a supine position with the neck in a neutral position and they are instructed to refrain from swallowing during scanning and to breathe through their nose with their mouth closed. Then the patient will be asked to sleep and then the images will be acquired once the patient starts snoring and apnea happens. The image analysis is done on a workstation with the determination of the level and cause of obstruction. Two-dimensional distances and diameters of the upper airway or its related structures are measured. We can evaluate the volumes of the soft-tissue structures such as the tongue, the soft palate, or the pharyngeal walls or the remaining compromised or noncompromised airway spaces. We can also obtain 3-dimensional data, volumes based on cross-sectional areas, and slice thickness by various computerized models [22, 23].

Dynamic MR imaging can obtain rapid images (1 image per second) that are temporally spaced a short time apart. It can show the dynamic motion of the upper airway, thereby allowing visualization of the changing shape and configuration of the airway during respiration and evaluation of the relationship between the soft tissue of the upper airway such as adenoid, palatine tonsils, and soft palate and the degree of airway collapse [24, 25].

Dynamic MR obtained during a normal sleeping state shows the patent nasopharynx and retroglossal airway with minimal airway motion. The degree of movement of the retroglossal airway is less than 5 mm. Dynamic MR in OSAS patients shows complete airway collapse at the level of the soft palate and base of the tongue

during apneic events. Sedation is usually not recommended in these studies, especially in adults as it carries the risk of prolonged airway obstruction. It can be used in children to simulate natural sleep.

Recently, a real-time MR imaging platform for synchronous, multiplanar visualization of upper airway collapse in OSAS at 3 Tesla can be performed to promote natural sleep, with an emphasis on lateral pharyngeal wall visualization [26].

21.6.4 Dynamic Sleep MRI in Diagnosing OSAS

Current theories on OSAS pathogenesis involve a combination of abnormal anatomy of the pharynx and the physiology of the upper airway dilator muscles. Anatomical changes in OSAS include decreased anteroposterior, lateral, cross-sectional, and volumetric measurements at different pharyngeal levels. In addition, dynamic sleep MRI helps to identify the level, pattern, degree, and cause of upper airway obstruction.

21.6.5 Level of Airway Obstruction

Retropalatal and retroglossal level of obstruction is the most typical site of upper airway obstruction. Identifying the level of obstruction is crucial in deciding treatment planning and single or multilevel surgery.

21.6.6 Degree of Airway Obstruction

Measuring the anteroposterior and transverse diameters and cross-sectional area and volumetric assessment of the airway and soft-tissue structures can help determine of the degree of airway obstruction in patients with OSAS. The measured soft tissues are adenoid tonsils, lingual tonsils, palatine tonsils, soft palate, tongue, lateral pharyngeal wall, and fat pad area. The measurement is usually done at the largest section of the soft tissue and the most narrowed section of the airway. The cross-sectional area of the soft tissues and the airway at different levels is calculated. Measurement of the upper airway revealed enlarged soft-tissue structures and narrowed pharyngeal airway in patients with OSA. The values are calculated and compared when the patient is awake and while sleeping and snoring.

21.6.7 Advantage and Limitations

Magnetic resonance imaging provides an image with excellent contrast of the soft-tissue structures in patients with OSA. A fast MR imaging can show the anatomical obstruction dynamically during apnea. Magnetic resonance imaging does not

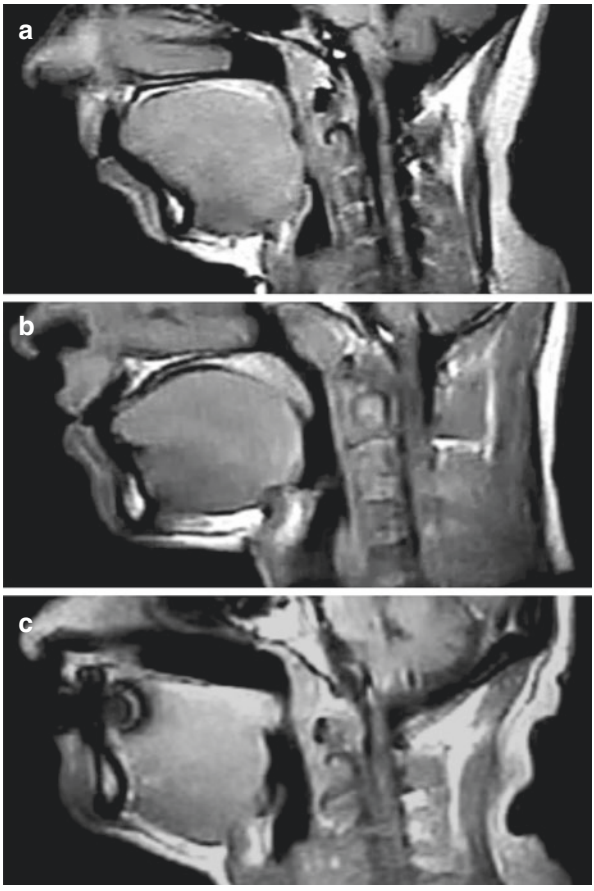

Fig. 21.6 Dynamic MRI sagittal view of OSAS patient showing different pattern of palate, (**a**) tunnel shaped soft palate, (**b**) funnel shaped soft palate, (**c**) long hard palate with very short soft palate

expose patients to ionizing radiation, and allowing imaging in multiple planes. The major limitations of MR imaging are as follows: long examination time, noisy scanning, claustrophobic effects experienced by many people while in the gantry tube, and high cost. The lack of a comfortable sleep environment also limits the ability to use MR imaging during sleep [27, 28].

The major advantages of dynamic MRI compared to drug-induced sleep endoscopy are easy differentiation of primary from secondary soft palate collapse and identification of various patterns of soft palate such as tunnel or funnel-shaped soft palate and also the length of the hard and soft palate (Fig. 21.6). If the soft palate is very short, any soft-tissue surgery may not improve the surgical outcome. For a long hard palate, bony framework surgery like transpalatal advancement pharyngoplasty can be planned.

21.6.8 Structures Causing Airway Obstruction

Obstructive sleep apnea syndrome is caused by obstruction anywhere in the upper airway, from the nasopharynx to the larynx. Due to obstruction at multiple It may occur due to obstruction at multiple levels, either simultaneously or in an alternating pattern [23, 29]. It may due to enlargement of soft-tissue structures and alterations of craniofacial structures. Enlargement of soft tissue includes an enlarged adenoid, the palatine tonsils, the lingual tonsils, the soft palate, and the tongue as well as accumulation of fat in the parapharyngeal walls. Alternations in craniofacial structures such as retroposition of maxilla and mandible and inferior positioned hyoid bone are reported in patients with OSAS (Fig. 21.7) [30, 31].

21.6.9 Nasopharynx

Enlarged adenoids are the most typical reason for airway obstruction, especially in children. It can also be one of the reasons for obstruction in adults. They reach a maximum size between 2 and 10 years of age and then begin to decrease in size during puberty. The normal size of the adenoids is between 7 and 12 mm. Adenoids larger than 12 mm in size are abnormally enlarged, which can be easily measured in sleep MRI (Fig. 21.8).

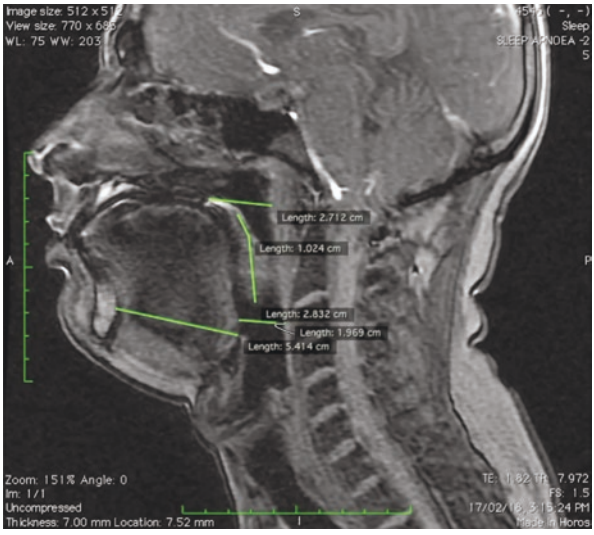

Fig. 21.7 Dynamic MRI of an OSAS patient showing soft tissues measurements

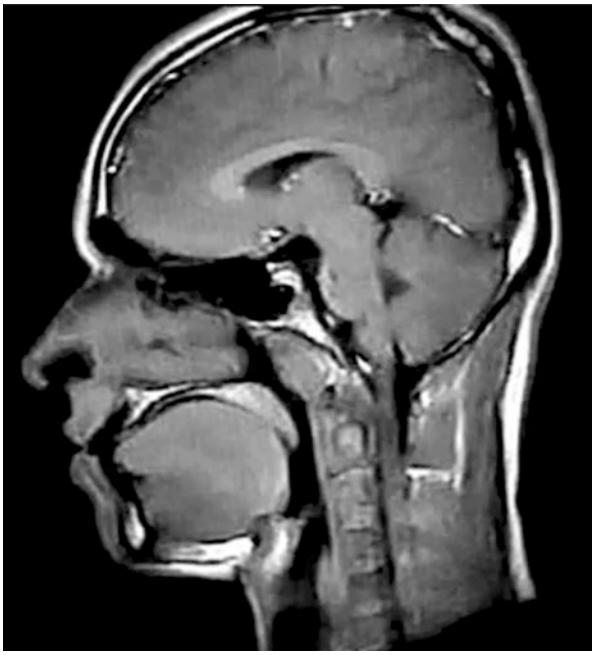

Fig. 21.8 Dynamic MRI of an OSAS patient showing adenoidal hypertrophy

21.6.10 Velopharynx

21.6.10.1 Enlarged and Elongated Soft Palate

Typically, the soft palate is isointense to tongue musculature on T2-weighted images. When the soft palate becomes edematous, it becomes high in signal on T2-weighted and thickens (>1 cm). The soft palate thickens in OSA because of microtrauma from fluttering during snoring. Thickened soft palate contributes to the worsening of OSAS by taking up more potential airway space. Criteria to consider a soft palate to be "elongated" include when the soft palate is draped over abutting the tongue or soft palate is posteriorly positioned abutting the adenoids and obstructing the nasopharynx, and when the soft palate hangs inferiorly, below the mid tongue or touches the epiglottis (Fig. 21.7) [23, 32].

Likewise, Drug-Induced Sleep Endoscopy, with an axial view of dynamic MRI, we will also be able to identify the different patterns of airway collapse at the level of velum. Figure 21.9 shows a circular, anteroposterior, and lateral pattern of collapse at the level of velum, which will help the surgeon decide which technique of surgery will improvise the surgical outcome.

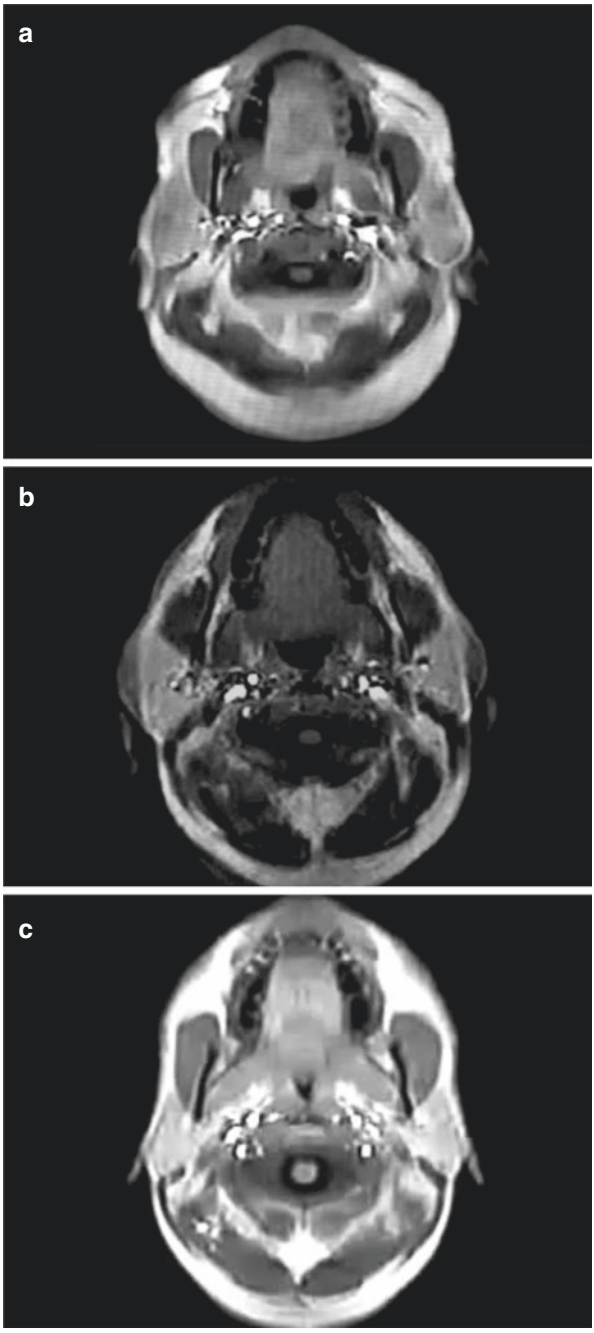

Fig. 21.9 Dynamic MRI axial view of OSAS patient showing different pattern of retropalatal collapse (**a**) circular collapse, (**b**) anteroposterior collapse, (**c**) lateral collapse

21.6.11 Oropharynx

Enlarged faucial tonsils are another common cause of obstruction in both adults and children. They have been graded as per Friedman's classification depending upon the size of the tonsil (Fig. 21.10).

21.6.12 Enlarged Lingual Tonsils

Typically, the lingual tonsil appears as a small disk of a high T2-weighted signal at the posterior aspect of the inferior tongue. When the lingual tonsils are enlarged, they appear as a large high T2-signal mass posterior to the tongue, often obstructing the velopharynx. When they enlarge, the tonsils appear as one large dumbbell-shaped mass rather than 2 discrete lingual tonsils (Fig. 21.11). The lingual tonsils were noted as markedly enlarged if the anteroposterior diameter is more than 10 mm [33, 34].

21.6.13 Macroglossia

Macroglossia is defined as a resting tongue that protrudes beyond the alveolar ridge. The posterior aspect of the tongue sits near the posterior wall of the retroglossal airway, resulting in a consistently narrowed airway (Fig. 21.12). The

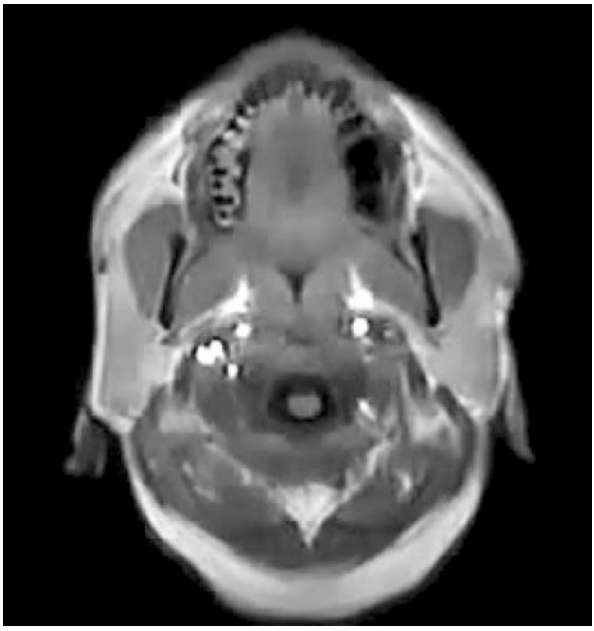

Fig. 21.10 Dynamic MRI of an OSAS patient showing Tonsillar hypertrophy

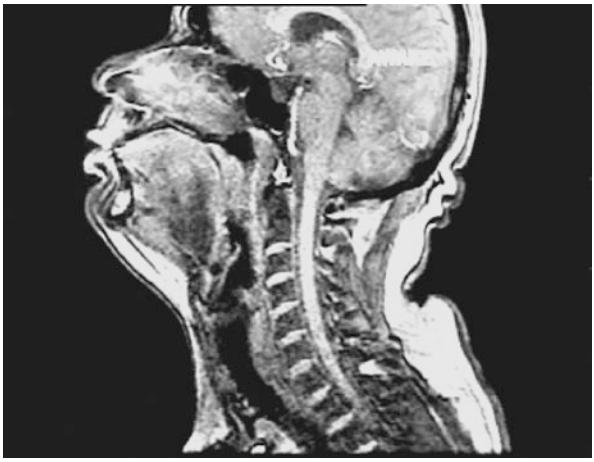

Fig. 21.11 Dynamic MRI of an OSAS patient showing Lingual Tonsillar hypertrophy

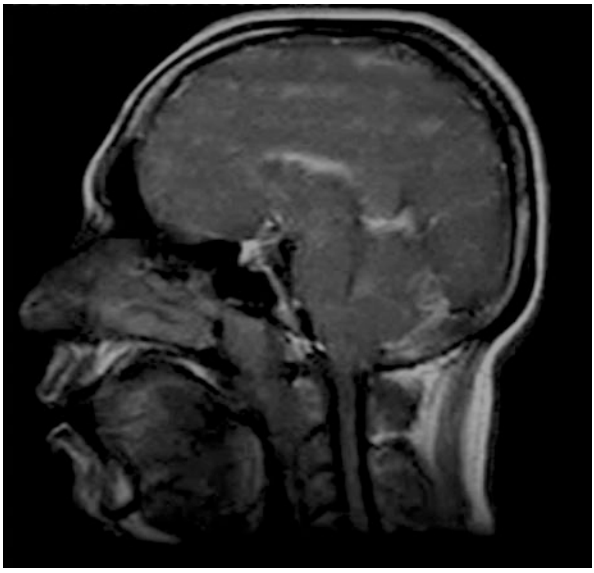

Fig. 21.12 Dynamic MRI of an OSAS patient showing tongue base hypertrophy

tongue may be relatively large in patients who have a small mandible (micrognathia) (Fig. 21.13), which is termed relative macroglossia. An enlarged tongue can fall posteriorly during sleep, obstructing the retroglossal airway. Magnetic resonance imaging helps assess the size of the tongue and the degree of compression along the retroglossal airway. It also helps in identifying secondary palatal collapse where the tongue base itself pushes the palate backward and obstructs the retropalatal airway.

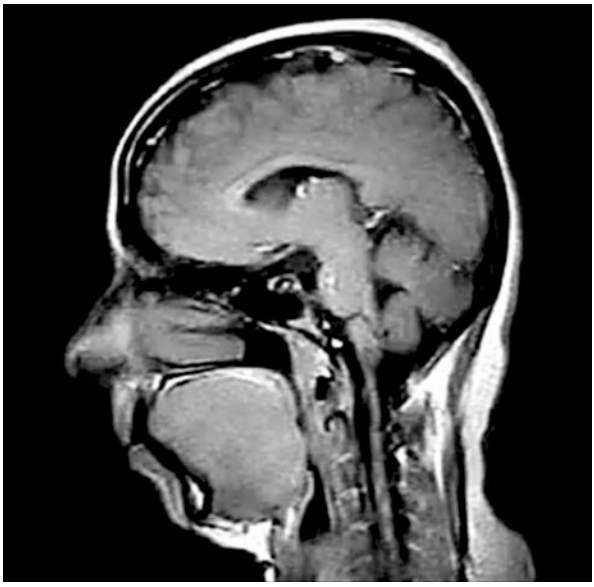

Fig. 21.13 Dynamic MRI of an OSAS patient showing micrognathia pushing the tongue base posteriorly

21.6.14 Glossoptosis

Glossoptosis is defined as the posterior motion of the tongue during sleep. With glossoptosis, the posterior border of the tongue intermittently moves posteriorly and abuts the posterior pharyngeal wall obstructing the retroglossal airway. Glossoptosis is associated with macroglossia, micrognathia, or decreased muscular tone. Dynamic sagittal MR imaging demonstrates the tongue to "fall" posteriorly, abutting the velum and the posterior wall of the pharynx, which causes upper airway obstruction. In severe glossoptosis, the tongue can also push the soft palate posteriorly, causing intermittent obstruction of the nasopharynx. On axial images obtained at the level of the middle portion of the tongue, the predominant motion is anterior to the posterior motion, intermittently obstructing the retroglossal airway. In contrast, the lateral and the posterior aspects of the retroglossal airway remain stable in position [35].

21.6.15 Hypopharyngeal Collapse

Hypopharyngeal collapse is the term given to the collapse of the retroglossal airway that is related to decreased muscular tone. In contrast to glossoptosis, where there is the abnormal posterior motion of the tongue during sleep, the hypopharyngeal collapse shows the tongue moving posteriorly and the posterior wall of the pharynx moving anteriorly. Certain patients, particularly those with Down syndrome, will have both components of glossoptosis and a floppy airway at risk for hypopharyngeal collapse [27, 28].

21.6.16 Hypopharyngeal and Laryngeal Lesions

Vallecular cysts of the hypopharynx and other soft-tissue tumors such as lipoma in the hypopharyngeal region have been associated with OSA. In most cases, the larynx can be involved as a site of obstruction, at the epiglottis level. Edema and granulomatous lesions of the epiglottis as scleroma may be associated with OSA [27, 29, 36].

We will be able to easily differentiate the primary from secondary epiglottic collapse in the sagittal and axial view of dynamic MRI. In primary epiglottic collapse, vallecular air-filled space can be appreciated between epiglottis and tongue base. However, in secondary epiglottic collapse, the tongue pushes the epiglottis back, and an absence of air is seen between the epiglottis and the tongue base (Fig. 21.14).

21.6.17 Fat Deposition in Parapharyngeal Space

Excess adipose fatty tissue deposition in the parapharyngeal space may be associated with OSA [6, 8]. This is one of the most exclusive situations where sleep MRI helps in assessing the parapharyngeal space fat deposition. In dynamic MRI, we will also be able to evaluate large deposits of fat in the posterolateral aspect to the oropharyngeal airspace at the level of the soft palate; fatty streaks can be noted in the tongue, anterior to the laryngopharyngeal airspace, in the submental regions and around the collapsible segment of the pharynx [37].

21.6.18 Retropharyngeal Lesions

Soft-tissue tumors of the retropharyngeal space such as lipoma and Schwannoma narrow the airway with OSA. A retropharyngeal abscess associated with bacterial or tuberculous infection may be associated with OSA. Lastly, bony tumors such as exostosis from the cervical spine may be related with OSA [27, 38].

21.6.19 Craniofacial Abnormalities

Craniofacial abnormalities such as retrognathia, inferiorly positioned hyoid bone, and maxillary and mandibular retroposition are associated with OSA. Cephalometry and computed tomographic scans are essential for detecting osseous changes; however, MRI has a role but is of limited value. There is a relationship between surface facial dimensions and upper airway structures measured at MR imaging in patients with OSAS [39, 40].

Mandibular hypoplasia may be idiopathic but more commonly associated with certain inherited disorders and syndromes, such as Treacher–Collins syndrome, Nager syndrome, Goldenhar syndrome, hemifacial microsomia, trisomies 17–18 and 13–15, Cri du chat syndrome, and Pierre–Robin sequence. Magnetic resonance

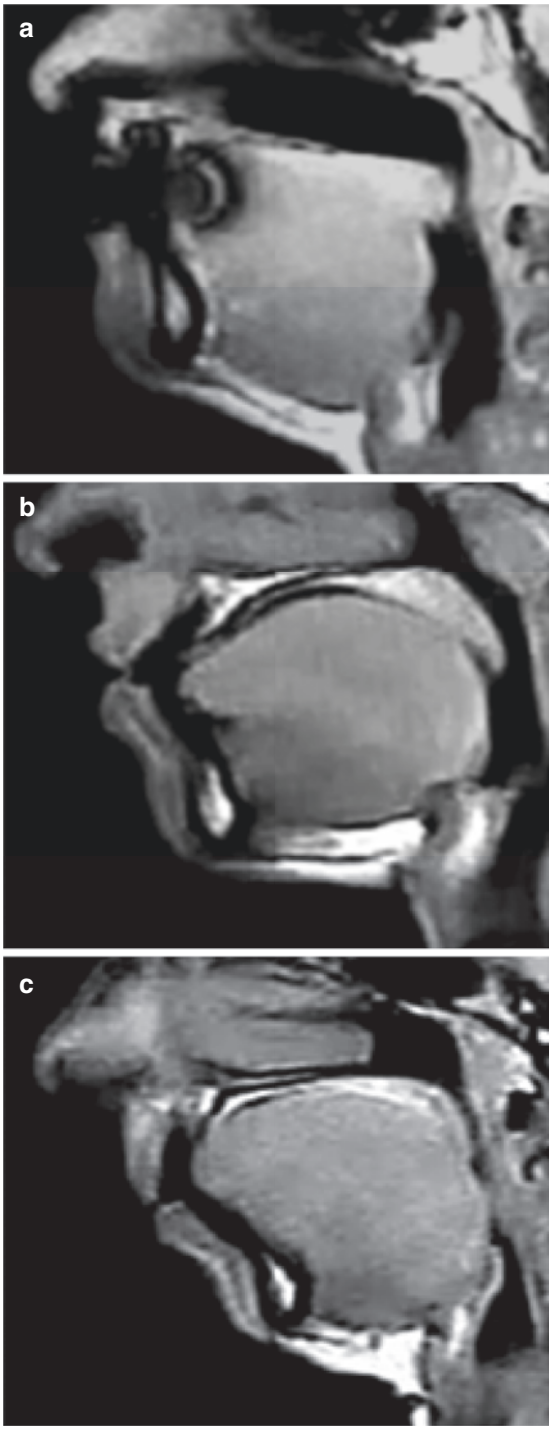

Fig. 21.14 Dynamic MRI of an OSAS patient showing different position of epiglottic collapse, (**a**) normal position of epiglottis, (**b**) primary epiglottic collapse, (**c**) secondary epiglottic collapse

imaging helps in establishing the size and position of the tongue in relation to the hypoplastic mandible and the degree of airway compromise [24, 25].

21.6.20 Associated Disorders

In Down syndrome, there is no true or absolute macroglossia but relative macroglossia in relation to the size of the oral cavity. Obstructive sleep apnea syndrome occurs in 30–60% of patients with Down syndrome [41]. Congenital conditions affecting craniofacial development (Fig. 21.15) such as Chiari, Marfan, Down, and the Pierre–Robin syndrome predispose to OSAS [7, 8]. Endocrinologic conditions such as acromegaly and hypothyroidism are associated with a higher prevalence of OSAS [42].

Magnetic resonance imaging is essential for the diagnosis and treatment planning of OSAS as it can detect the level, degree, and causes of the upper airway obstruction. It also has a role in predicting treatment response and monitoring patients with OSA after therapy. It has always been complementary to other investigations to identify the site of obstruction.

21.6.21 Neuroimaging in OSA

OSA is clinically characterized by chronically fragmented sleep and intermittent hypoxemia, defined as repeated episodes of deoxygenation that alternate with episodes of reoxygenation. OSA-related hypoxemia is associated with an increase in sympathetic vasoconstriction and a coinciding decrease in vascular protective mechanisms, resulting in changes to the structure and function of the blood vessel.

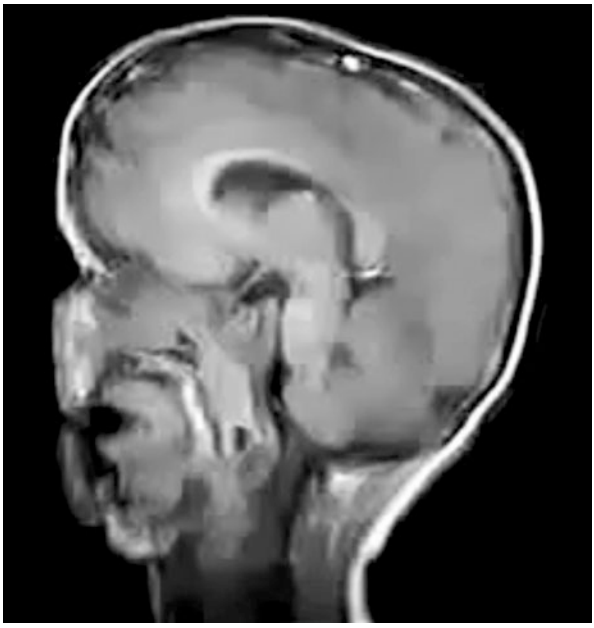

Fig. 21.15 Dynamic MRI of an OSAS patient with craniofacial anomaly showing airway collapse

This imaging technique can clarify abnormalities in neural control of respiratory function in OSA by examining the relationship between respiratory challenges and brain function measured in the magnetic resonance imaging (MRI) scanner. Neuroimaging can also help identify neural abnormalities associated with vascular function in OSA. It helps identify individuals with OSA at the most significant risk for poor outcomes by examining relationships between brain integrity and functional response to treatment. These results may subsequently serve as a potent clinical motivator for OSA individuals struggling with treatment adherence. There are, however, limitations to the use of neuroimaging techniques. Some forms of neuroimaging, such as positron emission tomography, are invasive and not easily repeated over time.

The neurological sequelae of untreated OSA have been studied by conventional and functional imaging techniques of the brain. Moderate to severe OSA is an independent risk factor for white matter disease demonstrated by MRI because of Transient ischemic attack or an ischemic or hemorrhagic stroke.

MRI diffusion tensor imaging (DTI) has recently been used to demonstrate evidence of a reduction in white matter fiber integrity in multiple brain areas in patients with OSA [28] and complete reversal of white matter abnormalities after 12 months of CPAP treatment [24]. Widespread changes in gray matter concentration have been found in patients with OSA using the functional MRI technique of voxel-based morphometry (VBM) (Fig. 21.16) [43–45].

Structural MRI (sMRI) is an important tool that promotes the examination of neuroanatomic volumetric and morphometric abnormalities that may be involved in pathologic processes. sMRI also provides an essential context to consider both neurochemical and neurofunctional findings. The voxel-based morphometric analytic technique will help assess regional gray matter loss in the frontal cortex, parietal cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum of patients with OSA. The extent of the volumetric decline was related to the severity of OSA, with patients with more severe OSA demonstrating the most significant amounts of gray matter volume loss.

21.6.22 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is an imaging technique that permits the investigation of neuronal cellular chemical activity by examining neurotransmitters and amino acids. In existing MRS studies of populations with OSA, spectral

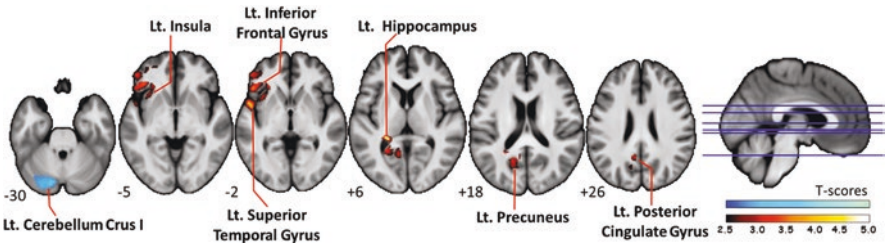

Fig. 21.16 Regional gray matter volume differences between OSA baseline and OSA follow groups. Hot color map, OSA baseline > OSA follow; cold color map, OSA follow > OSA baseline (corrected $p < 0.05$)

resolutions of *N*-acetyl aspartate (NAA), choline (Cho), creatine (Cre), and myo-inositol (mI) metabolites have been examined.

NAA, an amino-acid derivative, is primarily located in neurons and is thought to be a marker of neuronal viability. Reductions of NAA may reflect neurodegeneration [46, 47]. Abnormal levels of Cho suggest inflammation, cellularity, and membrane degradation associated with demyelination [48]. A decrease in the ratio of NAA to Cho has been utilized as an indicator of cerebral metabolic injury, such as gliosis and impairment of neuronal and axonal function [49–51].

MRS is a useful neuroimaging tool for OSA study, because it provides a measure of cerebral metabolic change that may reflect pathologic insults to brain integrity.

21.6.23 Functional Neuroimaging

Functional neuroimaging helps to examine cerebral activation in response to an external probe. fMRI images are generally acquired using the blood-oxygen-level-dependent (BOLD) technique. This noninvasive, high spatial and temporal resolution technique enables the acquisition of images dependent on the MR signal's sensitivity to excesses of cerebral blood flow associated with an increase of synaptic activity in the brain.

Functional neuroimaging techniques are ideal for investigating acute changes in the brain associated with the performance of various challenges like respiratory and cognitive. These neuroimaging findings support the presence of OSA-associated neurofunctional and white-matter impairments, particularly in the frontal lobes and hippocampus. Such impairment is consistent with proposed models of the central nervous system and cognitive dysfunction in OSA implicating small vessel disease [52] and the prefrontal cortex [53].

21.7 Role of Ultrasound in Identifying the Airway Obstruction

Ultrasonography (USG) is increasingly being explored as a tool for evaluating upper airway anatomy and pathologic characteristics, with clinical use developing in areas as broad as the diagnosis of laryngeal and swallowing abnormalities, guidance for percutaneous tracheostomy and cricothyrotomy, and also in sleep apnea.

The use of conventional ultrasound systems to image the upper airway has been limited because the air column attenuates ultrasound energy. A computer-controlled bidirectional ultrasound system combines two conventional ultrasound devices with computer image processing to yield images of upper airway structures.

Submental ultrasonography of neck can be used to assess tongue base thickness, subcutaneous fat thickness, palatal thickness, retropalatal diameter, retroglossal diameter and upper airway length during normal tidal expiration, forced inspiration, and Muller's maneuver (Fig. 21.17).

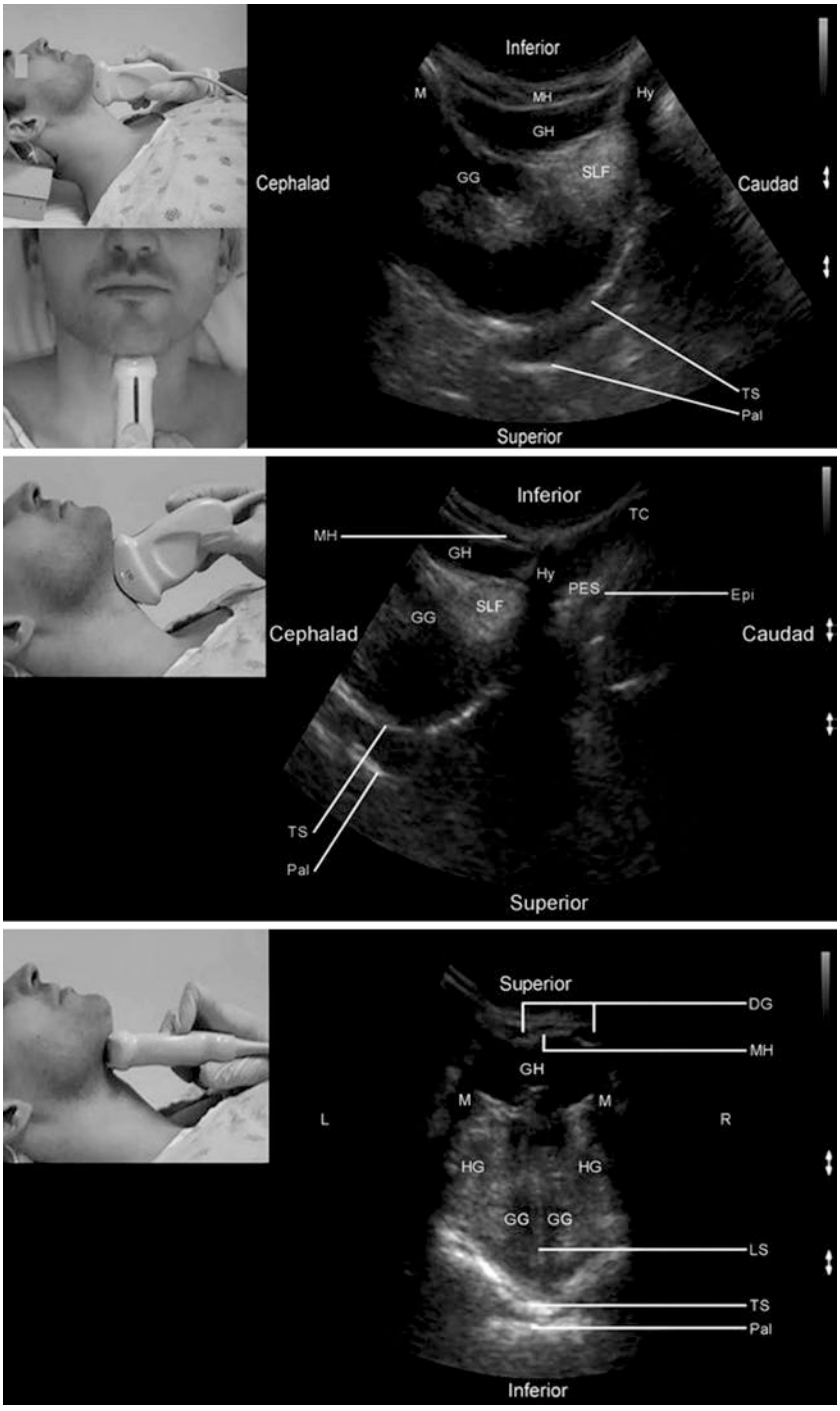

Fig. 21.17 Submental USG image of upper airway in various position

Due to the convenience, inexpensiveness, no irradiation, and office-based procedure, it can be commonly used to examine the neck in OSAS patients. USG has been used for sleep disorder patients, to evaluate the carotid intima-media thickness and level of obstruction in recent years [54–56]. Lahav et al. [57] first used a tongue base USG to measure the width of the tongue base and demonstrated the possible role of USG in diagnosing OSAS. Shu et al. [55] used the retropharyngeal diameter to determine the severity of OSA and proposed a prediction model. Chen et al. [56] verified the tongue base thickness, providing a quantitative assessment of the retroglossal airway. These reports show a promising role for USG in diagnosing OSAS.

Take-Home Message

- Imaging the upper airway is essential for the diagnosis and treatment planning of OSA patients because it can detect the level, degree, and causes of the upper airway obstruction. In addition, it has a definite role in predicting treatment response and monitoring of patients with OSAS after therapy.
- X-ray nasopharynx will help us measure the size of adenoidal hypertrophy and document the difference after treatment. Lateral cephalometry and 3D reconstructed imaging of facial bone are important imaging modalities when planning for any skeletal framework surgery. Both CT and MRI can provide an excellent evaluation of the various anatomical planes of the site of obstruction, which enables better clinical assessment as well as better planning for a possible surgical approach. With dynamic MRI, we perform a volumetric analysis of the airway and the surrounding structure. Functional MRI is mainly used to analyze cognitive function to assess the severity of OSAS and its effect on the brain. In addition, submental USG are still in research phase where it needs further development for routine practice.
- There are various radiological modalities of investigation available for the upper airway assessment. We need to choose the right examination for our patient. Sometimes, more than one investigation may be needed, and they may be complimentary to each other.

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Allergic Rhinitis and OSA

22

Alvaro Carvallo and Gabriel Gastaminza

22.1 Allergic Rhinitis

Allergic rhinitis (AR) is the most prevalent allergic disease. It affects a significant portion of the population, with a prevalence of confirmed AR of up to 28% among European adults, a number that seems to be increasing worldwide [1]. In Spain, it is also the most frequent reason for consultation in allergy departments in both adult (62%) and pediatric (54%) populations [2, 3]. Its prevalence increases during the first years of life. Nasal symptoms are persistent (almost 30%) during the third decade of life and lower above 60 years [4]. The symptoms that most frequently establish a diagnosis of rhinitis are nasal congestion, anterior and posterior rhinorrhea, sneezing, and nose itching. AR is frequently and characteristically accompanied by ocular symptoms (conjunctival erythema, epiphora or pruritus) and bronchial symptoms (cough, wheezing, and dyspnea). Other allergic diseases, such as atopic dermatitis and food allergy, are also more frequent among AR patients.

In AR, the symptoms are elicited by exposition to an allergen. For this reason, during a study of a patient with rhinitis, it is essential to carry out a complete clinical history on the temporality of the symptoms, their geographical or seasonal variation, and their relationship with specific exposures. It is essential to ask about the characteristics of the home environment, the products to which the patient is exposed at work, the hobbies they may practice, or any pets they might own.

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22.1.1 Mechanisms of Allergic Rhinitis

Allergen exposure causes inflammation of the mucosa that is part of type 2 inflammation, which is also involved in chronic rhinosinusitis with nasal polyps (CRSwNP). This inflammation is driven by Th2 lymphocytes or group 2 innate lymphoid cells (ILC2) and induced by local dendritic cells. Typical cytokines involved are IL-4, IL-5 and IL-13. IL-4 induces the production of local immunoglobulin E (IgE) antibodies (specific to the allergen in AR or polyclonal in the case of CRSwNP) [5, 6]. IL-5 is a potent stimulator of the recruitment and survival of eosinophils [7]. IL-13 is a significant contributor to the development of a late nasal response and can be responsible for the persistent nasal blockage in AR [8]. A representation of this allergenic response, including type 2 inflammation, can be seen in Fig. 22.1.

Specific IgE to a perennial or seasonal allergen can be locally produced in the nasal mucosa, without being present in serum. In patients suffering a local AR (LAR), skin prick testing (SPT) with aeroallergens and specific IgE determination in serum yield negative results. LAR diagnosis can only be confirmed with a nasal challenge test. Most of these patients are monosensitized to a single allergen, but almost 40% of them are polysensitized [9]. In addition, some patients suffering symptoms of perennial rhinitis have positive SPT to seasonal allergens only. These patients can be labeled as mixed rhinitis (coexistence of AR and NAR) or dual AR (coexistence of AR and LAR). In these patients, with discordance between clinical history and SPT results, accurate diagnosis can only be established with a nasal

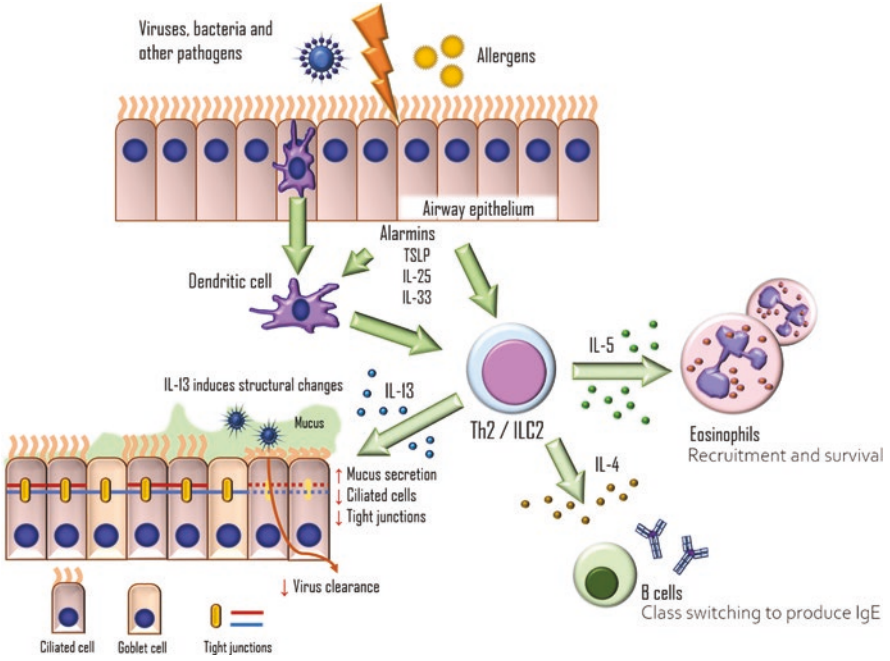

Fig. 22.1 Mechanisms of type 2 inflammation in the upper airway epithelium

challenge test or by performing an in vitro challenge test with the patient's basophils, the Basophil Activation Test (BAT) [10].

22.1.2 Clinical Relevance in Allergy Diagnosis

Sensitization to an allergen is not equal to allergy. Clinical relevance is required to label a patient as allergic, which means there must be congruence between clinical history and the results obtained by allergy tests. Not every sensitization found on allergy tests elicits symptoms and thus does not always equal allergy. Therefore, careful interpretation of allergy tests, positive or negative, is required to perform an accurate diagnosis. When no clinically relevant allergens are identified, a diagnosis of non-allergic rhinitis (NAR) can be established. When exposition to the allergen is continuous, as is the case with house dust mites and pets, the relationship between symptom onset and contact with the allergen can be lost. For this reason, some patients are sensitized to dust mites or other non-seasonal allergens that do not have the suspicion that their symptoms might be allergy related. In these cases, the main symptom is usually nasal congestion. Table 22.1 shows the main allergens that commonly cause respiratory allergies.

Table 22.1 Main allergens causing respiratory allergy

House dust and storage mites	*Dermatophagoides pteronyssinus*
	Dermatophagoides pharinae
	Lepidogliphus destructor
	Blomia tropicalis
	Tyrophagus putrescentiae
	Acarus siro
Pets	Cat
	Dog
	Rodent
Grass pollen	*Lolium perenne*
	Phleum pratense
Tree pollen	*Cupressus arizonica*
	Olea europaea
	Platanus acerifolia
	Betula verrucosa
Weed pollen	*Parietaria judaica*
	Plantago lanceolata
	Ambrosia elatior
	Chenopodium album
	Salsola kali
	Artemisia vulgaris
Molds	*Alternaria alternata*
	Cladosporium herbarum
	Aspergillus fumigatus
	Penicillium notatum
Other allergens	Natural rubber latex
	Ispaghula
	Horse
	Cockroach

A problem that allergy specialists must deal with frequently is a low degree sensitization to a perennial allergen, usually to house dust mites. In these cases, doubts arise about the clinical relevance of this sensitization. The first option to elucidate this problem would be to conduct a nasal provocation test with a mite extract. However, this test needs to be standardized, is time-consuming, and may sometimes be unavailable. Another possibility, as mentioned above, is to perform a BAT. In this test, basophils are isolated from the patient's blood and incubated in vitro with the mite extract; subsequently, the percentage of basophils that have been activated (defined as expressing protein CD63 in their membrane) with different concentrations of the extract is measured, obtaining a dose/response curve [10]. Another helpful method would be the determination of specific IgE to recombinant allergens. Finally, the presence of sensitization to certain mite allergens (Der p 7 and Der p 23) has been more frequently associated with the presence of allergic symptoms after exposure to mites [11].

Clinical Relevance
A allergy diagnosis requires three elements: a symptom suggestive of allergy, a proven sensitization to an allergen, and clinical relevance between the first two elements. Careful interpretation of allergy test results is paramount to performing an accurate diagnosis.

22.2 Rhinitis and OSA

22.2.1 General Findings

The relationship between rhinitis and OSA has been a topic of study due to their shared involvement of the upper airways. Nasal obstruction during the day, which AR patients commonly experienced by, has been identified as an independent risk factor for OSA [12]. Rhinitis symptoms are common among OSA patients, with a prevalence of 56% in this population [13]. Rhinitis not only coexists with OSA in a significant proportion of patients but is also linked with several sleep parameters and OSA outcomes. In addition, the severity of rhinitis symptoms positively correlates with increased daytime sleepiness and negatively correlates with continuous positive airway pressure (CPAP) compliance [14].

22.2.2 Rhinitis and CPAP Use

The impact of rhinitis on CPAP tolerance and compliance is a matter of interest. Continuous CPAP use causes an early inflammatory response of the nasal mucosa [15], which explains why rhinorrhea, nasal congestion, and sneezing are reported as side effects of CPAP [16, 17]. Neutrophils in the nasal mucosa experience a

threefold increase after 5 h of continuous CPAP use, accompanied by up-regulation of pro-inflammatory chemokine MIP-2 [15]. In long term, baseline neutrophilic local inflammation in AR patients significantly increases after 2 months of continuous CPAP treatment [18]. Thus, CPAP tolerance might be more impaired in patients with rhinitis, as there would be an added component of CPAP-induced nasal inflammation to the preexistent one. This would be troubling, since early CPAP rejection rates are already high (up to 50%) among OSA patients, even before the initial titration [19]. Therefore, rhinitis patients should be the target of strategies to increase CPAP acceptance and compliance. CPAP is the first-line treatment of OSA, and aside from its benefits in reducing apnea events, it also improves subjective nasal and ocular symptoms in OSA patients with AR [18]. There seems to be a delicate balance between baseline inflammation due to rhinitis, the added inflammatory response due to CPAP, and symptom improvement attributed to this therapy. Thus, the relationship between rhinitis and OSA is multifactorial and requires consideration during the clinical approach and decision-making. Despite these findings, rhinitis does not seem to be directly associated with OSA severity as measured by the apnea/hypopnea index [13].

22.2.3 Other Allergy-Related Issues Regarding CPAP

Aside from the previously mentioned findings regarding the relationship between rhinitis and CPAP therapy, there have also been cases of contact dermatitis attributed to CPAP. Scalf (1999) reported a case of allergic contact dermatitis due to sensitization to a component of the CPAP mask strap. In this case, eczema developed symmetrically on the patient's scalp after 1 month of using the mask [20]. Patch testing, the cornerstone of contact allergy diagnosis, yielded positive results to the neoprene rubber strap, and dialkyl thioureas. The lesions entirely resolved after replacing the rubber strap with a cloth one. Dialkyl thioureas are used as accelerators in vulcanization and are a known cause of contact allergy to rubber products. Egesi (2012) reported two cases of facial eczema following CPAP use, well-demarcated and localized on the contact zones with the mask itself [21]. In both cases, patch testing yielded negative results, and the patients were diagnosed with irritant contact dermatitis and treated with topical corticosteroids. Despite being a seemingly rare occurrence, contact dermatitis to CPAP mask components is another issue that could interfere with tolerance and compliance with this therapy and should be adequately studied if suspected.

22.2.4 Rhinitis and Response to Surgery

In OSA patients with anatomical abnormalities, non-invasive treatment might prove insufficient. These patients may benefit from surgical intervention to correct the identified anatomical anomalies that contribute to sleep apnea. While flexible nasal endoscopy might reveal some treatable pathologies such as a deviated septum,

turbinate hypertrophy, and tonsillar hypertrophy, others may require further endoscopic studying. Drug-induced sleep endoscopy (DISE) allows for direct evaluation of the upper airway during sleep and may reveal the specific location and cause of obstruction. This allows for targeted surgery such as palatopharyngoplasty and robotic tongue-base resection.

Few studies have evaluated the relationship between rhinitis, its etiology, and response to corrective surgery in OSA patients. A recent study on 35 patients with OSA undergoing nasal surgery (septoplasty and inferior turbinate reduction) to correct symptomatic nasal obstruction found that those with AR had higher success rates (50%) than those without this diagnosis (4%), In contrast, the overall success rate was 14% [22]. Thus, AR patients with OSA might benefit more from nasal surgery than their non-allergic counterparts, although nasal surgery alone may often prove insufficient. Therefore, evaluating response to surgery particularly important in AR patients, given the potential difficulties with CPAP compliance in this group. Further studies are warranted comparing response rates to surgery between AR and NAR patients in other anatomical levels other than nose.

22.3 Allergic Rhinitis and OSA

Although the relation between rhinitis and OSA has been widely studied, the impact of the specific etiology of rhinitis is not clear. A 2004 study showed that OSA patients were more likely to be sensitized to perennial allergens (house dust mites and dog dander) than controls [23]. Atopy was also more prevalent among OSA patients (32%) than controls (7%). A later study by Zheng (2017) reported that perennial allergens were the predominant sensitization among OSA patients diagnosed with AR [13]. 49% of these patients were sensitized to perennial allergens only; 29% to both seasonal and perennial allergens; and 22% were sensitized to seasonal allergens only.

Both types of rhinitis-AR and NAR-seem to affect sleep quality, but to which extent one might be more impactful than the other is not yet clear. Few studies that compare OSA parameters directly between AR and NAR patients. Zheng (2017) conducted a study of 240 OSA patients, of which 27% were diagnosed with AR and 29% with NAR. They found that OSA patients with AR suffered lower sleep efficiency than those diagnosed with NAR and those without rhinitis [13]. On the other hand, NAR patients had lower oxygen saturation than those without rhinitis. Kalpaklioğlu (2009) compared patients with AR and NAR and performed polysomnography evaluations. They found lower sleep efficiency and shorter sleep duration in the NAR group than in AR patients [24]. The proportion of subjects diagnosed with OSA was significantly higher in the NAR group (83%) than in the AR group (36%), and NAR correlated with OSA diagnosis and apneas. A recent meta-analysis of 27 observational studies reported that OSA patients with AR presented more sleep disturbances and daytime dysfunction than the control groups. However, the quality of evidence was reportedly low [25]. Thus, which rhinitis subtype has more influence on OSA still lacks a clear answer.

The mechanisms involved in allergenic inflammation are complex and dynamic, several elements might explain the effects of the etiology of rhinitis on OSA parameters. As previously mentioned, IL-4 is an integral part of the inflammatory response in allergic rhinitis. IL-4 also seems also related to sleep quality, as it positively correlates with time to onset of REM sleep and negatively correlates with REM sleep time [26]. Thus, sleep in AR patients would be less restorative, contributing to more daytime dysfunction and other observed sleep-related disturbances. It is worth noting that IL-4 expression in atopic individuals seems to be independent of the presence and intensity of rhinitis symptoms, while other cytokines such as IL-5 are more expressed in symptomatic individuals during pollen season [27]. This would mean that sleep efficiency, related to IL-4, might be more impaired in allergic individuals independently of symptomatic seasonal variations. Thus, the relationship between AR and OSA may go well beyond the presence of nasal congestion. Further investigation is warranted to determine whether the effect on sleep parameters is due to allergenic inflammation, the persistence or seasonality of nasal symptoms, a combination of both, or some other factor.

Take-Home Message

- Allergic rhinitis and OSA seem interwoven, although the specific physiological mechanisms that explain the observed differences in OSA characteristics between AR and NAR patients require further study. The available evidence points to an association between baseline allergenic inflammation and lower sleep quality and efficiency in these patients. There is also a link between AR and compliance and response to non-invasive and invasive OSA treatment. Thus, evaluation by an allergy specialist is recommended when approaching a patient with a suspicion of sleep apnea and nasal symptoms. Further investigation is warranted regarding the relationship between these two frequently coexisting pathologies.

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Psychiatric Illness and Obstructive Sleep Apnea

23

Hector Olivares Rodriguez

23.1 Introduction

Despite multiple meta-analyses and articles that have addressed the issue of psychiatric illness and obstructive sleep apnea for decades, there is an inconsistent correlation between these medical conditions that persists, causing significant bias handling guidelines of both, not only in clinical practice but more significantly in the information that students receive in medical schools worldwide.

The purpose of this chapter is to emphasize that the chronic presence of undiagnosed sleep apnea in the presence of certain mental illness can increase the severity of the condition and provide poor pharmacological treatment that worsens both medical conditions. Thus, I will address the most related psychiatric conditions, like depression, attention-deficit disorder and hyperactivity, eating disorders, and insomnia.

23.2 Depression

The WHO defines depression as a disorder characterized by persistent sadness and a lack of interest or pleasure in previously rewarding activities. In addition, it can alter sleep and appetite, often accompanied by tiredness and lack of concentration. It is a significant cause of disability worldwide and significantly impacts morbidity.

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It is estimated that at least 322 million people worldwide suffer from depression, up 18% from a decade ago. Depression and anxiety increased by more than 25% only during the first year of the pandemic [1, 2].[1]

In the DSM V, the term depression is used primarily to refer to any depressive disorder.

For the diagnosis of major depression, ≥5 of the following symptoms must have been present almost every day for a given period of 2 weeks, and one of them should be depressed mood or loss of interest or pleasure:

Depressed mood most of the day.

A marked decrease in interest or pleasure in all or almost all activities most of the day.

Significant increase or loss (>5%) of weight, or decrease or increase in appetite.

Insomnia (often sleep-maintaining insomnia) or hypersomnia.

Agitation or psychomotor delay observed by others (not reported by the same patient).

Fatigue or loss of energy.

Feelings of worthlessness or excessive or inappropriate guilt.

Decreased ability to think or concentrate, or indecision.

Recurrent thoughts of death or suicide, attempted suicide, or a specific plan to commit suicide [3].

The ICD currently defines obstructive sleep apnea (OSA), when one of these two criteria is met

1. The presence of an apnea–hypopnea index (AHI) ≥15 h, predominantly obstructive.
2. The presence of an AHI 5 and 15 accompanied by one or more of the following factors: excessive daytime sleepiness, nonrestorative sleep, excessive tiredness, and/or sleep-related deterioration of quality of life, not justifiable by other causes [4].

OSA is a disease characterized by total or partial occlusion of the upper airway of patients during sleep. Because of this, breathing stops until a microarousal occurs that reactivates the muscles and reopens the airways. Apnea occurs when the elements that tend to close the airway cannot be compensated by the ability of the dilator muscles of the pharynx and/or respiratory centers to keep it open.

Due to these apneas, which produce hypoxia and sleep fragmentation, patients cannot sleep and rest properly and, during the day, they usually suffer from daytime sleepiness or tiredness [4].

In physiological terms, several symptoms of a depressed mood are the consequence of sleep apnea, and the impact of hypoxemia and hypoxia at the cellular level is considered a result of a neuro inflammatory process [5] (Fig. 23.1).

[1] American Psychiatric Association, DSM V Diagnostic Criteria Consultation Guide, Arlington, VA, American Psychiatric Association, 2013.

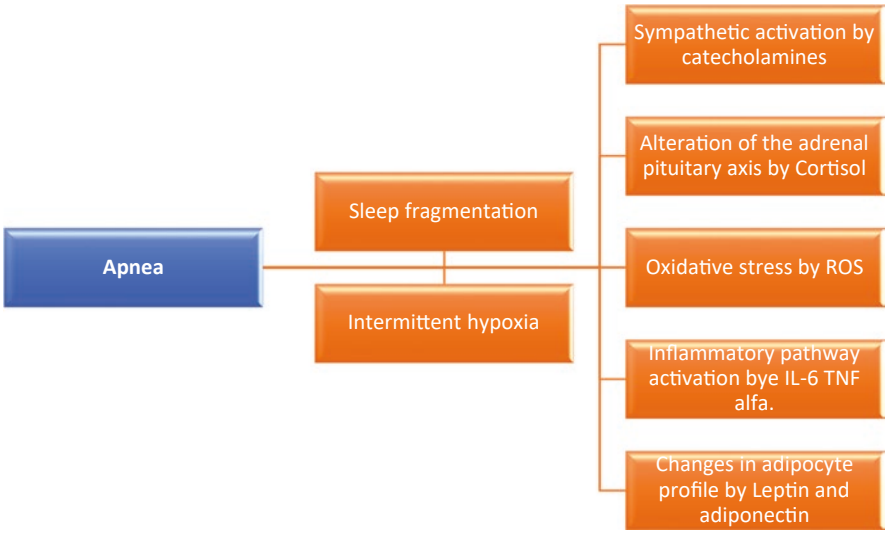

Fig. 23.1 Effects of apnea on cellular metabolism

23.3 Neuroinflammation Theory

Neuroinflammation is defined as the brain's response to injury, infection, or disease. In general, the purpose of inflammation is to remove or inactivate potentially harmful agents or damaged tissue. This response is mainly mediated through two cellular systems: the central nervous system glia and the hematopoietic system's lymphocytes, monocytes, and macrophages.

The results of studies suggest that patients with a major depressive disorder show changes in immunological markers, including an increase in proinflammatory cytokines activity [6].

In addition, chronic low-grade inflammation can lead to changes in brain structure and synaptic plasticity that led to neurodegeneration. Therefore, it should be added that neuronal repair due to increased glucocorticoid levels may be the initial markers of depression and a prelude to dementia in older people [7].

Significantly, chronic stress can exacerbate the release of proinflammatory cytokines and thus precipitate depressive episodes. It has been shown that stress, through its interaction with the immune system, can increase levels of proinflammatory cytokines such as **tumor necrosis factor TNF-α, interleukin IL-1β, IL-6, and IL-2R** [8, 9].

Inflammatory markers, such as IL-6, IL-1β, CRP, and TNF-α, are increased in inflammatory diseases and otherwise healthy people with MDD.

23.3.1 Relation Between Inflammatory Process and Depression

Cytokines make changes to the central nervous system through four pathways [10, 11]

1. Cytokines can activate primary afferent neurons.
2. Cytokines, released by macrophage-like cells in response to disease-causing agents, diffuse through the cerebral circumventricular organs.
3. Cytokine transporters saturate the blood–brain barrier.
4. Cytokine IL-1 activates receptors on perivascular macrophages and endothelial cells of brain venules and generates the local release of prostaglandin E2.

23.3.2 Analysis

After reviewing the contexts of global nomenclature of both medical conditions and the physiology of the inflammatory processes that occur in OSA, the correlation between the two can be appreciated, which must be included in every patient's clinical history. Both in people with depressive symptoms and respiratory alterations should be intentionally explored. In people with the already assigned diagnosis of OSA, the presence of depression or depressive symptoms should be explored since this causes depression that ends up being classified as resistant or poorly addressed. On the other hand, the results in the approaches to OSA will not be those expected by the health professional due to the omission of the condition of depression in the patient's medical history [12].

The most common symptoms shared by both medical conditions are shown in Table 23.1.

23.3.3 Conclusions

It is essential that the curricula of medical schools are updated and devote more hours/class, in sleep medicine, since the panorama reported by the WHO is worrying in the issue of the incidence and prevalence of depression in the last year, and if the problem continues to be addressed as before, the numbers will only continue to be exposed (Fig. 23.2).

Table 23.1 Most common symptoms shared by both medical conditions

Cognitive and emotional symptoms	Physical symptoms
Difficulty in the ability to acquire	Excessive daytime sleepiness
Decreased memory capacity	Hypersomnia
Decreased attention span	Fragmented sleep
Loss of interest in conducting activities	Alterations in appetite
Labile mood	Low libido
Apathy	Impotence

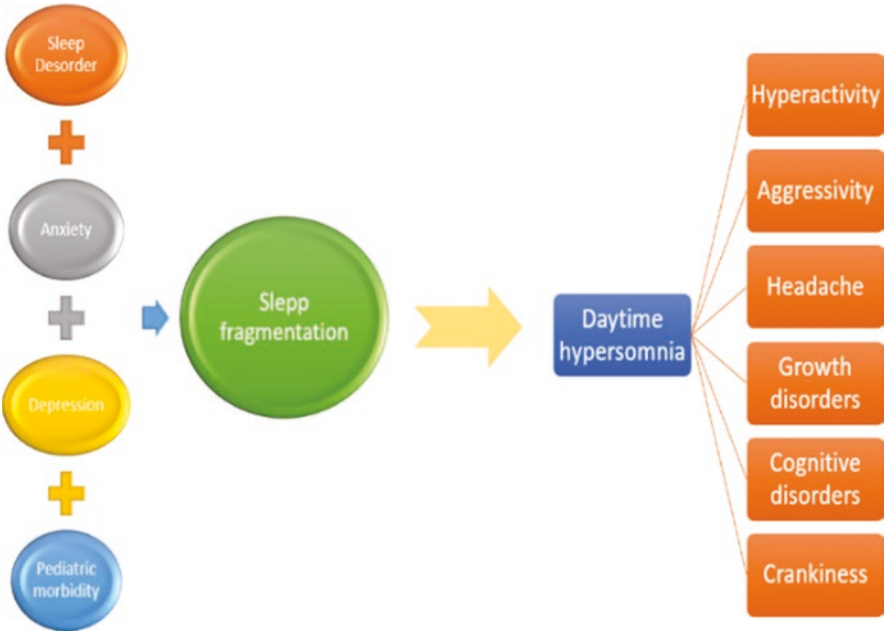

Fig. 23.2 Common consequences of fragmented sleep

Multidisciplinary work is needed in the treatment of major depressive disorder, a medical condition of multifactorial origin, ranging from the molecular, the genetic, the cellular, the systemic, including to the environment, and is not reduced only to "a neurochemical imbalance of certain substances in the brain".

It is key to prove solid foundations of physiology and understand the concept of general systems theory, taking it to clinical practice, to be able to see the real picture and not just a part of it.

Returning to the term "allostasis" would help a lot to understand that many conditions that we classify as "diseases" are simply the way in which the body, after being subjected to situations of stress, makes physiological changes to readapt and maintain its viability.

23.4 Insomnia

Most people are not adequately informed about what it is to sleep well and therefore do not know how to distinguish between sleeping well and poor sleeping or sleeping poorly and the consequences of not doing so.

Sleeping well is one of the healthiest and most fruitful habits, but unfortunately one of the least practiced and is treated as a "great luxury."

The WHO considers insomnia the difficulty in falling asleep or maintaining sleep; or the complaint feeling of nonrestorative sleep that generates a significant

discomfort or interference with social and work activities and occurs on at least three nights a week [1].

Excessive daytime sleepiness is a condition that makes the person feel very sleepy during the day and is considered a continuum of insomnia or sleep disturbances.

Without the presence of insomnia or any disorder that affects the quantity and quality of sleep, there is no presence of excessive daytime sleepiness [13].

According to the World Health Organization, lack of sleep represents one of the most common problems in people: 40% of the world's population has insomnia [1].

23.4.1 Statistical Impact

In the United States, according to the Sleep Foundation [14], with data updated to May 2022, between 10 and 30% of adults struggle with chronic insomnia. Women have a lifetime risk of insomnia that is up to 40% higher than men. As many as 15–30% of men and 10–30% of women meet a broad definition of obstructive sleep apnea. The second sleep disorder with the highest incidence and prevalence is obstructive sleep apnea. It has a prevalence of 10–30%, which together with insomnia represent 80% of the causes of poor sleep (Fig. 23.3).

The impact of insomnia on during the pandemic was that the incidence and prevalence rate increased more than any other mental health condition [15].

The body takes insomnia as an inflammatory process, which will have repercussions at the genetic, cellular, systemic, and environmental levels.

23.4.2 Aftermath of COVID-19

Insomnia is the most common sequelae of persistent COVID-19. U.S. researchers have found that moderate to severe sleep disturbances are prevalent among the post-acute sequelae of SARS-CoV-2 infection.

As per a team of researchers from the Cleveland Clinic (USA) who presented at the SLEEP 2022 meeting, almost 40% of people with persistent COVID-19 suffer from a sleep-related problems.

They analyzed data collected from 962 patients with long COVID-19 or persistent COVID-19 between February 2021 and April 2022. Patients recovered from COVID-19 and completed sleep disturbance and fatigue questionnaires.

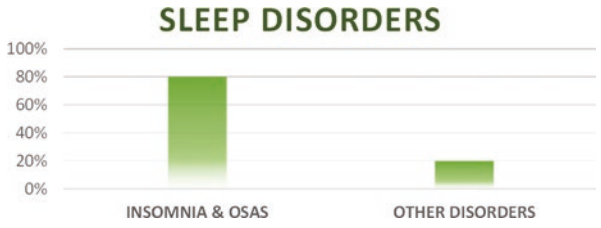

Fig. 23.3 Sleep disorders

Eight percent of patients reported severe sleep disturbances, while 41.3% reported moderate sleep disturbances [16].

23.4.3 Conclusions

Normalizing insomnia will make us contract a sleep debt that will not recover anymore and will result in conditions like cardiovascular and metabolic diseases, for examples, addictive behaviors, risk of certain cancer types, endocrine diseases, and be prone to occupational and traffic accidents.

23.5 Attention-Deficit Hyperactivity Disorder and Obstructive Sleep Apnea

According to the DSM V, attention-deficit hyperactivity disorder (ADHD) is a persistent or continuous pattern of inattention and/or hyperactivity and impulsivity that is maladaptive and incoherent concerning the child's level of development and can continue through adolescence and adulthood. It can be classified into three subtypes: inattentive predominance (20–30%), hyperactive-impulsive predominance (10–15%), and combined predominance (50–70%) [3].

The World Health Organization estimates that there is a prevalence of 5% worldwide.

ADHD is a public health problem that affects people's development and quality of life. It begins before the age of six, with an incidence of 5–7% in boys and a little less in girls; during adolescence, symptoms prevail, and in adulthood, it persists by up to 50% [17].

Both obesity and mental illness have increased among young people since the beginning of this century. Researchers have long observed a connection between obesity and ADHD, depression, and eating disorders, but it has rarely been studied [18].

One study involved 48 adolescents (73% girls) with an average age of 15 and an average BMI of 42, which is severe obesity. Half of the participants received medical treatment for obesity, while the other half underwent surgery.

Parents of the teens completed questionnaires to measure their children's ADHD symptoms. In addition, the teens themselves answered questions about binge eating and symptoms of depression.

Results showed that more than half of the parents estimated that their teenage children had difficulties resembling ADHD, even though only some had been previously diagnosed with these conditions [19].

23.5.1 Analysis, Theories, and Proposals

In several publications and articles, two aspects of ADHD are continuously discussed: on the one hand, if it is underdiagnosed, and on the other hand, if it is overdiagnosed.

And if it is misdiagnosed for not considering the variable presence of obesity and sleep apnea in the initial evaluation?

Not all is ADHD. The presence of some respiratory disorders that was never explored or the presence of some type of apnea or snoring may emulate a picture of ADHD in many situations (Table 23.2; Fig. 23.4).

A multidisciplinary approach is needed when we talk about diagnosing ADHD.

A misdiagnosis or a bad approach will decide the quality of life in the child, until adulthood.

Rather than discussing the underdiagnosis or overdiagnosis of ADHD, let's focus on updating health professionals and sharing our knowledge with evidence and numbers.

Sleep medicine is such a critical area and, at the same time, remains so unknown to many.

Table 23.2 Some ADHD symptoms

Emotional symptoms	Cognitive symptoms	Behavioral symptoms
Depressive mood	Inattention	Impulsiveness
Anxious mood	Deconcentration	Hyperactivity
Low frustration tolerance	Memory difficulties	Concern
Irritability	Difficulty measuring risks	Not finishing most activities
Emotional lability	Difficulty in planning	Risk of drug exposure

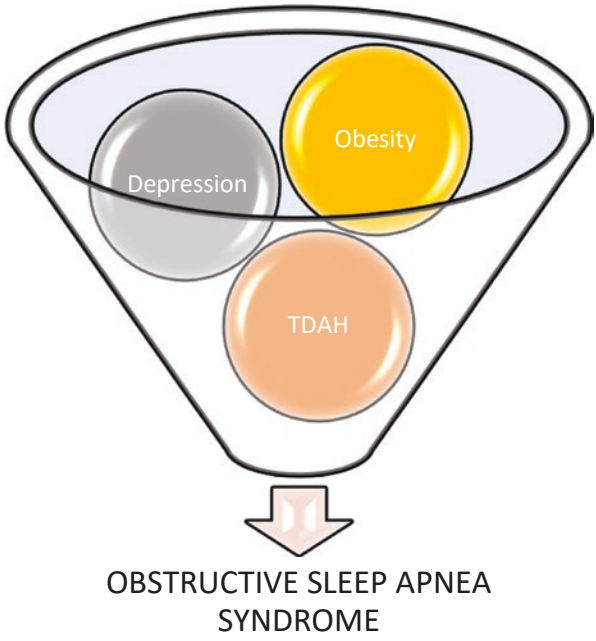

Fig. 23.4 Symptoms that occur in both ADHD and OSA

The only professional "interest" that there should be is to do our professional work as well as possible.

> What we know is a drop of water; what we ignore is the ocean.
> —ISAAC NEWTON

23.6 Eating Disorders in Obstructive Sleep Apnea

According to the WHO, eating disorders are severe mental health conditions. They involve serious problems about how the patient manages food and their eating behavior. They are considered a medical disease [1].

Globally, the number of cases of eating disorders has doubled in the last 18 years: Prevalence has doubled from 3.4% of the population to 7.8% between 2000 and 2018 [20].

Eating disorder prevalence ranges from 0.3 to 2.3% in teenage females and 0.3 to 1.3% in adolescent males. Eating disorders are associated with short-term and long-term adverse health outcomes, including physical, psychological, and social problems [21].

In particular, a type of disorder that is more associated with OSA is a binge-eating disorder with a nocturnal predominance and an eating behavior pattern that occurs in day-after-day pattern, more pronounced in the afternoon, eating small amounts of some food rich in carbohydrates and fats, intermittently.

23.6.1 How Common Is Binge-Eating Disorder?

Binge-eating disorder is the most common eating disorder in the United States [22].

Out of every 100 women, just over 3 will have binge-eating disorder at some point in their lives.

In men, 2% will have binge-eating disorder at some point in their lives [23].

Binge disorders occur in people of any weight; however, it is more frequent in obese or overweight patients [24], and there is a close correlation between OSA and eating disorders [25].

Poor sleep quality is associated with a decrease in leptin (an appetite-suppressing hormone) and an increase in ghrelin (an appetite-stimulating hormone), which can increase cravings for high-calorie foods (Fig. 23.5).

Studies show that lack of sleep directly affects how we eat.

This is mainly explained by a hormonal disturbance. Hunger and satiety are sensations regulated by ghrelin and leptin, respectively.

Ghrelin is responsible for hunger, and leptin tells our body that we have eaten enough [26].

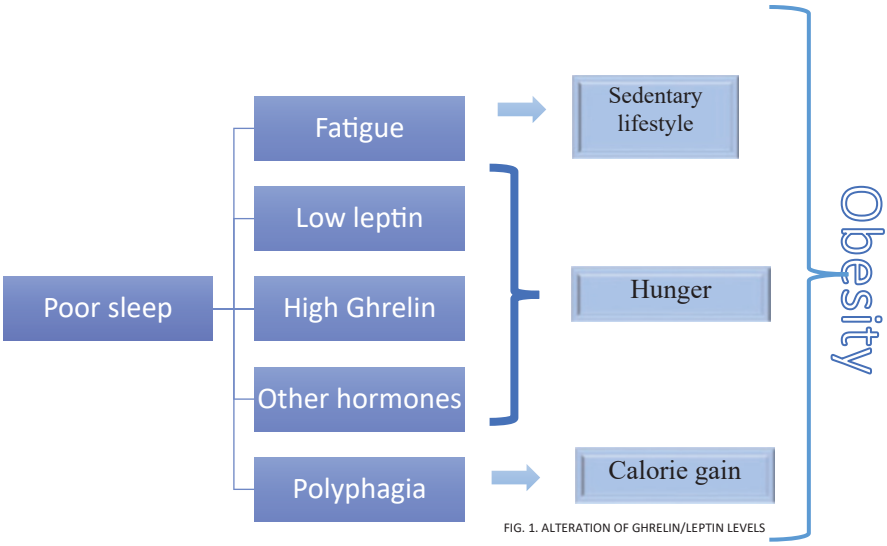

Fig. 23.5 Alteration of ghrelin/leptin levels

When we don't get enough sleep, the levels of these hormones are disturbed, and while ghrelin is produced in excess, leptin production doesn't reach the levels it should.

According to studies, 2 days of poor sleeping and without rest are enough to alter these hormones.

The consequences of this hormonal imbalance translate into a greater appetite and a considerable drop in energy [27].

23.7 Endocannabinoid System and Fat

Recent discoveries concerning cannabinoids have begun to shed light on these processes. Current knowledge indicates that the endocannabinoid system plays a vital role in the appetite and consummatory phases of food motivation, possibly mediating cravings and pleasure for the most desired meals that are generally highly calorically dense foods. In addition, endocannabinoid system appears to modulate central and peripheral components associated with fat and glucose metabolism [28, 29].

23.8 Relationship with High Cortisol Levels

Cortisol should not be high during the night, although prolonged stress can lead to high cortisol levels. Hyperactivity of the main stress response system (HPA axis) is associated with sleep disturbances, such as chronic insomnia. People with OSA have elevated cortisol levels at night and before bedtime.

Cortisol causes an increase in insulin, and this raise triggers an increase of appetite, mainly for consumption of sweets and starches. This favors the storage of fat, generating high levels of inflammatory substances in the liver.

On the other hand, the brain is also affected, because when trying to relieve stress with food, we activate the reward center; for example, eating ice cream or chips creates a sense of well-being, but once the effect has passed, we feel the need to consume more of those foods that, supposedly, relax us [30, 31].

23.9 Malfunction or Degeneration of the Orexinergic/Hypocretinergic System

The orexinergic system is composed of two different neuropeptide hormones, which are secreted in the hypothalamus, and neuron cells of the intestine, stomach, and pancreas. They participate in the modulation of multiple functions such as the regulation of the sleep–wake cycle, energy homeostasis, the regulation of temperature, neuroendocrine and autonomic regulation, regulation of muscle tone, and locomotion and have as main function of giving intestinal responses to the brain; therefore, they have an enormous influence on nutrition, intake, and appetite control. It has been called the brain–intestinal axis [32].

1. Orexin A or hypocretin 1
2. Orexin B or hypocretin 2

Generally speaking, any alteration that affects the hypothalamus in any way will result in loss of orexinergic/hypocretinergic neurons and, therefore, clinically in low or absent concentrations of orexin A/hypocretin 1 in CSF.

Orexins are essential in stabilizing the awake state and have been studied mainly concerning the increase in alertness and motivation by positive reinforcers. Thus, the orexinergic system participates in appetitive learnings in which an association occurs between a relevant stimulus and rewards such as food.

Orexin levels in an individual also depend on the demands of the environment, intrinsic or extrinsic, so it promotes appetite or aversive responses based on the body's previous experience. In this sense, orexin can intervene in the state of hypervigilance that underlies anxiety and stress states and that increases the salience of environmental stimuli. In these circumstances, the role of orexin would be to orchestrate the components of the stress response as an increase in activation, attention, and anxiety [33].

Take-Home Message

- Chronic undiagnosed sleep apnea in the presence of a specific mental illness can increase the severity of the condition.
- The most frequent conditions associated are depression, insomnia, attention deficit hyperactivity disorder (ADHD), and eating disorders.
- Poor pharmacological treatment worsens both medical conditions (mental illness and OSA).

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Psychologic Disturbances

24

Guadalupe Jovanna Teran, Débora Yoaly Arana Lechuga, and Javier Velázquez Moctezuma

24.1 Introduction

Obstructive sleep apnea (OSA) is a common disorder that, has been increasing significantly in recent years due to its relationship with overweight. It is estimated that between 4 and 10% of the population suffers from OSA, representing a major public health problem [1].

Intermittent episodes of upper airway obstruction characterize OSA during sleep. These episodes can be partial, known as sleep hypopnea or total, sleep apnea. Both sleep apneas and hypopneas are associated with oxygen desaturations (intermittent hypoxia), changes in heart rate, microarousals, sleep fragmentation, an increase in light sleep, and a decrease of both slow-wave sleep and REM sleep. As a consequence, the quality of sleep is severely damaged in these patients [2].

One of the most effective treatments for the control of OSA is the use of Continues Positive Airway Pressure (CPAP) during sleep to prevent the collapse of the upper airway and the resulting pathogenic events (desaturations, microarousals, changes in heart rate, etc.) [3].

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The most frequent nocturnal features observed in these patients are snoring, waking up with suffocation, oral dryness, sweating, sudden movements, and nocturia. On the other hand, the daytime symptoms most commonly associated with OSA are daytime sleepiness, irritability, headache, fatigue, neurocognitive impairment [4], impaired sexual function, increased risk of accidents, and psychiatric disorders, mainly impaired mood and anxiety [5]. This chapter will focus specifically on cognitive decline and mood disorders.

24.2 Cognition

Sleep is a fundamental biological process for our physical and mental restoration, but it is also related to different higher cognitive processes that are decisive in our daytime functioning [6].

For several decades, sleep has been proven essential for cognitive processes such as the consolidation of learning and memory, problem-solving, decision-making, language processing, and creativity. Sleeping well is necessary to guarantee an optimal cognitive state [7]. Figure 24.1 shows a scheme of the cognitive processes.

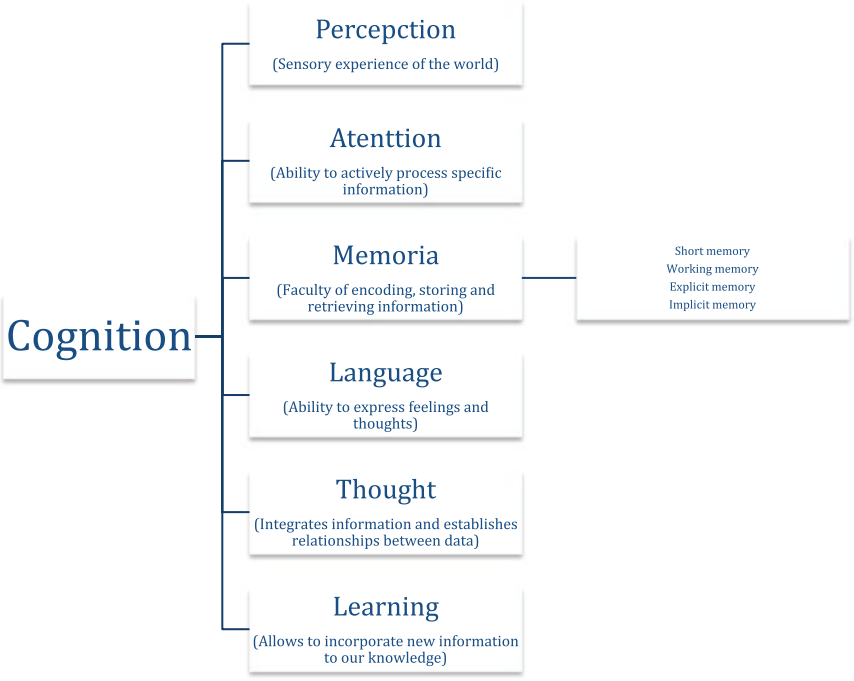

Fig. 24.1 Scheme that describes the processes that make up cognition

However, sleep restriction, either by a decision to prioritize other activities before sleeping or illness or disorders that alter the quantity or quality of sleep, harms several aspects of the patient's life, including cognitive functions.

The memory process is not an isolated function that helps us with work or academic issues. Memory is an unbreakable process that defines us and describes what we are. Memory storage contains our life and memorable matters, including several motor skills. All the knowledge we acquire and can be recalled is linked to memory.

But how are these processes carried out?

While we sleep, the information acquired throughout the daytime experiences, is reorganized, and stored. Sleep facilitates memory consolidation; current information is integrated with existing data in long-term memory, updating pre-existing data networks [8]. Furthermore, the sleep process prepares our brain acquire new knowledge.

While we sleep, we consolidate diverse types of memories. Declarative memory refers to episodes and facts. The nondeclarative memory is related to conditioning and motor skills, but it also allows us to reanalyze and restructure the content of the stored information. In particular, the information consolidated, with special significance or relevance for us [9]. The most studied mechanisms of this phenomenon are the connections of the hippocampus with the neocortex and the thalamocortical connections [10].

24.3 Cognition and OSA

And how are these cerebral mechanisms affected by OSA? As we mentioned before, memory defines us. We are essentially what we can recall of ourselves. The memories we can store and recall related to our daily lives depend on our cognitive processes. Our decisions, our interaction with the world, how we solve problems, and our ability to respond to any situation, depend mainly on sleep quality. Therefore, patients with OSA have sleep restriction induced by sleep fragmentation secondary to respiratory events, including intermittent nocturnal hypoxia.

According to neuroimaging studies, the prefrontal cortex is the most susceptible cerebral region affected by sleep restriction. This characteristic would explain the deterioration in attention tasks and working memory observed in sleep-restricted subjects. However, there are different theories about the part of cognition that has been affected. Diverse determining factors, such as emotional content and networks, the level of alertness and attention, and the general cognitive state can be involved [11].

One of the most notorious effects of sleep restriction is the increased response time in simple attention tasks. In addition, this cumulative effect contradicts the idea that some people have about their ability to sleep just a few hours at night and be completely restored. This effect on attention has been described widely in psychomotor vigilance tasks. As sleep restriction increases, the response time increases, and microsleep periods or lapses without response appear [12].

Nevertheless, studies on cognition and OSA have yielded controversial results. Several factors must be considered: the severity of OSA, the time of evolution, age, the cognitive status of the people evaluated, and the type of task. However, there is a negative impact on cognition, at least in attention processes and response time to different tasks. These effects could be mediated by sleep fragmentation and nocturnal hypoxia, which alters gas exchange, resulting in chemical and structural cellular lesions in areas associated with cognitive functioning. One of the cerebral structures involved is the prefrontal cortex, which, as described above, integrates cognitive processes [13].

On the other hand, the daytime sleepiness that most OSA patients present is also responsible for attention disturbances and the ability to solve different tasks that require optimal alertness and vigilance.

In electrophysiological studies of OSA patients, an effect has been reported in the levels of attention and executive functions compared to the control group. Patients with OSA respond more slowly and have significantly more errors. This was assessed in tasks such as visuospatial n-back tests, which evaluate working memory with different difficulty levels, and the complete mirror-drawing and Trail-Making tests. These tests were performed in addition to the electroencephalographic record and the P300 test to objectively determine the response in each task. The results suggest that patients with OSA can respond adequately to explicit memory and simple working memory tasks [14].

24.4 Imaging Studies and Cognitive Tasks

But how does this deterioration occur? Which cerebral areas are involved? Canessa et al. studied the morphological correlation of these effects. OSA patients were assessed through neuroimaging studies. Subjects aged 30–55, displaying an abnormally high apnea/hypopnea index (AHI), were studied before and after treatment. They found a decrease in gray matter in areas such as the hippocampus (ento-rhinal cortex), left region of the prefrontal cortex, and right superior frontal gyrus. After 3 months of treatment with positive airway pressure (CPAP) equipment, they significantly improved attention, memory tasks, and executive functions. These changes correlated with increased gray matter volume in the hippocampus and frontal structures. These results could be explained due to the susceptibility of the hippocampus to intermittent nocturnal hypoxia and hypercapnia. However, it must also consider a high plasticity structure that could help recovery after a short treatment period [15]. Remember that the hippocampus is one of the cerebral regions strongly linked to cognitive processes and responsible for memory processes. The hippocampus also has an essential connection with cortical structures, such as the prefrontal and parietal cortex, which are also susceptible to sleep restriction and episodes of hypoxia [16].

Another neuroimaging study in recently diagnosed OSA patients without treatment included subjects aged 18 and 65 years and an AHI >10. The participants performed the tasks of autobiographical memory (AM) recollection task and a

n-back (2-back) working memory (WM) task to evaluate memory work and explicit memory. The authors found a slight impairment in autobiographical memory in OSA patients compared to the control group. Regarding working memory, differences were only observed in the more complex N-back task (3-back). However, there is a greater activation of connections in patients with OSA in the more straightforward tasks. However, this effect was decreased in younger people. Regarding hypoxia, a correlation is observed with greater activation of the occipital cortex and the cerebellum during working memory tasks. According to the authors, this effect may reflect a compensatory mechanism, increasing attention control to maintain performance during the cognitive challenge [17].

Moreover, in OSA patients, magnetic resonance spectroscopy studies consistently showed reduced density and decreased metabolism in the hippocampus, white matter, and parieto-occipital cortex [18].

Diffusion Tensor Imaging (DTI) studies were performed on another group of patients who were recently diagnosed OSA and without treatment, presenting moderate to severe AHI. The study aimed to determine the integrity of normal brain tissue through fractional anisotropy. The group included 41 patients, with a mean age of 46.3 years. The results showed that white matter is highly affected in OSA patients. Specifically in axons that link the major structures of the limbic system, the pons, frontal, temporal, and parietal cortices, and projections to and from the cerebellum. The authors suggest that this is probably a consequence of intermittent nocturnal hypoxia, oxidative stress, chronic inflammation, and local ischemia [19].

Torelli et al. described that some changes in patients with OSA depend on age, such as the total volume of the hippocampus, the amygdala, and the brain parenchyma fraction (BPF). Thus, the older the patient, the more structural damage is observed. These changes were not detected in control subjects, which leads us to reconsider the importance of early diagnosis [20].

To conclude, patients with OSA have impaired performance, specifically in attention tasks. However, this is not observed in all patients. In some cases, impairment has even been shown in verbal and visuospatial tasks, and some authors suggest even deterioration in the explicit memory processes.

Thus, the consequences of OSA are complex. For instance, it is difficult to determine the disorder's evolutive time because some patients unaware that they suffer from it, until many years later when the disease is already serious. On the other hand, young adults are less vulnerable to structural damage in brain areas associated with cognitive functions [17].

Another essential variable is the comorbidity suffered by OSA patients with chronic diseases such as hypertension, cardiovascular events, neurological and metabolic disorders, and even with a higher risk of mental disorders such as anxiety and depression. In addition to these conditions, obesity has been studied as a predictor of executive impairment. Hilsendager et al. (2015) refer that obese patients are more vulnerable to cognitive impairment, mainly in executive functions [21]. Review Fig. 24.2 to identify the structures affected by obstructive sleep apnea.

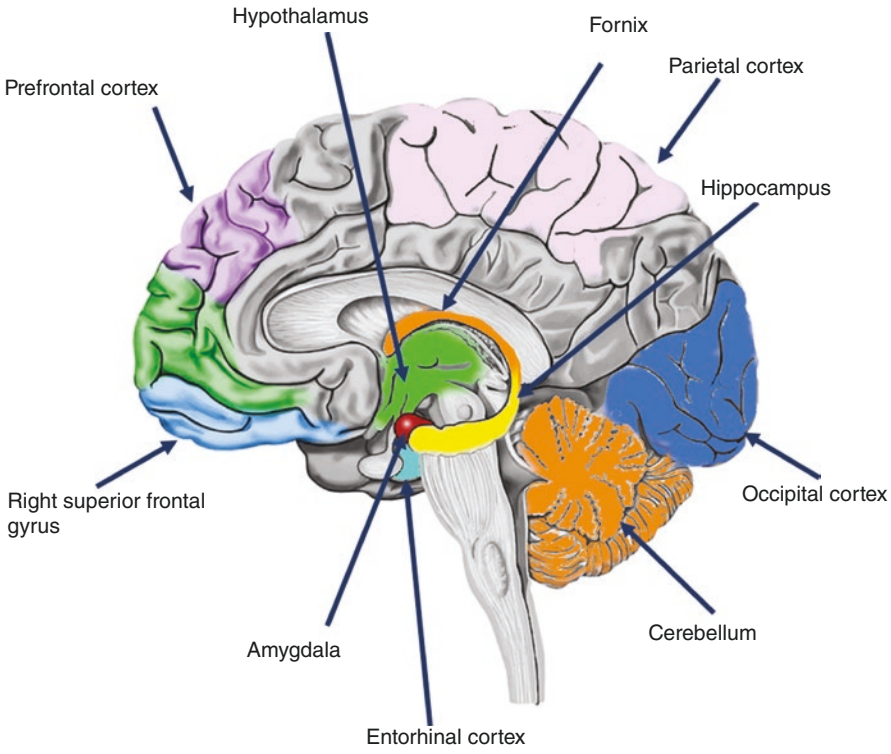

Fig. 24.2 Brain image of the studied structures in patients with obstructive sleep apnea

24.5 Cognitive Decline and Dementia

The main objective of determining these relationships is to prevent serious neurodegenerative diseases. For this reason, different studies try to predict what OSA component plays a significant role in diseases such as Alzheimer's dementia and mild cognitive impairment, among others.

Yaffe et al. (2011) suggest that approximately 50% of patients with OSA could have some memory altered. The authors studied a sample of women with OSA, without treatment, with a mean age of 82 years, and compared it with those without sleep disorders. This study assesses the risk of developing cognitive impairment and/or dementia over a 5-year follow-up period. This risk significantly correlates with increased oxygen desaturations and the percentage of time spent with apnea/hypopnea episodes. In this study, sleep onset and continuity parameters were also analyzed to determine the effect of sleep fragmentation. However, no impact was detected. The tests they analyzed included: Trails

B, the Modified Mini-Mental State Examination (3MS), a 100- point extended version of the MMSE with superior accuracy for dementia screening. The California Verbal Learning Test (CVLT) (Second Edition Short Form), Digit Span (from the Wechsler Adult Intelligence Scale-Revised), and category and verbal fluency tests [22].

Osorio et al. studied an original cohort of 2470 patients diagnosed with mild cognitive impairment, Alzheimer's disease, or normal cognition. Aged between 55–90 years. Those patients who presented with other sleep disorders or les with missing data were discarded. The statistical analysis found that patients diagnosed with OSA showed an early diagnosis of mild cognitive impairment. In these patients, using CPAP treatment delayed the onset of symptoms. OSA patients were also correlated with early diagnosis of Alzheimer's disease [23].

Longitudinal studies of patients receiving treatment show that the decrease in daytime sleepiness would be a factor that positively impacts cognitive functioning; that is, patients with controlled diurnal sleepiness have better performance in memory and attention tests [24].

This effect is seen even in older adults with a diagnosis of mild cognitive impairment and dementia; when they start treatment promptly, they delay the disease's development and generally perform better in memory tasks. In these patients, using CPAP improves sleep parameters and, consequently, cognitive function [25].

Regarding Alzheimer's, attempts have been made to identify biological markers correlating the risk of developing the disease with intermittent hypoxia, hypercapnia, or other factors. However, the studies in this regard are not conclusive. Specifically, B-amyloid and TAU protein deposits have been sought, associated with these neurodegenerative diseases. The results are contradictory, although there is a clear tendency to present these biomarkers in patients with OSA. These differences may be due to the type of tests performed and other associated factors, such as comorbidities, total sleep time, and genetic factors [24].

On the other hand, there is a clear relationship between sleep restriction and the risk of developing these diseases. Acute sleep deprivation increases TAU levels in human cerebrospinal u id (CSF), and chronic sleep deprivation accelerates the spread of tau protein aggregates in neural networks. Finally, recent evidence suggests that the accumulation of tau aggregates in the brain correlates with decreased slow-wave activity in nonrapid eye movement (NREM) sleep. Thus, a bidirectional effect is generated. Sleep deprivation contributes to protein accumulation, affecting sleep patterns [26].

In general, it isn't easy to establish a direct relationship. The elderly patient suffers from adverse circumstances that put him at risk of developing dementia or mild cognitive impairment. These circumstances include the use of drugs, the risk of cardiovascular disease, chronic diseases, insomnia, decreased activity, sedentary lifestyle, change in diet, and the risk of psychiatric disorders. However, if timely interventions are conducted, effective treatments and behavioral measures to improve lifestyle and sleep patterns will improve patients' health and quality of life at any stage of development.

24.6 OSA and Psychiatric Disorders

There is a high prevalence of psychiatric disorders together with the presence of OSA [27]. Alterations in mood, mainly depression, are the most frequent and, therefore, the most studied correlation [28].

Sharafkhaneh et al. studied a cohort of more than four million veterans with and without psychiatric disorders. He observed that 118,105 of the volunteers, suffered from OSA, representing 2.9% of the population. 21.8% suffered from depression, 16.7% from anxiety, 11.9% from posttraumatic stress disorder, 3.3% from bipolar disorder, and 5.1% from psychosis. Compared to veterans without OSA, this prevalence was significantly higher for each condition [29].

Another study on veterans found this prevalence even higher, describing that 6.5% of the population with some psychiatric disorder, also displayed OSA symptoms [30].

More recently, Babson determined the relationship between the presence of OSA and the diagnosis of a psychiatric disorder in obese veterans. Using a generalized linear mixed model, the authors concluded that veterans with OSA are more likely to receive a mood or anxiety disorder diagnosis. The most frequent diagnoses: major depression (MD) and posttraumatic stress disorder (PTSD). Furthermore, this relationship was maintained after controlling the overweight [31].

According to other reports, in the general population (nonveterans), MD is accompanied by OSA in up to 18% of cases, while MD accompanies OSA in up to 17.6% [32].

Given this high prevalence, common mechanisms (both neurobiological and psychosocial) have been studied and proposed including the a causal relationship [27].

Finally, this exact prevalence shows the need for a targeted evaluation to rule out and, if necessary, treat OSA to avoid or prevent psychiatric manifestations in these patients.

As mentioned above, one of the most frequent psychiatric disorders in patients with OSA is depression. Multiple studies have shown the relationship between these two entities. Macey et al. (2010) described that 25% of newly diagnosed OSA patients had required psychiatric care for depression before their OSA diagnosis [33]. Another group of researchers described that 50% of patients with OSA had experienced symptoms of depression. These same researchers concluded that patients with Major Depression (MD) have a fivefold higher risk of suffering from OSA than the general population [34].

The mechanisms by which there is a higher prevalence of depression in patients with OSA are not entirely clear. Some authors suggest participating in neurobiological mechanisms, while many others consider psychosocial components the leading cause.

One possible neurobiological mechanism by which OSA contributes to developing or exacerbating depression is intermittent hypoxia (IH). This symptom is experienced by patients with OSA and is associated with respiratory pauses. IH is characterized by cycles of hypoxemia, followed by re-oxygenation. It expresses

itself with symptoms different from the sustained hypoxemia seen in other illnesses, such as pulmonary disorders or sudden changes in altitude.

IH associated with OSA elicits oxidative stress by increasing the production of reactive oxygen species. Thus, it promotes angiogenesis, generates sympathetic activation, increases blood pressure, and contributes to systemic and vascular inflammation. These factors have been linked to endothelial dysfunction [35].

Therefore, IH-inducing neuroinflammation, endothelial dysfunction, and hypoperfusion could be determining in generating depression, mainly vascular depression [36]. This term refers to cases of depression where a neurovascular origin is suggested.

With all this, there is growing evidence how IH contributes to cardiovascular, metabolic, cognitive dysfunction, cancer risk, and altered mood [37].

Additionally, previous reports have pointed to obesity as a factor associated with the development of depression occurring in adults, adolescents, and children [38, 39]. However, given that obesity is one of the most critical risk factors for developing OSA, it is necessary to consider it as a mechanism involved in depression in these patients [40].

Moreover, a group of researchers described that, in patients with depression, OSA, and obesity, the OSA factor contributed more than obesity to the severity of depression. This study was done in a cohort of 95 patients with recently diagnosed moderate and severe OSA (without treatment). The authors applied to each participant the Beck Depression Inventory second edition (BDI-II), the Epworth sleepiness scale, the severity of OSA, and the Body Mass Index (BMI). In addition, they showed that apnea severity correlated significantly with BMI and depression scale but not with sleepiness levels [41].

Regardless of these findings, it is essential to note that obese patients present with chronic low-grade inflammation. Thus, it is associated with increased proinflammatory interleukins, such as IL1B, IL-6, tumor necrosis factor α [42], and dyslipidemia. Both disturbances (chronic low-grade inflammation and dyslipidemia) have been associated with vascular dysfunction. Therefore, obesity could generate depression by mechanisms similar to intermittent hypoxia [43].

Furthermore, the psychosocial mechanisms that contribute to depression in patients with OSA have also been studied. Cognitive impairment in OSA patients, excessive daytime sleepiness, and the risk of accidents have been proposed. Therefore, having a negative impact on mental health [44].

Sforza et al. (2002), studied the levels of depression, anxiety, maintenance of wakefulness, and excessive daytime sleepiness in 66 patients with sleep-disordered breathing (16 primary snoring and 44 with OSA). The authors described that the daytime sleepiness score explained 17% of the variation in depression levels. The report also indicates that higher depression scores are correlated with impaired alertness. Therefore, they concluded that the somnolence experienced by OSA patients could play a role in depression [45].

It is essential to underline that patients with depression and OSA without treatment have a lower response to antidepressant drugs, higher severity rates of depression and a higher risk of suicide. Some studies have found that the severity,

refractoriness, and suicidal thoughts are reduced once the respiratory problem is controlled during sleep. In addition, these patients' quality of life improves [46]. Means et al. (2003) showed that in 51 patients with OSA and depression, treatment with CPAP for 3 months improved symptoms of depression using the Beck scale [47]. However, other studies have not found this effect, mainly in short-term CPAP treatments (2–3 weeks) [48].

A study conducted on 224 elderly patients (70 years or older) with severe OSA showed that CPAP improved symptoms of both depression and anxiety in this group. These authors also found a higher prevalence of psychiatric disorders than previous studies. Approximately 23.2% of the sample had depression and 17% anxiety. Furthermore, more than 25% used an antidepressant drug [49].

Unfortunately, it has also been described that patients with OSA and depression have less adherence to CPAP. Therefore, it is necessary to consider these factors to develop strategies to improve adherence to CPAP and thus, offer a comprehensive and efficient treatment [50].

Concerning antidepressant drugs, the most common treatments include monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants. The latter, in overdose, can alter cardiovascular function, so it is essential to consider it in patients with OSA without treatment [51]. Additionally, overdoses of SSRIs such as venlafaxine, fluoxetine, paroxetine, and citalopram, among others, have been reported to cause drowsiness and hypotension [52]. Therefore, OSA should also be ruled out and, if necessary, treated before starting antidepressant drugs.

24.7 OSA and Anxiety

Fewer studies correlate anxiety disorders and the presence of OSA. However, a high prevalence of OSA has also been described in patients with anxiety disorders. One study showed that developing OSA in patients with anxiety was significantly higher than in patients without it (2.5% vs. 1.1%) [53].

Another study indicates that 16.7% of military veterans with OSA also have an anxiety disorder [29]. Furthermore, in patients with PTSD and panic disorder, the presence of OSA has been associated with increased nocturnal panic attacks and more severe symptoms of the psychiatric disorder compared with patients with these same psychiatric disorders but without OSA [54].

On the other hand, greater refractoriness to treatment has been described for PTSD that have OSA. In this sense, CPAP treatment in OSA patients with anxiety disorders decreases the severity of anxiety and panic attacks in patients with PTSD [55].

Unfortunately, patients with PTSD also show lower adherence to CPAP treatment than the general population. It has been reported that more than 50% of veterans with PTSD did not display good adherence to CPAP, unlike veterans without PTSD. This data suggests that anxiety disorders and OSA interfere with treatment success [56].

Take-Home Message

- In conclusion, there is a high prevalence of OSA in patients with psychiatric disorders. Therefore, making a timely diagnosis and offering adequate treatment for the respiratory disorder is essential in this population. OSA, without treatment, reduces adherence and response to treatment and is associated with greater severity of psychiatric symptoms and increased relapses. Therefore, identifying and treating OSA in these populations could de ne the course of the disease [33].
- Patients with both psychiatric disorders and OSA report poor quality of life. The source of this impairment could be that it impacts cognitive functions, performance, concentration, mood, and many other areas. However, when both illnesses are present in the same patient, a significant effect on their quality and life expectancy is commonly observed.
- Considering the high prevalence of OSA in patients with psychiatric disorders, we believe it is essential to rule out the presence of symptoms associated with respiratory conditions. This is of primary importance in those patients who are refractory to treatment, with residual symptoms, overweight, or elderly [57].
- In elderly patients with depression, diagnosing OSA should be implemented as part of the standard protocol. Frequently, antidepressant drugs do not control symptoms of depression associated with OSA in this group of patients [58].
- Particular attention should be taken to pharmacological treatment for different psychiatric disorders in the choice of drugs. Some of the most common treatments, including benzodiazepines, opioids, clozapine, and clopixol, are contraindicated in patients with OSA without treatment since these drugs have been associated with respiratory failure. In addition, these drugs can exacerbate OSA manifestations due to their muscle relaxant effect.
- Additionally, it must be considered that some antidepressant drugs can exacerbate symptoms associated with OSA, such as drowsiness. Therefore, before starting pharmacological treatment, these factors must be reviewed.
- Finally, it must be considered that treatment success in patients with psychiatric disorders largely depends on controlling respiratory disorders. Therefore, implementing strategies to improve adherence to CPAP use is essential. Offering therapeutic support to corroborate the use of the equipment and ruling out residual apneas will be essential for the success of any treatment.

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Endocrinology

25

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25.1 Obesity

The relationship between obesity and OSA is well-known and has been the subject of multiple studies for years. Obesity is one of the main components contributing to OSA. The incidence of OSA in obese patients is significantly higher than in the general population. Thus, OSA is present in 40% of patients with obesity, and 70% of patients with OSA are obese [1]. In addition, a 10% weight gain is associated with a sixfold increase in the risk of development of sleep apnea [2].

Obesity is a complex disease associated with a large number of comorbidities. About 13% of the world's adult population were obese in 2016, and the worldwide prevalence of obesity nearly tripled between 1975 and 2016 [3]. As the prevalence of obesity has increased, so have the many associated comorbidities, including OSA.

Obesity is defined as an excessive increase in body fat. There is also an excess of body fat in overweight, although less than in obesity. Even though the defining characteristic of the disease is excess body fat, the clinical diagnosis of overweight and obesity is usually made with the body mass index (BMI). As defined by the

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World Health Organization BMI is the patient's weight in kilograms divided by the square of his height in meters (kg/m^2). Overweight is defined by a BMI greater than or equal to 25 kg/m^2, and obesity is diagnosed with a BMI greater than or equal to 30 kg/m^2 (see Table 25.1) [4]. It is a simple formula, easy to obtain only by knowing the weight and height of a subject. Still, does not entirely fit the definition of obesity since an individual's excess weight is not always due to fat mass. For example, a subject with a lot of muscle mass may have excess weight but not necessarily fat mass. Thus, the estimation of the absolute amount of fat—adiposity—that a patient has can be done with the so-called body composition methods, of which there are several types. The most common body composition assessments are Bioelectrical Impedance Analysis (BIA), Skinfold Test, Air Displacement Plethysmography (BodPod®), and DEXA Scan. Using these methods, we can obtain the percentage of body fat concerning the total weight of a specific individual. For example, a man is considered overweight with a body fat percentage between 20 and 24.9% and obese when it is equal to or greater than 25%. In women, these fat percentages to define overweight and obesity are 30–34.9% and ≥35%, respectively, because women have a higher fat percentage than men. In this way, using air displacement plethysmography, it has been described that up to 30% of women with normal BMI have a percentage of body fat compatible with obesity. In men, this n ding occurs in 25% of subjects with normal weight [5].

But not only is adiposity essential in the development of obesity comorbidities. The distribution of body fat also plays an important role. The central deposition of fat (android, perivisceral; characteristic of males), as opposed to the gluteal-femoral (gynoid, subcutaneous; characteristic of females), is associated with a higher risk of comorbidities, mainly cardiometabolic. Differences have been found between both forms of fat storage concerning the size and number of adipocytes, their innervations, vascularization, and their metabolic and secretory activity (adipokines), which may explain their different cardiometabolic risk profile [6]. There are various methods and indices to assess the type of fat deposit in an individual. The most used are the waist circumference, waist/height ratio, the waist to hip ratio, or the measurement of abdominal fat using radiological methods such as computed tomography scan (CT scan) or magnetic resonance imaging (MRI).

Table 25.1 WHO classification of weight status

Weight status	Body mass index (BMI, kg/m^2)
Underweight	<18.5
Normal range	18.5–24.9
Overweight	25.0–29.9
Obese	≥30
Obese class I	30–34.9
Obese class II	35–39.9
Obese class III	≥40

BMI = weight (kg)/height^2 (m^2)

25.1.1 Obesity and the Pathophysiology of OSA

The pathophysiology of OSA is complex and involves several factors, such as airway anatomy or neuromuscular function (Fig. 25.1). Obesity occupies a very relevant place in the pathophysiology of OSA due to several factors. Firstly, a pharyngeal fat deposit would cause a decrease in the luminal diameter, facilitating the collapse of the airway during sleep. In addition, the pharyngeal cross-sectional area may be smaller because of reduced functional residual capacity (lower lung volume), a common fin ding in patients with obesity and a large abdomen [7]. Thus, OSA has been related to neck circumference since it is a marker of adiposity in that area [8, 9], waist circumference, and other indices of central obesity [10]. Another relevant factor is decreased upper airway muscle protective strength or altered muscle structure secondary to fatty infiltration [11]. In short, obesity is related to greater upper airway collapsibility that predisposes to OSA, which improves significantly with weight loss [7].

Adipokines or adipocytokines are peptides and proteins secreted mainly by adipocytes and play diverse roles in body homeostasis. Adipose tissue has emerged as a metabolically active tissue implicated in many processes, such as metabolism, inflammation, and cardiovascular diseases. Current evidence suggests that adipokines (leptin, adiponectin, chemerin, etc.) may play a role in the complex relationship between OSA and metabolic disorders [12].

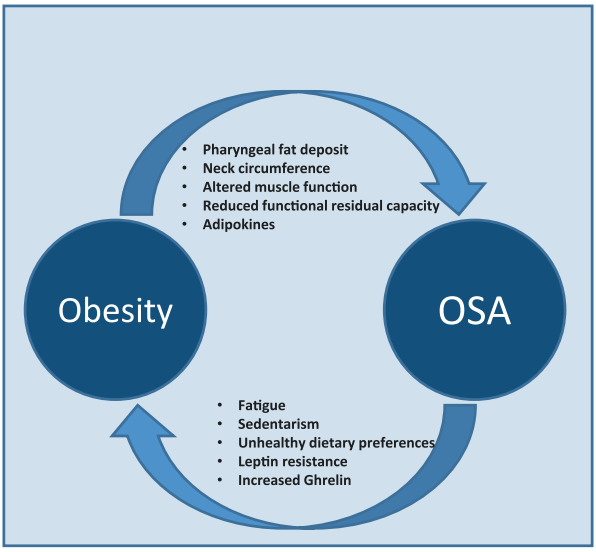

Fig. 25.1 Pathophysiology interaction between obesity and OSA

25.1.2 OSA and Weight Gain

OSA is one of the most common sleep disturbances that can severely compromise sleep quality in affected individuals. There is evidence that insufficient sleep may promote metabolic, hormonal, and behavioral changes that lead to weight gain [13], which could help perpetuate the vicious circle of obesity-OSA.

Daytime fatigue and sleepiness secondary to inadequate sleep quality contributes to asthenia, sedentary lifestyle, and less physical exercise, which causes a decrease in energy expenditure and facilitates weight gain. In addition, an inverse relationship exists between physical activity levels and OSA severity [14].

OSA severity is associated with unhealthy dietary preferences contributing to obesity and greater cardiometabolic risk [14].

Several peptides and hormones play a role in the complex appetite/satiety regulating system. Leptin is a significant adipokine secreted mainly by the adipocytes of the white adipose tissue and is positively correlated with fat mass. It has a fundamental role in regulating energy balance by reducing energy intake (anorexigenic effect) and increasing energy expenditure. Leptin acts at the hypothalamus, decreasing appetite, and is elevated in obese patients (hyperleptinemia) due to excess fat mass. However, leptin resistance has been described in these individuals, which, despite presenting high levels of it, appetite does not decrease [15].

An increasing amount of evidence suggests that long-term exposure to chronic intermittent hypoxia, as occurs in OSA, may contribute to leptin resistance, negatively affecting food intake control [16]. In some studies, CPAP treatment decreased leptin, but this effect was not observed in others [17].

Ghrelin is a peptide secreted from the oxyntic glands in the gastric fundus. Among other actions, ghrelin stimulates the appetite (orexigenic effect), and thus its plasma levels increase during fasting and decrease during the postprandial period. There is some evidence for an increase in the level of ghrelin in patients with OSA, which could be related to intermittent hypoxia and sleep fragmentation. In some studies, CPAP treatment contributed to decreased ghrelin, but others did not observe this effect [17].

OSA increases the resting metabolic rate, the main component of energy expenditure. This finding is paradoxical since this phenomenon should favor weight loss or maintenance. It has been suggested that the impact on the energy balance produced by the increase in resting metabolic rate would be counteracted by a surge in caloric intake [18].

25.1.3 OSA and Weight Loss

Obesity treatment focuses on achieving a healthy diet and physical activity habits that promotes weight loss. On this basis, pharmacological or surgical treatments can be added. As a matter of fact, due to their close association, one of the main goals of patients with OSA and obesity is weight loss, for it can reduce fatty deposits in the

neck and tongue [19] as well as abdominal fat [20], improving airflow during sleep. Lifestyle-induced weight loss studies in patients with OSA have demonstrated that at least 5–10% loss of the initial body weight can improve the severity of the syndrome [21], even in patients with moderate or severe OSA [22]. Obese patients should be encouraged to lose weight to improve OSA, and counseling regarding diet modification and exercise with a weight management team (dietitian, endocrinologist, psychologist, etc.) may be beneficial [23].

In recent years, the pharmacological treatment of obesity has experienced significant progress thanks to the inclusion of glucagon-like peptide-1 (GLP-1) receptor agonists. The Sleep Apnea Scale study demonstrated a reduction in weight (−5.7% of initial weight) and improvement in the apnea–hypopnea index (AHI) (−12 events h^{-1}) with Liraglutide [24]. The most novel Semaglutide improves Liraglutide results in weight loss, so a more significant effect for improving AHI occurs, although this aspect is currently under study [25]. Pharmacological treatment of obesity is indicated in patients with any degree of obesity and even in those with overweight and associated comorbidities.

Bariatric surgery has developed remarkably in the last two decades as an effective and safe intervention for obesity management. For instance, on average, it can generate more weight loss in obese patients (≈30% of initial weight) compared to conservative treatment. Although many surgical techniques have been implemented, the two most used today are the sleeve gastrectomy and Roux-en-Y gastric bypass. OSA is a common comorbidity in bariatric patients, with an estimated incidence of 35–96%. A recent meta-analysis confirmed a significant decrease in AHI after bariatric surgery (−25.1 h^{-1}) [26]. In addition, the patients who improved their weight after the intervention and those who previously presented a greater severity of OSA experienced a higher decline in AHI [27]. Furthermore, the American Academy of Sleep Medicine recommends discussing referral to a bariatric surgeon to adults with OSA and obesity (BMI ≥35 kg/m^2) who are intolerant or unaccepting of positive airway pressure (PAP) as part of a patient-oriented discussion of alternative treatment options [28]. Also, other organizations, such as the National Heart, Lung, and Blood Institute, recommend bariatric surgery for individuals with BMI ≥35 kg/m^2 and OSA, regardless of PAP adherence.

Finally, although CPAP treatment can improve various aspects of weight gain, studies are inconclusive on its benefit for weight loss [29]. Some of them even relate it to weight gain [30], highlighting the complexity of obesity pathophysiology.

25.2 Diabetes

Type 2 diabetes is associated with an increased risk of developing OSA. Patients with type 2 diabetes have an increased adjusted incidence rate ratio (1.48) of OSA than those without [31]. Several factors could explain this association. Diabetic autonomic neuropathy, which can affect the control of breathing at different levels, has been related to a higher incidence of OSA [32]. AHI disturbances have also

been independently associated with higher odds of diabetic microvascular complications (nephropathy, retinopathy, and peripheral neuropathy) [33]. The high prevalence of OSA in type 1 diabetes patients suggests a pathophysiological role of hyperglycemia and chronic micro and macrovascular complications [34].

In another aspect, it has been described how the intermittent hypoxia that appears in OSA can worsen insulin resistance through, among other factors, activation of the sympathetic nervous system, disturbances of oxidative stress, or systemic inflammation [35]. However, in the various studies carried out to date, PAP therapy has failed to improve glycemic control in type 2 diabetes patients [36], although sleep apnea treatment improves this group's blood pressure and quality of life. In this sense, the American Diabetes Association (ADA) clinical guidelines recommend checking patients with diabetes for the presence of symptoms suggestive of obstructive sleep apnea (e.g., excessive daytime sleepiness, snoring, or witnessed apnea) and considering OSA screening in this group [37].

25.3 Metabolic Syndrome and Lipids

Metabolic syndrome is a term applied to the coexistence in the same individual of abdominal overweight/obesity, dyslipidemia, type 2 diabetes, and high blood pressure. This combination of factors increases cardiovascular risk. Although there are different diagnostic criteria for metabolic syndrome, it is estimated that up to a third of the adult population may present with it.

Obstructive sleep apnea has been associated with metabolic syndrome or its core components. The pathophysiological mechanisms previously described in the relationship between obesity, diabetes, and OSA are also linked to metabolic syndrome. Thus, the beneficial effects of CPAP on glucose metabolism and insulin resistance in patients with OSA are not constant in all the studies carried out [38]. However, arterial hypertension is associated with OSA, and several studies have demonstrated that PAP therapy significantly reduces blood pressure and improves cardiovascular risk and metabolic syndrome [39]. Dyslipidemia is another essential component of metabolic syndrome, typically manifested by hypertriglyceridemia and low HDL-cholesterol (atherogenic dyslipidemia). The association between the presence of OSA and atherogenic dyslipidemia is inconsistent and is influenced by possible confounders such as obesity, diabetes, or insulin resistance. Still, data from the European Sleep Apnea Database Cohort (ESADA) showed that OSA severity was independently associated with cholesterol and triglyceride concentrations [40].

Furthermore, OSA was positively associated with serum triglyceride levels in men with a normal waist circumference [41]. Several mechanisms can mediate this relationship, including chronic intermittent hypoxia, sympathetic activation, or sleep fragmentation. Although studies on the possible benefit of CPAP treatment on the lipid profile are inconsistent, a recent meta-analysis showed that CPAP treatment decreases total cholesterol at a small magnitude but has no effect on other dyslipidemia markers in OSA [42].

25.4 Other Endocrinological Diseases (Fig. 25.2)

25.4.1 Acromegaly

Acromegaly is a low-prevalence disease resulting from growth hormone (GH) excess, usually in the context of a GH-producing pituitary tumor. It is associated with a phenotype characterized by an increase in the size of the acral parts of the body (hands and feet) and several changes in facial features (prognathism, and enlargement of the forehead, lips and nose). OSA prevalence is 69% in patients with acromegaly [43]. By the time the diagnosis of acromegaly is made, which is usually late and with evident morphological alterations since it is a slowly evolving disease, has an influence on the development of OSA. Consequently, the presence of pharyngeal/tongue thickening, increased collagen production, or tissue edema contributes to narrowing the upper airway, facilitating OSA [44].

25.4.2 Hypothyroidism

Hypothyroidism is a common endocrine disorder involving the failure of the thyroid gland to produce thyroid hormone. Overt hypothyroidism has an estimated OSA prevalence between 25 and 50% [45]. Subclinical hypothyroidism is a common disorder diagnosed when peripheral thyroid hormone levels (free thyroxine or T4) are within normal reference laboratory range. Still, serum thyroid-stimulating hormone (TSH) levels are mildly elevated. In a moderate or severe OSA population, 16.4% of patients had some thyroid disorder, and 8% were newly diagnosed with

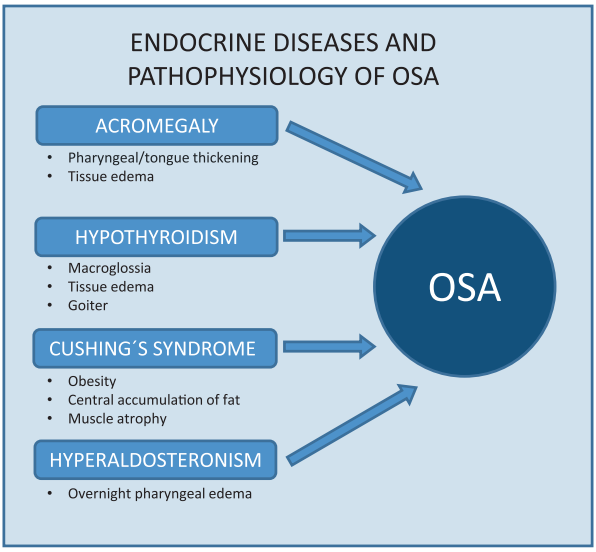

Fig. 25.2 Endocrine diseases and pathophysiology of OSA

subclinical hypothyroidism [46]. The presence of tissue edema, macroglossia, or goiter may explain this higher prevalence, but other mechanisms have been suggested, such as alterations in ventilatory drive and respiratory muscle function. Levothyroxine replacement therapy improves symptoms of OSA and sleep efficiency for some patients with overt hypothyroidism. Therefore, it can be deduced that hypothyroidism- ism contributes to OSA, but not a determining one. Another study showed no difference in the frequency and severity of OSA among euthyroid patients and those with either treated or untreated subclinical hypothyroidism [47].

25.4.3 Cushing's Syndrome

Cushing's syndrome results from prolonged exposure to exogenous or endogenous glucocorticoids. The most common cause is iatrogenic Cushing's syndrome due to the exogenous administration of glucocorticoids with therapeutic intent. It is associated with the appearance of a typical phenotype characterized by obesity with a central accumulation of fat and muscle atrophy. It also presents multiple metabolic manifestations such as type 2 diabetes, high blood pressure, or dyslipidemia. This characteristic phenotype explains the increased prevalence of OSA detected in patients with the syndrome through an accumulation of fat in the cervical area and more significant muscle weakness. In one study, the prevalence of OSA was higher (50% vs. 23%) in patients with Cushing's syndrome compared with control subjects [48].

25.4.4 Primary Hyperaldosteronism

Primary hyperaldosteronism is caused by excess aldosterone secretion by one or both adrenal glands, leading to sodium retention, intravascular volume expansion, and arterial hypertension. It is frequently associated with hypokalemia, although it is not an essential finding for diagnosis. OSA prevalence in patients with primary hyperaldosteronism is high, 45.8–67.6%. Treatment for hyperaldosteronism, either surgical (adrenalectomy) or pharmacological (spironolactone or amiloride), can significantly improve the AHI. A higher prevalence of primary hyperaldosteronism has also been described in patients with OSA (34%). Several studies have demonstrated higher aldosterone levels in patients with OSA; this excess, as seen in hyperaldosteronism; may exacerbate its severity. The overnight fluid shifting into the neck and consequent pharyngeal edema can also contribute to upper airway obstruction and OSA [49].

25.4.5 Male Hypogonadism

Male hypogonadism is a clinical syndrome characterized by a deficit in the testosterone production by the testis. It can be of primary (testis) or central (hypothalamic–pituitary) origin. Symptoms depend on the age of onset, but in adults, it is

characterized by erectile dysfunction, decreased libido, gynecomastia, muscle weakness, or low bone mineral density, among others. A worsening of sexual function has been described in men with OSA, which could be related to a decrease in testosterone levels. However, this relationship is complex and poorly understood [50]. On the other hand, testosterone treatment in hypogonadal men could be associated with a greater tendency to fluid retention and edema, which can worsen OSA. Moreover, testosterone treatment can increase the hematocrit. In addition, the Endocrine Society recommends against testosterone replacement therapy in hypogonadal men with elevated hematocrit or untreated severe obstructive sleep apnea [51].

Take-Home Message

- There is a relationship between OSA and obesity, diabetes, or metabolic syndrome.
- The central deposition of fat (android, perivisceral; characteristic of males), as opposed to the gluteal-femoral (gynoid, subcutaneous; characteristic of females), is associated with a higher risk of comorbidities, mainly cardiometabolic.
- Other classical endocrine disorders such as Acromegaly, Hypothyroidism, Cushing's syndrome, primary hyperaldosteronism, and male hypogonadism show a high incidence of OSA.
- The pathophysiological mechanisms involved in these associations are diverse and, in some cases, poorly understood.
- Although beneficial in many aspects, treatment of OSA with positive airway pressure (PAP) does not always show improvement.

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Dermatologic Changes Related to Patients with Obstructive Sleep Apnea

26

Pedro Redondo

26.1 Introduction

The central nervous system regulates the control of breathing. Central apneas are produced in the ventilatory control centers of the nervous system when respiratory effort begins during sleep [1]. Central apneas are usually associated with other medical disorders such as congestive heart failure, stroke, and neurologic disorders or are secondary to the use of substances that have a respiratory depressant effect, such as opioids. However, they can also occur at high altitudes [1].

Obstructive sleep apnea (OSA) is a respiratory disorder characterized by narrowing or closing of the upper airways during sleep. Obstruction of the upper airways may be partial and recurrent (hypopnea) or complete (apnea) with recurrent oxygen desaturation and periodic changes in heart rate, blood pressure, intrathoracic pressure, and sympathetic activity. In adults, a diagnosis of OSA is considered when five or more apneas or hypopneas occur per hour of sleep or when the apnea–hypopnea index (AHI) is greater than or equal to five events per hour [1].

The most conservative estimates suggest that the prevalence of OSA is 4% in males and 2% in females, although it is likely to be higher [1]. Obstructive respiratory evens (apnea or hypopnea) last at least 10 s, are associated with a fall in blood oxygen saturation, and generally conclude with brief awakenings that fragment sleep and manifest as cortical activation/awakenings on electroencephalograms. Furthermore, OSA may lead to structural changes in sleep, including shortening or loss of stage 3 of deep sleep and/or rapid eye movement (REM) sleep.

The skin and the central nervous system are closely connected and have a common embryonic origin, the ectoderm. It is a popular saying that the face, the skin of the face, is the mirror of the soul, and without doubt, it is evident how restful sleep

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improves the appearance of the skin while, in contrast, the lack of nighttime rest negatively affects the skin.

Skin disorders are a common comorbidity of sleep apnea, and sleep apnea itself may deteriorate the skin. Indeed, in a study with patients with OSA, they compared photographs taken before and after treatment with CPAP and showed that treatment made patients look younger and more attractive [1].

As for the epidemiologic association of sleep and the skin, a study using data from the national Danish Registry assessed 19,438 patients with OSA and controls matched for age and gender and found a higher likelihood of skin disorders in patients with OSA (OR 1.18 [1.07–1.30]) [2]. This finding was confirmed in a pediatric cohort in the same research group with an OR of 1.32, 95% CI: 1.02–1.71 [3]. These findings indicate a general relationship that may be bidirectional between OSA and skin disorders.

OSA is associated with activation of the sympathetic nervous system, systemic inflammation, metabolic dysregulation, and increased coagulation and endothelial dysfunction [4].

Psychiatric comorbidities [5] in skin disorders such as major depressive disorder and posttraumatic stress disorder, associated with a high sympathetic tone, are also commonly associated with OSA [6]. Without doubt, the interface between sleep and skin disorders is complex and multifactorial [7].

This chapter reviews the literature on the association between OSA and dermatologic disorders. OSA may be an associated factor in complex medical patients (e.g., diabetic patients with complications) with dermatologic problems which are refractory to treatment. We will not discuss the possible role of OSA in dermatologic manifestations of systemic diseases, which also may be comorbid with OSA.

26.2 Pathogenesis

OSA is an inflammatory disease associated with obesity and mechanical obstruction of the airways leading to episodes of tissue hypoxia. Let us first consider each one of these factors individually.

– **Inflammation**: OSA is considered a low-grade chronic inflammatory disease of the airways with abnormal neuromuscular control of breathing [8, 9]. A direct link exists between OSA and skin disease through inflammation. This occurs in psoriasis and atopic dermatitis. The inflammation induced by the sleep disruption caused by OSA, the increase in systemic interleukin (IL)-1, IL-6, and IL-12, and the fall in IL-10 further exacerbate psoriasis. Psoriasis also increases levels of TNF-α and IL-17, which is associated with greater atherosclerotic risk and possibly OSA itself [10]. The heightened inflammatory state caused by OSA, which may occur independently of body mass index [11], may be a predisposing and/or triggering factor of inflammatory dermatoses in patients at greater risk of developing such disorders. For example, a study of patients with OSA found that the serum levels of the inflammatory mediators IL-23 and C-reactive protein

were significantly higher in patients with OSA than to healthy controls [12]. A 3-month course of continuous positive airway pressure (CPAP) therapy led to a significant reduction in serum levels of IL-23 and C-reactive protein in patients with OSA. The changes in the levels of IL-23 were positively correlated with improvement in AHI scores and C-reactive protein levels [12].

Some studies suggest that OSA increases the release of catecholamines, which could induce a deviation of Th2 cells in the immune response. Several so-called proinflammatory cytokines such as IL-1 or TNF-α also exert a somnogenic effect. Alteration or dysregulation of these cytokines may lead to dysfunctional sleep. It is well known that the circadian rhythm of the release of TNF-α is significantly disrupted in patients with OSA. The physiologic nocturnal peaks of this cytokine almost disappear, and an additional daytime peak occurs. Patients with OSA have high levels of inflammatory mediators such as TNF-α and IL-6, and these abnormalities are reduced by treatment with CPAP. Several studies have shown that sleepiness is affected by certain drugs that neutralize TNF-α such as thalidomide, etanercept, and infliximab. Obese patients with OSA experienced significant and marked reductions in sleepiness following treatment with etanercept, which proved to be more effective than CPAP. It has also been reported that sleep disorders and mental alertness improve in patients with rheumatoid arthritis when treated with infliximab.

A recent study has identified 4 cytokines associated with autoimmune disease whose median serum levels were significantly different for patients with OSA who received therapy with CPAC as compared to patients with OSA who received no treatment: APRIL (5.2 times lower $P = 3.5 \times 10^{-11}$), CD30 (16 times higher, $P = 7.7 \times 10^{-5}$), IFN-α-2 (2.9 times higher mayor, $P = 9.6 \times 10^{-14}$) and IL-2 (1.9 times higher, $P = 0.0003$). Cytokine levels in the patients treated with CPAC were similar to the levels in the control subjects. These findings suggest that the levels of these four cytokines are affected by sleep disorders and perhaps by chronic hypoxia [13].

– **Obesity (metabolic syndrome, polycystic ovarian syndrome):**
A critical predisposing factor for OSA is excess body weight, and it is estimated that about 60% of moderate to severe cases of OSA are related to obesity [1]. Alternatively, OSA may increase insulin resistance and exacerbate the metabolic dysfunction of obesity [4]. Although it is thought that the prevalence of OSA in children is between 1% and 4%, it may be higher due to the epidemic of childhood obesity [1].

OSA causes oxidative stress. A study [14] showed that the expression of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase is elevated in the leukocytes of patients with OSA, which significantly increases the oxidative effect of leukocytes. Furthermore, intermittent hypoxia, the increase in the sympathetic nervous system activity and the hypothalamic–pituitary axis and the release of proinflammatory cytokines are considered potential mechanisms of OSA in relation to insulin resistance and glucose intolerance [15].

Several skin disorders are associated with obesity, which links with a greater risk of OSA. Diabetes is a metabolic disorder that may result in obesity and is associated with skin disorders such as diabetic ulcers. OSA in these patients may further affect wound healing, thus perpetuating the vicious cycle of diabetic ulcers.

- **Mechanical obstruction of the upper airways**: several syndromes and genetic abnormalities with involvement of the skin are associated with anomalies in the upper airways and a greater risk of OSA. Specifically, syndromes with lipodystrophy and some blistering or restrictive scarring diseases may also cause mechanical obstruction of the upper airways and OSA.
- **Hypoxia**: skin cancer, especially melanoma, may be associated with OSA due to the induction of neovascularization signals such as hypoxia-inducible factor (HIF)-1α and/or vascular endothelial growth factor (VEGF) sent systematically in OSA in response to the intermittent hypoxia.

Below we will deal in more detail with the skin diseases associated with OSA as related to these 4 etiopathogenic factors.

26.2.1 Skin Disease Related to Inflammation

26.2.1.1 Psoriasis

Psoriasis is a chronic inflammatory disease of the skin of autoimmune origin characterized by the presence of erythematous plaques which are well delimitated and covered by pearly scales located preferentially on joint surfaces such as the elbows or knees, and the scalp. It has a chronic progression and is variable both in its clinical features and progression. Thus, there are clinical pictures with very few practically asymptomatic lesions and others which are generalized and accompanied by nail and joint involvement which causes great functional disability.

Although the cause of the disease is unknown, two basic issues stand out in the pathogenesis: epidermal hyperplasia due to the increase in the number of germinative cells and the inflammatory infiltrate in the dermis. The inflammation is mediated by CD4+ T lymphocytes which release (together with keratinocytes) proliferative cytosines which stimulate the proliferation of epidermal cells. The inflammatory response is of the cellular type against a yet unknown autoantigen or a streptococcal superantigen in the case of psoriasis in postinfectious gouts. A series of genetic factors that lead to its appearance and development has been identified as the environmental factors responsible for triggering the episodes. The genetic predisposition toward suffering this disease is associated with the expression of class I antigens of the HLA Cw6, B13, B17, B27 Bw57 system, and class II DRw7.

Factors that trigger attacks include trauma, infections such as those of the upper airways caused by beta-hemolytic streptococci, drugs such as lithium salts, beta-blockers, antimalarials, nonsteroidal anti-inflammatories or the sudden discontinuation of the administration of corticoids, situations involving great emotional stress, and metabolic factors such as states of hypocalcemia and alcohol intake.

The course of psoriasis is unpredictable, with remissions and exacerbations of a variable length, although it is usually chronic. The complicated forms such as

arthropathic psoriasis may be disabling and the severe forms such as erythrodermic and pustular psoriasis may be fatal.

Psoriasis is without doubt, the skin disease with the most solid links to OSA [16–18]. The estimated frequency of OSA in psoriasis ranges from 13.7% to 61.4%. A study using data from the Danish National Register of Patients shows a two-way relationship between OSA and psoriasis, where psoriasis is associated with a greater risk of OSA and OSA is associated with a greater risk of psoriasis [19]. In addition, several observational studies [19–26] and one randomized controlled trial [27] have assessed the relationship between OSA and psoriasis.

A recent study included 12,336 patients with psoriasis aged over 21 years and 24,008 controls matched for age and sex. The prevalence of OSA in patients with psoriasis was higher than in the control group (2.7% and 1.5%, respectively, $P < 0.001$). Multivariate analysis adjusting for age, sex, race, body mass index, chronic obstructive lung disease, hyperthyroidism, hyperlipidemia and peptic ulcer disease revealed a significant association between psoriasis and OSA (odds ratio = 1.27, 95% CI: 1.08–1.49, $P < 0.001$) [28].

Another Polish observational study found that patients with OSA were four times more likely to have psoriasis than the general population with OSA had a two-times greater risk of developing psoriasis over a period of 3 years and that this increased risk was related to obesity and living in urban areas [26]. A European study also found a greater prevalence of psoriasis in patients with OSA, regardless of confounding factors such as obesity and other metabolic conditions [27].

It also appears that comorbidities such as hypertension increase OSA risk in patients with psoriasis [24]. OSA is associated with an increase in the nocturnal activity of the sympathetic nervous system which results in elevated blood pressure and of oxidative and inflammatory stress markers. These factors affect the cardiovascular system and may cause severe complications [29]. Furthermore, oxidative stress and inflammatory processes are involved in the pathogenesis of OSA and psoriasis. The systemic inflammation resulting from OSA/psoriasis is accompanied by autonomic activation / increase in sympathetic tone [16]. The autonomic activation may result from systemic inflammation or be simply due to the more significant number of awakenings. It has also been speculated that the autonomic activity in psoriasis leads to a greater incidence of restless leg syndrome, and an increase in the number of awakenings [16, 30]. Sleep disturbance in psoriasis leads to a greater frequency of N1 stage sleep, which may cause more frequent pharyngeal collapse [31]. Moreover, the frequent awakenings in OSA reduce the sleep quality and may increase itching [26]. This has also been demonstrated in a mouse model of psoriasis in which sleep deprivation exacerbated skin lesions.

Several cytokines common to the pathogenesis of the two diseases have also been identified. Indeed, transcription factors such as nuclear factor-kB and HIF-I, which are activated due to the intermittent hypoxia and the oxidative stress resulting from lesions due to reperfusion, lead to an increased regulation of the expression of TNF-α and IL-6 [10]. These same cytokines are elevated both in the skin and serum of patients with psoriasis [32].

Studies into treatment offer further evidence of the link between psoriasis and OSA. Thus, in three patients with refractive psoriasis and OSA, the severity of the

lesions decreased when the patients were treated with CPAP [26]. Although CPAP may decrease the symptoms of psoriasis, whether the treatment of psoriasis is effective to improve OSA remains unclear. Thus, when 20 patients with OSA and psoriasis were treated with adalimumab (an anti-TFN-α agent) for 8 weeks, no apparent improvement in OSA was observed [33]. Although it is unlikely that such short-term treatment with a TNF-α inhibitor would be effective, long-term data are lacking on the benefits of this approach for comorbid OSA. In addition, OSA is related to other inflammatory autoimmune disorders such as lupus erythematosus and rheumatoid arthritis [34].

26.2.1.2 Atopic Dermatitis

Atopic dermatitis (AD) is a chronic relapsing inflammatory disease of the skin that causes intense itching which preferentially affects the flexor surfaces of the elbows and knees and the cephalic pole. Its exact cause is unknown, but it is a multifactorial disease resulting from the interaction of genetic and environmental factors, defects in the skin's barrier function and a series of immunologic factors. Frequently it is erroneously attributed to "nerves" or "stress." Patients with AD often have a history of allergic conditions such as asthma, hay fever, eczema, or test positive in skin allergy tests. However, the disease is not caused by an external allergen and is rather seen as endogenous eczema (Fig. 26.1).

The prevalence of AD in the general population is between 2% and 5%, and about 15% in children and the young. But incidence has been reported to be as high as 20% in countries such as the United States, and world-wide incidence is increasing. The disease begins before the first year of life in more than 60% of patients, but the frequency falls with age reaching just 5% at 12 years. Onset in adulthood is infrequent although such cases tend to be more severe in their clinical course and progression.

Dysfunction of the skin barrier and dysregulation of the immune system are factors that trigger AD. The main proteins responsible for epidermal function are filaggrin, transglutaminases, keratins, and intercellular proteins. Defects in these proteins facilitate the entry of microbes and allergens into the skin. The skin barrier dysfunction is considered the first stage in the development of AD, although dysregulation of the immune system also disrupts the skin barrier [35, 36].

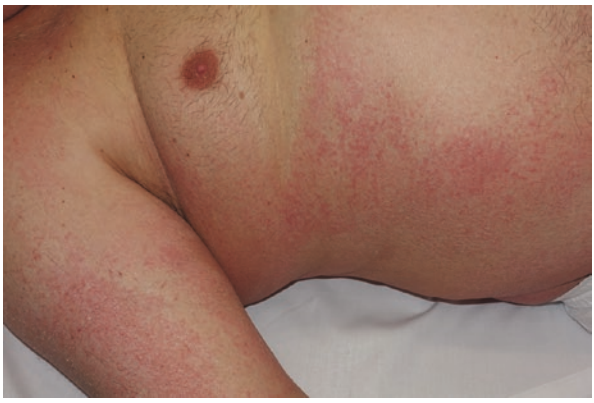

Fig. 26.1 Scaling eczematous lesions in an adult patient with atopic dermatitis

Patients with AD have an abnormal cellular and humoral immune response, facilitating the reaction with environmental antigens, increasing serum IgE, and abnormalities in lymphocyte subpopulations. Thus, atopic patients are predisposed toward mounting Th2 responses with the development of responses against inappropriate antigens such as environmental allergens, bacterial superantigens, and epidermal autoantigens. The onset of AD is associated with the production of Th2 cytokines (IL-4 and IL-13) involved in the acute phase of tissue inflammation. In contrast, IL-5, involved in eosinophils development and survival, predominates in the chronic form, as do GM-CSF, IL-12, IL-18, IL-11, and TGF-B1. In addition, the increased expression of chemokines (eotaxin, RANTES) contributes to the infiltration of macrophages, eosinophils, and T cells in acute and chronic AD lesions [37, 38].

A sizable Taiwanese retrospective study of pediatric and adult patients (1222 patients with OSA and 18,330 without OSA) has shown the epidemiologic link between AD and OSA is shown. The adjusted models showed that patients with a recent diagnosis of OSA were 1.5 times more likely to develop AD. Furthermore, this finding was more marked in children (subjects under the age of 18) with a proportion of 4.01, 95% CI: 1.57–10.26 [39].

As we have already mentioned in this chapter, the proinflammatory cytokines associated with OSA, such as IL-6, are accompanied in atopic (allergic) children by increased regulation of Th2 cytokines. The positive regulation of Th2 contributes to a greater susceptibility to developing AD and the exacerbation of existing AD.

The main risk factor for OSA in children is adenotonsillar hypertrophy, which is related to the repeated collapse of the airways [40]. Some published studies have established the association between AD and adenoids/adenotonsillar hypertrophy as an established comorbid factor in children [41], although Alexopoulos et al. suggest that AD is not related to cases in children who snore [42].

Obstruction of the upper airways is also more common in children with AD in part due to comorbid allergic rhinitis. As for mechanical obstruction, findings are mixed regarding the association with adenotonsillar hypertrophy in atopic children [43], although it is believed that the increase in leukotrienes in the allergic disease may contribute to r a rise in adenotonsillar hypertrophy, thus placing patients with AD at risk for apnea [44, 45].

Research into AD improves the detection and evaluation of sleep disorders [46].

Children with AD have a significantly higher risk of OSA than those without AD. After adjusting for age, sex, level of urbanization and underlying comorbidities (craniofacial anomalies, prematurity, laryngomalacia/tracheomalacia, diabetes mellitus, and adenotonsillar hypertrophy), patients with AD had a 1.86 greater risk of OSA. Thus, it is considered that AD is an independent risk factor for OSA. The risk for OSA was greater in the youngest children (under 6 years of age) and in those living in urban areas. Given that the onset of AD occurs relatively early in life, the early identification of risk factors and symptoms is essential to prevent OSA development. This is the first study [47] that indicates a greater risk for OSA in children with AD.

AD is a condition that disrupts sleep in patients suffering from it, which is partly attributable to the nighttime itching so characteristic of the disease [48]. In addition, several sleep disorders such as periodic limb movement disorder [49] and OSA are associated with AD.

High sympathetic tone may be present in certain dermatologic disorders such as AD [50]. There may be a high level of excitation during sleep, unrelated to the scratching, even when the AD is in remission.

Similarly, there seems to be an association between OSA and AD in adults [39]. A retrospective cohort study using data from the Taiwanese National Health Insurance database examined the incidence of AD in 1222 patients recently diagnosed with OSA between 2000 and 2005 compared to a matched cohort of 18,330 controls without OSA [39]. All the patients were followed up for 5.5 years. Patients with OSA were 1.5 times more likely to develop AD than the controls without OSA (Hazard risk = 1.5, 95% CI: 1.15–1.95) after controlling for age, sex, hypertension, coronary disease, obesity, allergies, allergic rhinitis, asthma, monthly income, and geographic location.

Episodic nasal congestion in the atopic patient with allergic rhinitis could be associated with OSA. However, a study of 150 adult patients with OSA [51] found no significant differences in polysomnographic findings, including OSA indices, between patients with persistent allergic rhinitis (n = 55) and the remaining 95 patients with OSA but without nasal problems.

26.2.2 Skin Diseases Related to Obesity

Without doubt, one of the most significant risks for OSA is obesity, which is mainly related to obstruction of the upper airways. Therefore, we must consider those diseases of the skin which have a greater prevalence in patients with obesity.

26.2.2.1 Diabetes

Type 2 diabetes, in particular, is one of the most prevalent diseases in obese patients, and the presence of diabetes is associated with a higher risk for skin ulcers in peripheral areas with poor vascular circulation. This problem which seems to worsen when OSA is simultaneously [52]. OSA could increase this risk due to the endothelial dysfunction associated with this disease and the neuropathy of small fibers [53]. Curiously, in a case series, treatment with CPAP resulted in a significant improvement in the granulation of wounds in diabetic patients [54]. Two patients had not been previously diagnosed with OSA, and another had a previous diagnosis of severe OSA but did not comply with the CPAP therapy. The two undiagnosed patients had an AHI of 41 and 49, respectively, and were successfully treated with CPAP and the standard care for ulcers. Both showed a marked improvement in the granulation and healing of wounds after CPAP therapy. The third patient refused to consider CPAP therapy and experienced deficient healing of the wound and *Pseudomonal* infection despite aggressive wound treatment [54]. Possible untreated OSA may affect the healing of diabetic foot ulcers.

26.2.2.2 Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a chronic inflammatory disease that courses clinically with episodes of abscesses and very painful nodules which are foul-smelling and recurrent, the formation of sinus tracts and scar tissue. It affects typically densely populated areas with apocrine glands, mainly the axillae, groin, buttocks and the perianal and submammary areas. It usually appears during puberty and tends to affect females more than males. Having this disease is usually associated with a reduction in the patient's quality of life, leading to frustration, depression, social isolation, and difficulty establishing social relationships. Treatment for hidradenitis includes general measures (weight loss, quitting smoking), drugs (antibiotics, isotretinoin, finasteride, prednisone, cyclosporine, etc.) and surgery (incision and drainage, closure by secondary intention, etc.). In the last 5 years the efficacy of biological drugs of the infliximab family (chimeric monoclonal antibodies) that act by inhibiting the proinflammatory action of TFN-α has been demonstrated.

Obesity is related both to HS and OSA, in which the intermittent obstruction of the pharyngeal airways causes hypoxia during sleep. The shared immunologic mechanisms may predict OSA risk of in patients with HS [55–57]. As in HS, the proinflammatory state in sleep apnea is characterized by the activation of nuclear factor-kappa b and IL-17 signaling, together with increased concentrations of inflammatory cytokines such as TNF-α and IL-6. The incidence of OSA in a cohort of patients with this disease was 3.5% compared to 2.5% in an obese control population. The risk was even higher in women and the youngest patients [58] (Fig. 26.2).

Epidemiologic studies report the prevalence of OSA in patients with HS as being higher than in healthy control populations [58]. One prospective trial used formal sleep studies to assess the prevalence of OSA in HS. All patients completed validated questionnaires to evaluate the prevalence of sleep apnea, including the Berlin, STOP-Bang, and Epworth sleep questionnaires. The patients with HS were more likely to be obese and smokers [59], with a well-known risk factor for OSA development [60]. Furthermore, both HS and OSA are associated with elevated serum levels of TNF-α and immune dysregulation [56, 61].

Thirty-eight percent ($n = 6/16$) of the patients with HS who underwent outpatient sleep tests had an AHI of >5 and were diagnosed with OSA. There was a positive

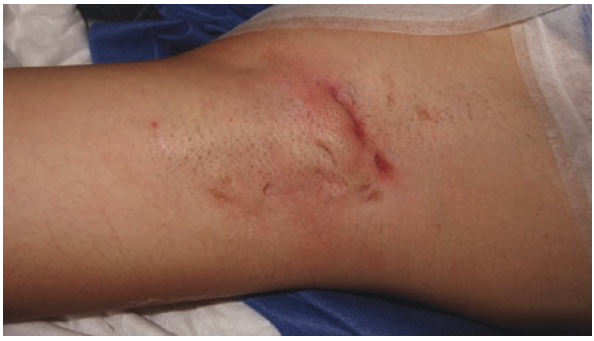

Fig. 26.2 Thirty-two-year-old woman with obesity and obstructive sleep apnea. Abscessified lesions and fistulas in the axillary region, compatible with hidradenitis

relationship between giving positive for OSA and stages 2 and 3 in the Hurley system (a scale of the severity of the disease) ($r = 0.49$, $P = 0.05$), and between giving positive for OSA and DLQI (quality of life) scores ($r = 0.56$, $P = 0.03$).

OSA is associated with elevated systemic inflammation [56, 61]. In a series of patients, those with a higher C-reactive protein level were more likely to be at risk for OSA (v2 = 4187; $P = 0.04$). Patients with severe HS were also at greater risk for OSA (OR 4.6; $P = 0.02$). However, this relationship continued to be significant even after controlling for other risk factors [62]. This study [62] shows that the prevalence of OSA in patients with HS is more significant than that suggested in epidemiologic studies [58].

26.2.2.3 Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS), also known as functional ovarian hyperandrogenism, chronic hyperandrogenic anovulation or reproductive metabolic syndrome is a metabolic and endocrine dysfunction with a high prevalence. It is the commonest cause of hyperandrogenism, with an incidence of 3% in adolescent and adult women. It is estimated to be present in 75% of hirsute women and in 10% of premenopausal women. Its presence should be suspected in any adolescent or woman of child-bearing age with hirsutism or other skin manifestations of hyperandrogenism, irregular menstrual periods, and obesity. Its etiology is uncertain, and it manifests by various symptoms and signs, especially irregular menstrual periods, skin manifestations of hyperandrogenism (acne, alopecia, seborrhea, and hirsutism), obesity, infertility, insulin resistance and the polycystic aspect of the ovaries on ultrasound examination (Fig. 26.3). Furthermore, most women with PCOS (60%–68%) present insulin resistance and compensatory hyperinsulinemia which may also be present in subjects of normal body weight. Insulin resistance plays a predominant role in the long-term metabolic consequences of the syndrome, among which type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease should be noted.

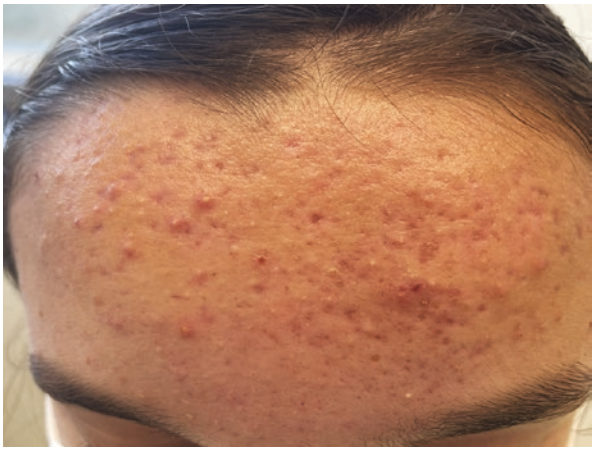

Fig. 26.3 Twenty-three-year-old woman diagnosed with polycystic ovary syndrome. Acne lesions on forehead

Women with PCOS are more likely to be insulin resistant than controls of the same weight. They have an exceptionally high prevalence of early onset type 2 diabetes and a substantially greater risk of hypertension, dyslipidemia, heart disease and other vascular disorders.

Evidence from small studies suggests that PCOS is independently associated with greater risk and severity of OSA [63–68].

It is known that the greater risk of OSA in patients with PCOS is related to obesity, insulin resistance, and hyperandrogenemia. Obesity has been identified as an independent risk factor for OSA [69].

The current literature provides associative but not pathophysiologic links between PCOS and OSA. The fact is that women with PCOS have the highest rates of obesity and, as they age, they have a greater risk of developing OSA. Therefore, physicians who treat obese women with PCOS should very clearly suspect the presence of OSA, mainly because both OSA and PCOS are independently associated with greater cardiometabolic risk and treatment of the OSA may reduce this risk [70–72].

Although most studies that have used matched groups or statistical adjustment have found OSA in patients with PCOS to be more prevalent and severe, two cross-sectional studies which analyzed the prevalence of OSA in women with PCOS found no increased risk of PCOS/OSA when using a validated questionnaire [73] to detect the disorder and polysomnography [74].

Lin et al. performed a longitudinal analysis using data from the Taiwan National Health Insurance Research database between 1998 and 2009 [75], which covers almost 98% of the entire population of Taiwan. The researchers identified 4595 women with PCOS aged 18 years or older (mean age 28.0 ± 6.79 years) using the relevant International Classification of Diseases (ICD-9-CM) code. These women did not have any concurrent diagnosis of sleep apnea before enrolling in the study. An equal number of female controls without PCOS or sleep apnea who were matched for age and time of enrollment were selected. The diagnosis of OSA was made after patients underwent polysomnography. The authors found that women with PCOS had a greater incidence of OSA than controls (1.71 vs. 0.631000 person-years $P < 0.001$). Even after adjusting for age, level of urbanization, income and comorbidities, there was still a significant relationship between PCOS and OSA risk (HR: 2.71, 95% CI: 1.62, 4.53). This study had various strengths, with the first and most important being the large sample size and its longitudinal design.

Another recent study [76] which analyzed 328 patients with PCOS, found that the prevalence of OSA was 40% (131/328) and that 6 cases (5%) were severe. Univariate analysis showed that body mass index and blood pressure were significantly higher in patients with OSA than in those without OSA ($P < 0.05$). At the same time, the anti-Mullerian hormone was lower in patients without OSA. As for glucose metabolism and lipids, glycosylated hemoglobin, fasting plasma glucose, and fasting insulin levels were significantly higher in patients with PCOS and comorbid OSA than those without OSA (all $P < 0.05$). The patients with OSA also had higher levels of triglycerides, low-density lipoprotein cholesterol,

high-sensitivity C-reactive protein levels, and lower levels of high-density lipoprotein cholesterol (HDL-C) ($P < 0.05$). Logistic regression analysis revealed that a higher body mass index, elevated serum testosterone, and lower HDL-C were correlated with the appearance of OSA ($P < 0.05$).

OSA in patients with PCOS is associated with multiple abnormalities in reproductive endocrine and metabolic disorders.

Anecdotally, a report has been published of a 15-year-old girl [77] with severe acanthosis nigricans of the neck and axillae with severe obesity (a body mass index of 46.7 kg/m^2) and many other medical comorbidities, who presented progressive worsening of OSA over 2 years. The patient showed evidence of insulin resistance, hypertension, dyslipidemia, PCOS, and nonalcoholic fatty liver disease. In this case, the multiple morbidities, probably mediated by severe obesity, seems to be the basis of the acanthosis nigricans and the OSA, but it is likely that the acanthosis nigricans and OSA are unrelated.

Common acne is one of the skin manifestations of adolescent and young adult women with PCOS. An open single-arm trial evaluated the use of 0.5 mg/kg of isotretinoin in subjects with common severe acne [78]. The authors assessed the severity of the acne, depression, excessive daytime sleepiness and the sleep variables of the participants using polysomnography before and after 1 month of treatment. The participants experienced improved sleep latency and efficiency but no change in AHI.

A retrospective case series relates keloid acne to OSA [79]. Keloid acne of the neck (KAN) is an inflammatory skin disease characterized by scarring of the hair follicles in the posterior aspect of the neck and scalp and is attributed to mechanical causes such as the use of razors or helmets and other external sources [80].

After studying 1.5 million patients, a study identified concomitant KAN and OSA in 17 individuals. Sixteen (94%) were male and 9 (53%) were white. OSA diagnosis was made before that of KAN in 10/17 individuals (58.8%). Eight patients (47%) had received treatment with positive pressure for several years before the diagnosis of KAN, which suggests that chronic follicular occlusion of the CPAC could contribute to the development of KAN. In two cases (11.7%), there was explicit evidence of the use of CPAC as a precipitating or exacerbating factor of the lesions.

Metabolic syndrome, a condition commonly associated with OSA, has been implicated in the pathogenesis of the disease due to chronic follicular occlusion. It is believed that the proinflammatory cytokines driven by the insulin resistance contribute to abnormal follicular keratinization, which increases the risk of common acne and hidradenitis suppurativa [81]. Through similar mechanisms, the metabolic abnormalities observed in OSA may also increase the likelihood of developing KAN in white patients, where the disease is less prevalent than in black patients.

Other rare diseases exist with skin manifestations that are associated with OSA due to the link with obesity, such as *Elephantisis Nostras Verrucosa* (chronic lymphedema) [82] and Klinefelter syndrome (ulceration of the lower extremities) [83].

26.2.3 Skin Disease Related to Mechanical Obstruction of the Upper Airways

26.2.3.1 Lipodystrophies

Lipodystrophy, an abnormal redistribution of fat, has also been linked to a greater risk of OSA due to mechanical obstruction of the upper airways in patients with Klinefelter syndrome.

Familial Partial lipodystrophy type 2 (also known as thick neck syndrome) is due to mutations in the LMNA gene, which encodes the lamins A and C, components of the nuclear lamina (MIM 151660). Patients are healthy at birth, but around puberty, they selectively lose fat deposits in the extremities and buttocks while visceral, facial, and neck fat deposits are conserved and may increase with excessive calorie intake. Using polysomnography OSA has been documented in 2 women with this disease [84].

Lipodystrophy resulting from antiretroviral treatment for HIV is another causal factor [85]. Protease inhibitors are a vital part of antiretroviral therapy in patients infected with HIV. Long-term use of these drugs may cause lipodystrophy, characterized by peripheral lipoatrophy and accumulation of central fat, which may increase the risk of developing OSA. Thus, some patients develop an extensive collection of adipose tissue around the neck and pharynx (the so-called "buffalo hump"), which could explain why 7% of patients with HIV have OSA as compared to 2%–4% of the normal population [86]. The increase in the circumference of the neck, body mass index with overweight or obesity and lipodystrophy are potential risk factors for OSA in patients with HIV. In general, they are patients of normal weight but with a fat content that is notably increased, particularly in the trachea area. This suggests that the association could be related to adipose tissue distribution that is characteristic of patients with this type of lipodystrophy.

One recent retrospective cohort study with 54 patients found no significant association between the length of use of protease inhibitors and OSA severity [87].

Multiple symmetric lipomatosis, also known as Launois–Bensaude syndrome, is another rare condition associated with OSA [88]. Blistering diseases which progressively compromise the upper airways may also cause OSA. A case series of 142 patients with cicatricial pemphigoid, a chronic blistering disease of the mucosa which frequently courses with subsequent scarring, reported that 24% of the participants had nasal manifestations, and 79% had subsequent nasal obstruction [89]. Of these patients, two were diagnosed with OSA. Lesions in the larynx were found in 9% of patients and in the oropharynx and hypopharynx in 8% of patients. Cicatricial pemphigoid may be a direct cause of OSA given the obstruction of the upper airways.

Anecdotally, there has been one report of severe OSA in two children, ages 10 and 14, with hypertrophic scarring after severe burns in the face and upper part of the body probably due to restriction of movement of the thoracic wall due to the use of a close-fitting garment, with significant oxygen desaturation [90]. Both children experienced an improvement in OSA symptoms once the tight-fitting garments were removed.

There are multiple studies of cases of OSA as a consequence of the obstruction of the upper airways secondary to localized tumors, postradiotherapy of the upper airways, and urticaria or angioedema affecting the uvula.

26.2.4 Skin Disorders Related to Hypoxia

26.2.4.1 Skin Cancer and OSA

Recently OSA has been shown to be associated with a greater prevalence, incidence, and mortality from skin cancer [91]. The systemic inflammation due to the hypoxia-reoxygenation cycles in OSA may activate several mechanisms which enhance tumor progression [92, 93]. Specifically, two recent studies have shown the existence of a relationship between OSA and the aggressiveness of cutaneous melanoma [94, 95].

Melanoma is a malignant tumor derived from melanocytes, dendritic cells originating from the neural crest and responsible for the synthesis of melanin. It may spread both through the lymph nodes or the bloodstream and may become established on normal skin. When it appears on an existing nevus, the main criteria which give rise to the suspicion of the diagnosis of melanoma are changes in size and uneven pigmentation. Although it has not been fully demonstrated, several sources of evidence indicate the fundamental role of ultraviolet (UV) radiation in the development of at least two-thirds of all melanomas. It has been verified that there is a statistically significant relationship between melanoma and intermittent sun exposure (odds ratio [OR] = 1.71), especially if this is accompanied by sunburn (OR = 1–91) and that the incidence and mortality from melanoma are higher in regions close to the equator where the intensity of UV radiation is greater. The risk of developing melanoma is higher in white patients, those of Nordic or Celtic origin and is lower among natives of Asia, Africa and South America and in dark-skinned subjects from the Mediterranean region. The danger is greater when the UV radiation interacts with a genetically determined phenotype characterized by subjects having fair skin that burns easily (phototypes I and II) and multiple nevi, especially if they are atypical.

Although melanoma represents 10% of all skin cancers, at least 65% of the deaths related to skin cancer can be attributed to melanoma. However, unlike non-melanoma skin cancer, this tumor is diagnosed at an earlier age (mean age of 55 years). It reaches the highest specific incidence by age in individuals over 65.

A cohort study conducted at the national level in the United States on 5.6 million people using data from a national health insurance database for employees found a greater likelihood of melanoma in patients with OSA (OR 1.14, IC 1.10–1.18) [91]. Some studies have also evaluated the possible mechanisms of the association. A Spanish cohort study of 350 patients recently diagnosed with melanoma and stratified by AHI, the researchers measured serum levels of biomarkers related to hypoxia and tumoral adhesion (VEGF), IL-8, intracellular adhesion molecule (ICAM) and vascular intracellular adhesion molecule (VCAM-1), and markers of tumor aggressiveness (S100 calcium-binding protein B, S100B) and melanoma inhibitory activity (MIA).

Levels of VEGF, IL-8, ICAM-1, S100B, and MIA were not related to the severity of OSA although VCAM-1 levels were higher in patients with OSA than in those without the disease (mild OSA: odds ratio (OR) 2.07, $P = 0.021$; moderate to severe OSA: OR 2.35, $P = 0.013$). In patients with cutaneous melanoma, OSA may contribute to tumorigenesis through the adhesion produced by this integrin [96].

In a Spanish prospective cohort study of 376 patients with cutaneous melanoma who underwent polysomnography, intermittent nocturnal hypoxia, calculated by the desaturation index, was found to have a weak association with HIF-1α (OR 1.03, 95% CI: 1.01–1.06), but not with VEGF [97]. Furthermore, in 436 consecutively enrolled patients, the aggressiveness of the cutaneous melanoma, as evaluated using well defined criteria such as the Breslow index increased in a markedly and independent fashion in patients with OSA, especially if they were younger [98].

A recent study with 56 patients consecutively diagnosed with melanoma [94] shows that the frequency and severity of respiratory disorders during sleep were independently associated with a greater rate of melanoma growth and greater tumor thickness, higher mitotic index, and more ulceration. These features are associated with a poor prognosis in cutaneous melanoma.

Multivariate analyses were used to examine the independent relationship between the severity of sleep respiratory disorders (AHI) and indices of nocturnal oxygen desaturation (ODI3% vs. ODI4%) and measures of aggressiveness of the cutaneous melanoma. All of these factors were independently associated with a higher rate of melanoma growth. 60.7% of patients had respiratory disorders during sleep (AHI ≥5) and 14.3% severe OSA (AHI ≥30) [94]. Other factors involved included oxidative stress and a high degree of systemic inflammation in OSA [99].

A recent meta-analysis including six studies with a combined cohort of more than 5 million patients suggests that patients with OSA are at greater risk for melanoma in comparison to those without OSA. This effect continued to be significant between the studies with at least 5 years of follow-up but lost importance for prospective studies and subgroups adjusted for obesity [100].

Related to pathophysiologic mechanisms, several factors need to be considered:

Firstly, the hypoxia in OSA may favor melanoma development by increasing tumorigenic biomarkers such as HIF [101], which coordinate the expression of the genes that promote tumor adaptation and survival, such as efficient angiogenesis metastasis and resistance to treatment [102].

Secondly, hypoxia may contribute even further to the tumorigenesis of the melanoma by promoting proliferation, the ability for self-renewal and the chemoresistance of the melanoma mother cells [103, 104].

Thirdly, the intermittent hypoxia and sleep fragmentation of OSA may enhance tumor growth by altering the host immune response. The macrophages associated with the tumor are an essential component of the tumor stroma and polarize into two functionally different phenotypes, M1 (tumor inhibitors) and M2 (tumor promoters) [105]. In addition, the intermittent hypoxia and sleep fragmentation of OSA may change the polarity of the macrophages toward the M2 phenotype, which enhances tumoral proliferation, migration, and invasion.

Fourthly, the increase in sympathetic activity due to OSA may favor melanoma development as the increase in beta-adrenergic receptors promotes angiogenesis [106, 107]. Some studies show that beta-adrenergic receptor antagonists may mitigate the progression of melanoma [108].

26.2.4.2 Others

Another possible association between skin diseases and OSA suggests that androgenetic alopecia or male pattern baldness is related to hypoxia. In a cross-sectional study of 932 men, those with OSA and a family history of hair loss were seven times more likely to have male pattern baldness than those who had neither risk factor (IC 3.70–12.56). The authors hypothesize that this phenomenon could be related to the chronic-intermittent hypoxia of OSA which interrupts the normal division of hair follicles and leads to iron deposition in tissues, which is associated with a reduction in the saturation of transferrin which in turn leads to the inadequate availability of iron to support the division of the follicles [109].

OSA may also be considered a risk factor for the survival of skin flaps in breast reconstruction [110].

26.3 Skin disease related to Treatment with CPAP

26.3.1 Local Skin Effects Secondary to the Use of Ventilation with Noninvasive Positive Pressure

OSA is often treated with various types of masks that administer noninvasive continuous positive pressure to the airways during sleep. In one study, up to 50% of CPAP users reported skin allergy, air leaks, or abrasions. However, these factors are not sufficiently serious to limit the use of the treatment [111]. In addition, the masks can cause several types of dermatitis.

Allergic contact dermatitis is associated with itching, redness, and, if sufficiently severe, blisters. In rare cases, the silicon component of the CPAC may be an allergen that triggers allergic contact dermatitis. One study evaluated the effect of the composition of the CPAP mask in adult patients undergoing treatment with CPAP for OSA and compared individually molded masks (71%) with industrial silicone masks (28%) [112]. The individually molded masks reduced nasal abrasions and red eyes and caused fewer contact allergic reactions than the silicone masks (13% vs. 5%). However, using a humidifier did not change the rate of adverse effects in the two groups. In the presence of eczematous lesions in the cephalic pole of patients with CPAC, the dermatologist must rule out allergic contact dermatitis using a standard battery of contact tests [113].

Patients with dry and easily irritable skin are at greater risk of presenting **irritative dermatitis** or **seborrheic dermatitis** (Fig. 26.4). Treatment with humectants before to the use of CPAP may protect the face from irritative dermatitis induced by the CPAP mask. The incorrect use of CPAP masks also increases the risk of patients' skin becoming dry due to air leaks from the mask.

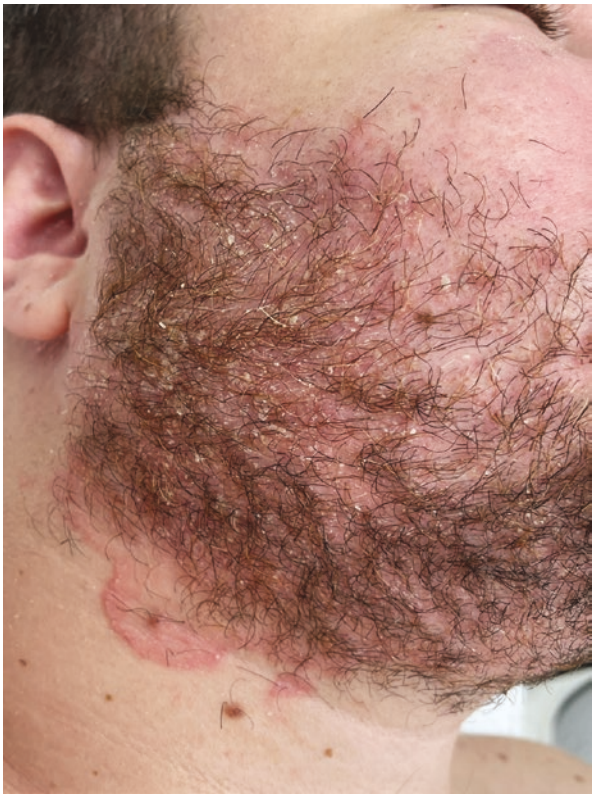

Fig. 26.4 Thirty-seven-year-old male with obesity and obstructive sleep apnea. Eczematous lesions compatible with seborrheic dermatitis in the central facial region and beard area, which worsen with the use of CPAP

An automated retrospective research study showed that patients with **rosacea** have a significantly higher risk of OSA [114].

Rosacea is a chronic inflammatory dermatosis characterized by the appearance of erythema, telangiectasias, papules and pustules in the centrofacial area. The etiology of the disease is unknown although the involvement of several factors such as vascular reactive disorders and an immunologic response to microorganisms such as *Demodex folliculorum* and *Helicobacter pylori* has been postulated. As a result of the limited knowledge of the physiopathology of the disease, therapeutic options are not directed against the pathogenic mechanisms and are not curative. Treatment is based on the use of antibiotics, anti-inflammatories, and retinoids administered topically or systemically, vascular laser, and, in severe cases, surgical techniques. Rosacea is a disease that typically affects subjects aged between 30 and 50. In Europe, it is estimated that it affects between 1.5% and 10% of the population.

A recent study reports that five patients with OSA developed rosacea or experienced worsening of the disease symptoms after using a CPAP mask that covered the nose and mouth. Two patients exhibited centrofacial symptoms restricted to the shape of the CPAP mask, and three patients had cutaneous nasal symptoms. It was postulated that the effect of the CPAP mask, which increases the humidity and

temperature of the skin, may induce lesions in patients with an underlying sensitivity to rosacea. This could have implications for the choice of the CPAP mask and the topical therapeutic options for the rosacea. Furthermore, OSA and its metabolic/cardiovascular comorbidities may also play a role in the development of rosacea symptoms [115].

26.3.2 Systemic Skin Benefits Following the Use of Ventilation with Noninvasive Positive Pressure

It is essential to highlight that CPAP may also be a therapy for the skin as adequately treated OSA may improve **wound healing**. In a case study, the use of CPAC was associated with the resolution of a dyshidrosis, an endogenous eczema of the hands. The authors speculate that improved oxygenation of the tissues and a reduction in sympathetic tone (due to fewer nocturnal awakenings) was the reason for the improvement [116]. It was found that two patients with OSA had yellow nail syndrome and the discoloration of the nails resolved with the use of CPAP [117]. Another adult had onychophagy and treatment with positive pressure, improved bot only the parasomnia improved, but also, the nail biting with resolution of the onychodystrophy [117].

In line with this, CPAP also seems to improve **excessive nocturnal sweating**. Sweating is controlled almost entirely by the sympathetic nervous system, and its primary function is to increase heat loss and maintain thermoregulation [118].

Habitual snoring in children is associated with OSA [119]. In a study of 1760 third grade German children, chronic snoring was more frequently associated with sleep hyperhidrosis (OR = 3.6, 95% CI 1.2–10.8) [120].

Two Icelandic studies have examined the relationship between OSA and sleep-related sweating in adults [118, 121]. In the first, with 15 patients with moderate to severe OSA, core body temperature, skin temperature and electrodermal activity (a measure of sweating) were evaluated in patients untreated for OSA (mean HAI 45.3 ± 3.9). At the beginning of the study, electrodermal activity was correlated with an increase in morning and evening systolic blood pressure and less rapid eye movement sleep. After treatment with CPAP for 107 ± 19 days, during which mean AHI dropped to 4.5 ± 0.9, electrodermal activity fell from 131.9 ± 22.4 to 78.5 ± 17.7. Treatment was also correlated with reductions in evening systolic and diastolic blood pressure reductions while rapid eye movement sleep increased. The second study [121] evaluated the effect of CPAP on sleep-related sweating in 700 participants from the Icelandic Sleep Apnea Cohort followed over 2 years. Frequent nocturnal sweating was observed in 30.6% of males and 33.3% of females with OSA compared to 9.3% of males and 12.4% of women from the general population ($P < 0.001$). In addition, the prevalence of frequent night sweating decreased after the full CPAP treatment from 33.2% to 11.5% ($P < 0.003$). Hyperhidrosis may be an index of sympathetic activation and dysregulation of the autonomous nervous system in OSA.

26.4 Conclusion

In conclusion, skin diseases have various epidemiologic associations with OSA. However, four etiopathogenic mechanisms that may explain the relationship of many dermatologic processes with OSA are as follows:

1. Systemic bidirectional inflammation associated with OSA and inflammatory skin disease (best exemplified by psoriasis) in each condition exacerbates the other.
2. Obesity itself and the conditions associated with obesity (such as type 2 diabetes) in which skin manifestations and concurrent OSA are frequently observed. Type 2 diabetes is an interesting example as it is believed that OSA induces deficient wound healing and may contribute to diabetic ulcers becoming infected.
3. Mechanical obstruction of the upper airways may be due to obesity and other specific conditions such as lipodystrophy in which fat deposits accumulate adjacent to the airways.
4. The hypoxia related to OSA may be associated with skin cancer, particularly melanoma. The intermittent hypoxia may produce proliferative neovascular signals which favor tumor growth. Joining these mechanisms is the autonomic dysfunction due to OSA. Excessive sympathetic flow toward the skin may accelerate aging and uncover or exacerbate preexisting skin disorders.

Concerning the secondary effects, continuous positive pressure in the airways may be locally associated with skin irritation, folliculitis, rosacea, irritative dermatitis, seborrheic dermatitis, and, very rarely, contact allergic dermatitis. However, the benefits of CPAP clearly outweigh the risks.

Many of these associations are clear and have been well studied and documented. However, more research is needed to describe better the mechanisms underlying the clinical associations between skin diseases and OSA and the potential therapeutic effects on skin diseases when treating OSA with CPAP or other interventions.

Furthermore, it is likely that in everyday clinical practice, specialists come across OSA in complex dermatologic patients who have one or more medical or psychiatric disorders, which are also associated with a greater risk for OSA.

Finally, dermatologists should be aware of the possible impact of OSA on the course of skin diseases, especially those associated with a mainly inflammatory physiopathology, and the great benefit offered by CPAP for the integumentary system.

Take-Home Messages

- Skin disorders are a common comorbidity of sleep apnea
- Sleep apnea itself may deteriorate the skin.
- Four ethiopathogenic mechanisms may explain the relationship of many dermatologic processes with OSA:

  - systemic bi-directional inflammation associated with OSA and inflammatory skin disease (best exemplified by psoriasis and atopic dermatitis) in which each condition exacerbates the other.
  - obesity itself and the conditions associated with it (diabetes, hidradenitis suppurativa, polycystic ovary syndrome);
  - Mechanical obstruction of the upper airways
  - Hypoxia related to OSA may be associated with skin cancer, in particular melanoma.
- Many of these associations are clear and have been well studied and documented.
- More research is needed to describe better the mechanisms underlying the clinical associations between skin diseases and OSA and the potential therapeutic effects on skin diseases when treating OSA with CPAP or other interventions.

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Laboratory Parameters Changes

27

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27.1 Complete Blood Cell Count

Complete blood cell count (CBC) is a medical laboratory test widely available, easy to obtain, and cheap. Systemic inflammation and altered platelet function are two mechanisms involved in the increased cardiovascular risk associated with obstructive sleep apnea (OSA). Through a hemogram, we can obtain a series of parameters related to these two physiopathological mechanisms. Red cell distribution width (RDW) is a measurement of the range in the volume and size of the erythrocytes. Inflammation can shorten erythrocytes survival, and elevated RDW has been described in OSA patients.

Nevertheless, this fact may be related to age or obesity. A significant positive correlation between RDW and apnea–hypopnea index (AHI) and oxygen desaturation index (ODI) has been found. Furthermore, RDW might be used as a marker of the response to continuous positive airway pressure (CPAP) treatment [1].

It is well known that hypoxia stimulates erythropoiesis and is associated with inflammation [2]. Hemoglobin and hematocrit are significantly increased in patients with severe OSA, but values remain within the normal clinical range. A negative

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association exists between hemoglobin, hematocrit, mean corpuscular volume (MCV), and mean peripheral oxygen saturation (SpO_2) [3]. One possible explanation are the high blood levels of erythropoietin (EPO) seen in OSA patients [4]. Atrial natriuretic peptide (ANP) is secreted by the cardiac muscle cells in response to an expanded extracellular fluid, and its natriuretic effect can contribute to hemoconcentration. The atrial natriuretic peptide is increased in untreated OSA patients and levels decrease during treatment with CPAP, suggesting a possible role in increased hemoglobin and hematocrit levels due to hemoconcentration [5].

Platelets play a crucial role in hemostasis and thrombosis. Platelet activation can increase blood viscosity which mediates between systemic inflammation and cardiovascular risk. Several platelet indices are usually part of the hemogram that can be used as markers of activity. Mean platelet volume (MPV) refers to the average size of circulating platelets and is associated with several cardiometabolic risk factors and cardiovascular events.

MPV is significantly increased in patients with OSA and could be used as a marker to predict cardiovascular disease in this group [6]. Furthermore, one study showed that six months of CPAP therapy causes significant reductions in the MPV values in patients with severe OSA [7]. However, MPV can be influenced by many factors such as age, gender, or blood sample processing, reducing the specificity of this parameter [8].

Platelet distribution width (PDW) refers to the variance in the size of circulating platelets. High PDW has been correlated with AHI in OSA, and CPAP can decrease this parameter [9].

Activated platelets can interact with leukocytes and neutrophils forming aggregates. Also, activated platelets can stimulate neutrophils, promoting the formation of neutrophil–lymphocyte complexes. Among other situations, the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) increase in systemic inflammation and cardiovascular diseases. The PLR value in OSA patients has been found to be less than the control group, showing an inverse correlation with AHI. In the same study, NLR increased as the time spent during the sleep with a lowering of arterial oxygen saturation below 90% [10].

27.2 Inflammatory Markers

OSA, inflammation, and cardiovascular risk are interconnected. It is well known that chronic vascular inflammation is related to the development of atherosclerosis, which is now considered an inflammatory disease. In addition to activating the sympathetic nervous system and derangement in endothelial function, OSA patients have a higher expression of systemic inflammatory markers [11]. The proinflammatory state associated with OSA is related to intermittent hypoxia, since cycles of hypoxia and reoxygenation are similar to ischemia-reperfusion injury which promotes oxidative stress [12]. Therefore, it is not easy to determine whether OSA itself or the obesity usually associated is responsible for this rise since obesity is associated with a proinflammatory state.

C-reactive protein (CRP), produced in the liver through interleukin-6 (IL-6) activity, is one of the most used inflammatory markers in clinical practice, and its elevated levels have been associated, among others, with diabetes or cardiovascular disease. Several studies have reported increased levels of CRP in OSA patients, and these levels tend to decrease with effective treatment. However, other studies have failed to confirm this relationship, suggesting that the association between OSA and CRP levels is influenced by other factors like obesity or diabetes [13].

IL-6 is an important proinflammatory cytokine that induces the synthesis of all acute-phase proteins, including CRP. Other biological activities of IL-6 are proliferation and differentiation of lymphocytes or immunoglobulin secretion. Similar to CRP, elevated levels of IL-6 are associated with higher cardiovascular risk through the propitiation of a proinflammatory state. Several meta-analyses confirm an increase in IL-6 in patients with OSA [14].

Tumor Necrosis Factor Alpha (TNF-α) is a proinflammatory cytokine secreted by immune cells and mediates the pathogenesis of several diseases such as cancer, atherosclerosis, or autoimmune diseases. A recent meta-analysis found a significant association between OSA and elevated TNF-α levels in adults. In this investigation, TNF-α levels were correlated with OSA severity [15].

Fibrinogen is a glycoprotein involved in the thrombogenesis process. Fibrinogen also acts as an acute-phase protein, and high levels are associated with inflammation and cardiovascular disease. Recently two meta-analysis showed that circulating fibrinogen levels are elevated in patients with OSA [16] and that CPAP treatment can reduce plasma fibrinogen levels in OSA patients, suggesting that elevated fibrinogen levels may be a link between OSA and cardiovascular disease [17].

Other inflammatory markers such as interleukin 8 (IL-8), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and selectins have also been found to be increased in patients with OSA [11].

27.3 Glucose Metabolism

Type 2 diabetes is associated with an increased risk of developing OSA. Patients with type 2 diabetes (T2D) have an increased adjusted incidence rate ratio (1.48) of OSA compared with those without [18]. However, positive airway pressure (PAP) therapy has failed to improve glycemic control in type 2 diabetes patients [19]. One mechanism that may mediate this association is insulin resistance, which is independently associated with OSA [20].

Diabetes mellitus is a heterogeneous disease of glucose metabolism characterized by impaired ability to produce or respond to insulin. Diabetes is characterized an elevated blood glucose level that, sustained over time, can be associated with the development of microvascular and macrovascular complications (retinopathy, nephropathy, neuropathy, and vascular disease). The most common form of diabetes is type 2 diabetes (T2D), which occurs more frequently in middle-aged and elderly people. There are several pathophysiological factors involved in T2D, among which the presence of obesity and insulin resistance stands out. Diabetes may be

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Fig. 27.1 Criteria for the diagnosis of diabetes*DCCT* Diabetes Control and Complications Trial, *FPG* Fasting plasma glucose, *OGTT* Oral glucose tolerance test, *WHO* World Health Organization, *2-h PG* 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Fig. 27.2 Criteria defining prediabetes**FPG* Fasting plasma glucose, *IFG* Impaired fasting glucose, *IGT* Impaired glucose tolerance, *OGTT* Oral glucose tolerance test, *2-h PG* 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range

diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or glycated hemoglobin (A1C) criteria (see Fig. 27.1). Prediabetes is the term used for individuals whose glucose levels do not meet the criteria for diabetes yet have abnormal glucose metabolism (see Fig. 27.2) [21].

Insulin resistance or impaired insulin sensitivity is a complex temporary or chronic condition in which muscle, liver, and fat cells don't respond as they should to insulin. Genetic predisposition, overweight or obesity (especially central obesity),

HOMA-IR= (fasting glucose in mmol/L x fasting insulin in μIU/mL)/22.5

HOMA-IR= (fasting glucose in mg/dL x fasting insulin in μIU/mL)/405

QUICKI = 1/[log (fasting insulin, U/ml) + log (fasting glucose, mg/dl)]

$ISI(Matsuda) = 10{,}000/\sqrt{[(Glucose_{fasting} \times Insulin_{fasting}) \times (Glucose_{OGTT}mean \times Insulin_{OGTT}mean)]}$

Fasting glucose and insulin data are taken from time 0 of the OGTT and mean data represent the average glucose and insulin values obtained during the entire OGTT

Fig. 27.3 Equations for the calculation of insulin resistance and insulin sensitivity indices

and a sedentary lifestyle contribute to the development of insulin resistance, favoring the elevation of plasma glucose [22]. Insulin resistance plays a pathophysiological role in T2D but is also associated with other entities such as obesity, hypertension and dyslipidemia, conditions that define the metabolic syndrome. There are various laboratory tests to assess the degree of insulin resistance being the gold standard the hyperinsulinemic-euglycemic glucose clamp. But this test is expensive and technically complex, so in epidemiological studies or daily clinical practice, the most suitable are the homeostatic model assessment for insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI), and Matsuda index.

The calculation of HOMA-IR is simple from fasting glucose and insulin. HOMA-IR has a good correlation with hyperinsulinemic-euglycemic glucose clamp. The higher the HOMA-IR, the higher the insulin resistance. However, there is significant variability in the threshold HOMA-IR levels to define insulin resistance, and there is no universal consensus on the reference values for the indices described, but published studies usually set it at a value >2–2.5 (see Fig. 27.3) [23].

QUICKI is an empirically derived mathematical transformation of fasting blood glucose and plasma insulin concentrations that provide a reliable, reproducible, and accurate insulin sensitivity index. It is derived simply from fasting glucose and insulin values. It correlates well with the hyperinsulinemic-euglycemic glucose clamp and measures insulin sensitivity, the inverse of insulin resistance. Thus, higher QUICKI levels are related to higher insulin sensitivity and lower levels of insulin resistance (see Fig. 27.3) [24].

Matsuda index is an insulin sensitivity index that reflects a composite estimate of hepatic and muscle insulin sensitivity determined from OGTT data. It is more complex than the previous one since it requires the performance of an OGTT, but this is not a particularly expensive or difficult test to perform and is frequently used in daily clinical practice (see Fig. 27.3) [24].

27.4 Metabolic Syndrome and Lipid Metabolism

Metabolic syndrome is a term applied to the coexistence in the same individual of abdominal overweight/obesity, dyslipidemia, type 2 diabetes, and high blood pressure. This combination of factors increases cardiovascular risk. Although there are

different diagnostic criteria for metabolic syndrome, it is estimated that up to a third of the adult population may present it. Obstructive sleep apnea has been associated with metabolic syndrome or its core components. The pathophysiological mechanisms previously described in the relationship between obesity, diabetes, and OSA are also found in the relationship with metabolic syndrome. Thus, the beneficial effects of CPAP on glucose metabolism and insulin resistance in patients with OSA are not constant in all the studies carried out [25].

Data from the European Sleep Apnea Database Cohort (ESADA) showed that OSA severity was independently associated with cholesterol and triglycerides concentrations [26]. Furthermore, OSA was positively associated with serum triglyceride levels in men with a normal waist circumference [27].

Although there are different diagnostic criteria, according to the guidelines from the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA), metabolic syndrome is diagnosed when a patient has at least three of the following five conditions [28]:

- Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia)
- Blood pressure ≥130/85 mmHg (or receiving drug therapy for hypertension)
- Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
- HDL cholesterol <40 mg/dL in men or <50 mg/dL in women (or receiving drug therapy for reduced HDL cholesterol
- Waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women

Dyslipidemias are lipid metabolism alterations with altered lipid concentrations, both by excess (hyperlipidemia) and by defect (hypolipidemia). Dyslipidemia is diagnosed routinely by measuring the serum lipid profile in fasting state that includes total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol. Unlike the other elements of the lipid profile, which are measured directly, LDL cholesterol is calculated from the Friedewald formula: LDL cholesterol = Total cholesterol − [HDL cholesterol + (triglycerides/5)]. A triglyceride level above 400 mg/dL invalidates the use of this formula. The main therapeutic target is LDL cholesterol since, it is the main cardiovascular risk factor within the lipid profile. However, although severe, hypertriglyceridemia (>500–1000 mg/dL) can be associated with pancreatitis and constitutes a therapeutic priority when it appears. Other parameters that study lipid metabolism and of diagnostic and therapeutic interest are Apolipoprotein B, non-HDL cholesterol, and Lipoprotein(a) [29].

27.5 Adipokines

Adipokines or adipocytokines are peptides and proteins secreted mainly by adipocytes and play diverse roles in body homeostasis. Adipose tissue has emerged as a metabolically active tissue implicated in many processes such as metabolism,

inflammation, and cardiovascular diseases. Current evidence suggests that adipokines may play a role in the complex relationship between OSA and metabolic disorders.

Leptin is a major adipokine that promotes satiety and is secreted mainly by the adipocytes of the white adipose tissue. Leptin is positively correlated with fat mass. Data suggest that long-term exposure to chronic intermittent hypoxia, as occurs in OSA, may contribute to leptin resistance, which negatively affects the control of food intake [30].

Adiponectin is another adipokine that improves insulin sensitivity and cardiovascular health. Patients with severe OSA have been shown to have lower levels of adiponectin. Also, improvement in sleep quality is associated with increased serum adiponectin levels [31].

An adipokine abundantly expressed in visceral fat, Visfatin, has an insulin-mimetic effect. Circulating visfatin levels are elevated in obesity, diabetes, or metabolic syndrome. In patients with severe OSA, visfatin levels were correlated positively with sleep latency and negatively with total sleep time and percentage of stage 2 and REM sleep [32].

Chemerin, among other actions, regulates adipogenesis and inflammation. Several studies have shown that chemerin levels are an independent determinant of OSA and correlated with the severity of OSA [31].

27.6 Urinary Parameters

First, it should be remembered that OSA can affect the urinary pattern, making the collection of samples for analysis more complicated. For example, Nocturia (waking up to urinate one or more times during the night) is more frequent in patients with moderate or severe OSA than in patients with mild OSA [33]. In addition, overactive bladder prevalence rates range from 49.6% to 79.3% in patients with OSA, and CPAP treatment can improve symptoms [34].

OSA is highly prevalent in patients with chronic kidney disease and is associated with accelerated renal dysfunction through several mechanisms such as hypertension, activation of the renin-angiotensin system, or hypoxia. In patients with end-stage renal disease, fluid overload contributes significantly to OSA [35].

Microalbuminuria is a marker of renal damage and is used as a diagnostic tool for early kidney dysfunction. OSA is associated with increased microalbuminuria, as indexed by the urinary albumin-to-creatinine ratio, depending on the severity of the disease and hypoxemia [36].

The relationship between OSA and hypertension may be produced by activation of the sympathetic nervous system induced by hypoxic stress and mediated by the release of catecholamines. Thus, OSA is associated with increased urinary concentrations of metabolites of catecholamines (normetanephrine and metanephrine), suggesting increased sympathoadrenal activity [37]. CPAP treatment significantly reduces urinary or plasma catecholamines and their metabolites, suggesting an intermediary role in the relationship between OSA and hypertension [38].

Sestrin2 is a crucial factor involved in oxidative stress. One study showed a higher urinary level of Sestrin2 in OSA patients and increased OSA severity, while it reduced with CPAP treatment [39].

Lipocalin-type prostaglandin D synthase is responsible for the biosynthesis of prostaglandin D2 and has been reported to be associated with cardiovascular disease and sleep regulation. Urinary Lipocalin-type prostaglandin D synthase has been linked with the AHI [40].

Take-Home Messages

- A significant positive correlation between RDW and apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) has been found.
- Several studies have reported increased levels of CRP, IL-6, Tumor Necrosis Factor Alpha (TNF-α), Fibrinogen, interleukin 8 (IL-8), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and selectins in OSA patients.
- OSA is associated with changes in glucose, lipid metabolism, adipokines and urinary parameters.

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Genetics of Obstructive Sleep Apnea

28

Ana Patiño-García

28.1 General Aspects of Obstructive Sleep Apnea Genetics

The prevalence of obstructive sleep apnea (OSA) is high, and its effects are potentially severe, leading to cardiometabolic disorders and increased cardiovascular risks. However, the unavailability of biomarkers for OSA makes diagnosing this disease an unmet need. In addition, ideal biomarkers should be able to identify the disease, correlate with severity, and give information about treatment outcomes and potential complications/comorbidities. These biomarkers can be different: DNA (single-nucleotide polymorphisms, SNPs, mutations, etc.), RNA (gene expression), miRNA (microRNA, posttranscriptional regulation), epigenetic modifications (methylation for gene expression regulation) and/or proteins, and their different nature and applications will be discussed in this chapter (Fig. 28.1).

OSA is a very complex trait from the clinical and genetic points of view. It is most probably conditioned by a plethora of low-risk genes, their interactions, and their interplay with a network of environmental factors. There is increasing evidence that OSA is a heritable, but maybe not an inherited, trait. Heritability is often defined as the variation of a given trait that can be attributed to genetic variation. It is used to estimate the risk of traits conditioned by multiple low-risk genetic variants interacting with complex multifactorial clinical variables. The estimation of heritability in complex traits such as OSA is highly influenced by the design of the analyses and the nature of the trait, mainly by the sample size, the different genetic backgrounds, and by the variability in the included phenotypes. Ovchinsky et al. performed a study with 445 first-degree relatives of 115 children with OSA. They concluded that 12.2% of the pediatric relatives had symptoms suggestive of OSA,

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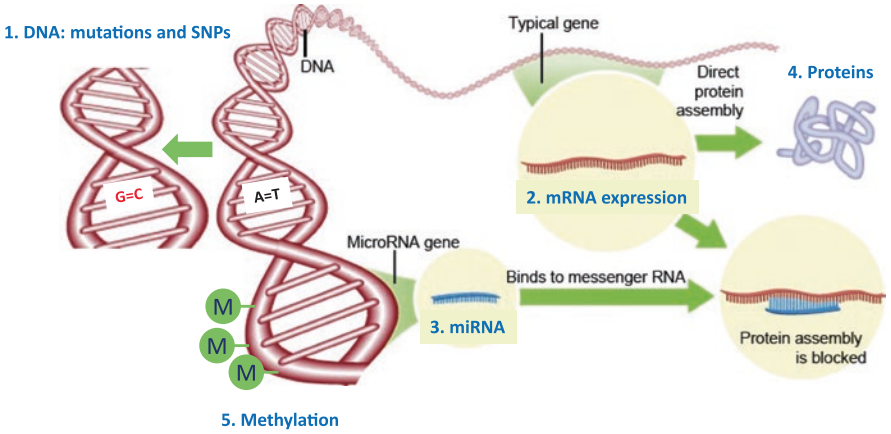

Fig. 28.1 Types of molecules that can be considered as biomarkers for OSA or OSA-related phenotypes

supporting the heritability of this trait [1]. Other research indicated that OSA prevalence in first-degree relatives of patients with OSA ranges from 22% to 84%. The OR of a first-degree relative having OSA ranges from 2 to 46 [2].

In addition, several studies suggest that around 40% of the apnea–hypopnea index (AHI) variance can be explained by genetic factors, and twin and family studies indicate that related phenotypes like ventilatory responsiveness to either hypoxemia or hypercapnia, obesity, craniofacial morphology also have heritabilities ranging from 30% to 70% [3].

28.2 Types of Analysis Aimed to the Identification of Sleep Apnea Biomarkers and Results Obtained

In general, the types of studies that aim for the identification of associations between genes and OSA can be included in different categories (Fig. 28.2):

1. **Linkage Analyses:** these studies rely on analyzing a high (or low) number of markers in pedigrees segregating a given complex trait. The design can include or not a segregation model in the family, being the model-free linkage analysis the most frequently used for complex traits with unknown inheritance patterns like OSA. Other approaches are gradually substituting this type of study.

   Palmer and colleagues [4] conducted a genome-wide analysis of 349 subjects belonging to 66 pedigree families sampled from the Cleveland Family Study (ref). They performed a multipoint model-free linkage analysis and identified candidate regions with evidence for linkage with AHI in chromosome regions 1p, 2p, 12p, and 19. Only the 2p region remained significant after adjusting for body mass index (BMI). They concluded that there is shared and unshared genetic variability underlying both OSA and obesity and that there may be shared pathways regulating both AHI and BMI.

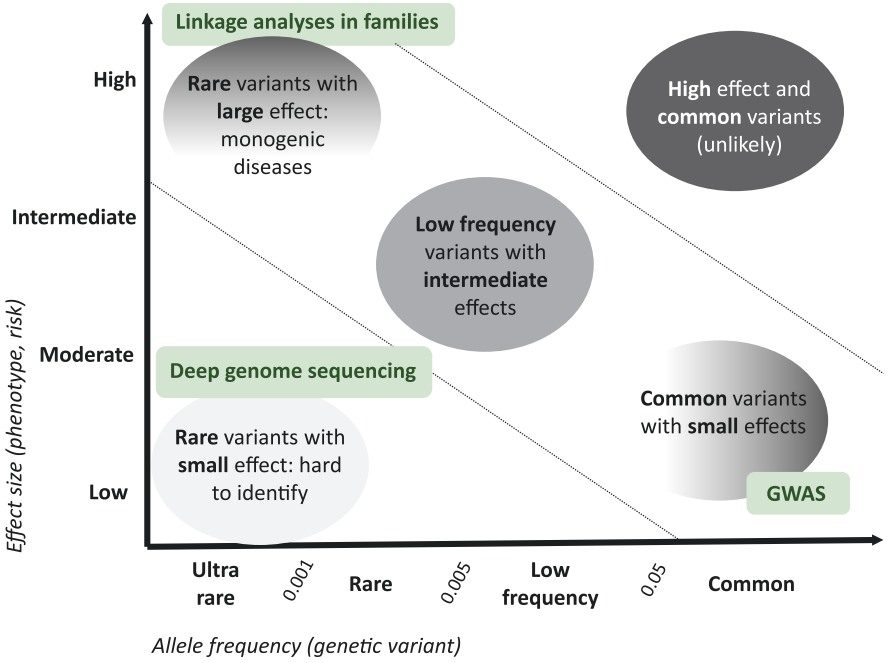

Fig. 28.2 Types of analysis and study designs for the identification of associations between genes and OSA

2. **Genome-wide association studies (GWAS)** have a case/control design with a high number of patients and controls to identify genetic variants that are differentially enriched between groups. This design relies on testing common genetic variants (MAF $\geq$ 5%). This hypothesis-free approach consists of scanning high-density markers distributed across the genome to identify genetic loci associated with a complex disease. GWAS findings are often not validated in further analyses due, among other factors, to the strict significance threshold. It is suggested that a gene should be considered positive if it reaches a genome-wide significance in any GWAS, either if it is validated or not [5].

   In addition, as a range of factors influence OSA, genes underlying OSA can affect one or more of these factors, making it critical to carefully consider which elements to include in any GWAS approach for OSA.

   The International Sleep Genetic Epidemiology Consortium (ISGEC) has already completed a study investigating the risk of moderate/severe OSA by conducting a GWAS in case and control samples from 9 independent European ancestry cohorts. In total, 8336 cases and 76,663 controls were investigated and although several analyses are ongoing, results have not yet been published.

   The GWAS database, known as the "GWAS catalog," hosted by the NHGRI-EBI, is a publicly available resource of published human GWAS ([6] https://www.ebi.ac.uk/gwas/downloads). This database, accessed on April 2,2022, includes three publications and five traits in its last data release on March 23, 2022:

(a) Publications:
- Genome-wide association study reveals two novel risk alleles for incident obstructive sleep apnea in the EPISONO cohort. Farias Tempaku P et al. 2019 Sleep Med PMID:31786426.
- Multi-ethnic Meta-analysis Identifies RAI1 as a Possible Obstructive Sleep Apnea Related Quantitative Trait Locus in Men. Chen H et al. 2017 Am J Respir Cell Mol Biol PMID:29077507.
- Genetic Associations with Obstructive Sleep Apnea Traits in Hispanic/Latino Americans. Cade BE et al. 2016 Am J Respir Crit Care Med PMID:26977737.

(b) Traits:
- Obstructive sleep apnea: 36 associations and 6 studies.
- Sleep apnea measurement: 117 associations and 27 studies.
- Sleep apnea measurement during REM sleep: 7 associations and 1 study.
- Sleep apnea measurement during non-REM sleep: 0 associations and 1 study.
- Sleep apnea: 38 associations and 16 studies.

Another recent GWAS on 12,558 Hispanic American ancestry participants considered different OSA-associated phenotypes, including AHI, mean oxygen saturation, and mean apnea and hypopnea duration. The associations detected were between a marker in *GPR83* and AHI and between the *ARRB1* gene and average apnea and hypopnea duration, which is interesting due to its function as a regulator of HIF1α, which plays a critical role in hypoxic sensitivity [7].

In a recent publication, the Finnish group of Strausz and coworkers conducted a large-scale GWAS of OSA using the FinnGen study ([8] https://www.finngen.fi/en) with 16,761 OSA patients. They identified the following *loci* associated with OSA: rs4837016 near *GAPVD1*, rs10928560 near *CXCR4*, rs185932673 near *CAMK1D*, rs9937053 near *FTO*. They identified a correlation between OSA and BMI and other comorbidities and a causal relationship between the two phenotypes [9].

The study of Baik and coworkers aimed to identify genetic variants associated with OSA and their effect on the association with OSA risk factors, namely obesity, and alcohol consumption. In their analysis, rs10097555, a common polymorphism of the *NRG1* gene (neuregulin-1) was the most significant association with OSA. Among 1763 participants, the *NRG1* polymorphism was inversely associated with OSA, and the association was modified by alcohol consumption [10].

3. **Candidate Gene Association Studies**, designed to identify pathogenic, rare and infrequent variants that can account for an important part of the phenotype. Sometimes, the candidate gene approach focuses on assessing single-nucleotide polymorphisms (SNPs) within genes that have a known role in a specific trait or disease. The genes with the strongest association with OSA are *APOE* (apolipoprotein E), *ACE* (angiotensin-converting enzyme), and *TNFRSF1A* (tumor

necrosis factor-alpha) [11]. Also, different SNPs in serotonin receptors and transporter genes (5-HT2A, 5-HT2C, 5-HTT) have been associated with OSA in given populations [12].

A considerable candidate gene association study for OSA using the Cleveland Family Study, consisting of European-American and African American subsamples, investigated 45,000 SNPs from approximately 2100 candidate genes. Only an SNP in the *PLEK* (pleckstrin) gene, rs7030789, within the African American subset and rs1409986 in the *PTGER3* gene (prostaglandin E2 receptor) in the European subsample were found to be associated with OSA [13]. In addition, in African Americans, an SNP in the *LPAR1* gene (lysophosphatidic acid receptor I) showed a genome-wide association with a quantitative measure of OSA severity, AHI [14].

4. **Whole-genome sequencing (WGS)** or deep genome sequencing can identify a complete set of DNA sequence variants. It can be achieved using next-generation sequencing (NGS) based on different sequencing platforms. As indicated in Fig. 28.1, WGS aims to assess the role of low frequency (MAF 1%–5%) and rare (MAF ≤1%) genetic variation. A variation of the technique, often less time and cost consuming, is **whole-exome sequencing** (WES), which relies on sequencing only the coding part of the genome.

   In a recent study, van der Spek and coworkers performed WES meta-analysis of symptoms of OSA in 1417 individuals of European descent. They identified 17 rare genetic variants with evidence of association in an identification cohort. Validation in an independent dataset confirmed the association of rs2229918 with symptoms of OSA, and this genetic marker overlaps with the 3′ UTR (untranslated region) of *ERCC1* and *CD3EAP* genes on 19q13 [15].

There are likely different phenotypic pathways to OSA, including obesity, usually the main confounding factor, neuronal control of respiration, upper airway morphology, craniofacial features, each with distinct genetic contributions. Thus, some researchers suggest that the search for genetic factors may be most fruitful if it is focused on each of the relevant intermediate traits and associated phenotypes [16, 17].

Li and coworkers analyzed five patients with severe OSA and paired controls using NGS to express genes associated with Alzheimer's disease (AD) since AD risk is known to be associated with OSA. They identified a differential expression of *CCL2, IL6, CXCL8, HLA-A*, and *IL1RN* in patients with severe OSA, which also significantly contributed to changes in the immune response, cytokine–cytokine receptor interactions, and nucleotide-binding oligomerization domain-like receptor signaling pathways [18].

In addition, some authors have used high throughput **expression assays** and reported differential expression of genes related to endothelial junction, proapoptotic and inflammatory gene signatures. Chen et al., aimed to identify molecular markers of chronic intermittent hypoxia with reoxygenation and adverse consequences in OSA in 48 patients with sleep-disordered breathing. In their analysis, AMOT P130 protein expression, an endothelial tight junction, was increased in

OSA patients with excessive daytime sleepiness. In addition, the proapoptotic proteins BIRC3 and LGALS3 were associated with OSA patients with hypertension and chronic kidney disease, respectively [19].

Other genetic biomarkers such as miRNA (micro-RNA) profiling and DNA methylation have been much less used as potential bridges to the gap between the pathophysiology and the clinical manifestations of OSA. These miRNAs are small noncoding RNAs that can regulate gene expression at the posttranscriptional level. Specific miRNAs are robust biomarkers for risk estimation, for example, in obese patients. Since obesity and other comorbidities are associated with OSA, identifying a miRNA signature would allow for the understanding of the pathophysiology of the disease at the molecular level. Still, but these data are not available today [20]. DNA methylation involves adding a methyl group to cytosine, thereby regulating gene expression in physiology and disease. Very few studies are available on the role of DNA methylation in OSA, but there are some related to OSA-related phenotypes. For example, hypoxia can lead to modification in the promoter methylation of *AR*, *NPR2*, *L1R2,* and *SP140* [21], and the methylation of other genes such as *FOXP3* and *IRF1* are determinants of inflammation [22].

Finally, some researchers have approached the association of biomarkers and OSA from the **protein** side. Recently, Ambati and coworkers [23] profiled over 1300 proteins in the serum of 713 individuals affected of OSA patients. They concluded that obstructive apnea–hypopnea index (OAHI) was related to increased proteins of the complement, coagulation, cytokine signaling, hemostasis pathways, and ROBO3, IGFBP3, and LEAP1 with different outcome measures. The analysis of these secreted markers achieved a 76% accuracy for identifying OSA. Other studies used either ELISA or Luminex to profile differences in OSA using plasma serum or CSF (cerebrospinal fluid) and showed associations with elevated Tau and amyloid-beta in CSF and elevated IL6, CRP, insulin, and high monocyte to HDL ratio in plasma. Other groups have tried to characterize the cognitive impairment in OSA by profiling a 254-serum protein panel by Luminex and identified an insulin-related signature. Finally, the red blood cell proteome characterization in OSA patients identified associations with proteins involved in response to stress or dysregulation of lipids (reviewed in [23]).

28.3 Conclusion

OSA is a complex disease with many potential genetic and environmental factors that combine and interact to produce the disease. The identifications and biomarkers for the disease and its comorbidities, and the underlying genetic background will probably involve the analysis of a high number of samples with whole-genome sequencing data. There are ongoing international efforts in GWAS and NGS and other massive technologies that will probably lead to the in-depth profiling of this disease in the coming years.

Take-Home Messages

- OSA is a very complex trait from the clinical and genetic points of view.
- It is conditioned by a plethora of low-risk genes, their interactions, and their interplay with a network of environmental factors.
- There are different genetic biomarkers of OSA as well as the different types of study designs for their identification, namely linkage analyses, genome-wide association studies (GWAS), candidate gene association studies, and whole-genome or exome sequencing by next generation sequencing (NGS).

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Maxillofacial Surgery in OSA

29

Stanley Yung-Chuan Liu and Kristoffer Schwartz

29.1 Diagnostic Features

29.1.1 Patient Selection

Maxillofacial surgery to treat OSA was first integrated into a systematic approach popularized by Riley and Powell of Stanford. The 2-phase approach begins with multilevel surgery with nasal surgery, uvulopalatal flap, and genioglossus advancement (GGA). In the 40% of patients that do not respond to phase 1, phase 2 may be offered. Phase 2 was characterized by maxillomandibular advancement (MMA). It was known from early in the surgical management of OSA that for select patients, both skeletal and soft tissue interventions were necessary and complementary for treatment success [1–3].

The protocol has since been updated at Stanford to incorporate medical and surgical interventions on a continuum of care for OSA patients. There has been advancement in the precision of phenotyping patients who are likely to achieve success with maxillofacial surgery. The cornerstones remain the same, with the careful interpretation of polysomnography (PSG) data, static and dynamic airway examination, including drug-induced sleep endoscopy (DISE) and facial skeletal analysis (Fig. 29.1). As part of surgical decision-making, it remains critical to account for patient preferences, expectations, and risk–benefit profile [4–6].

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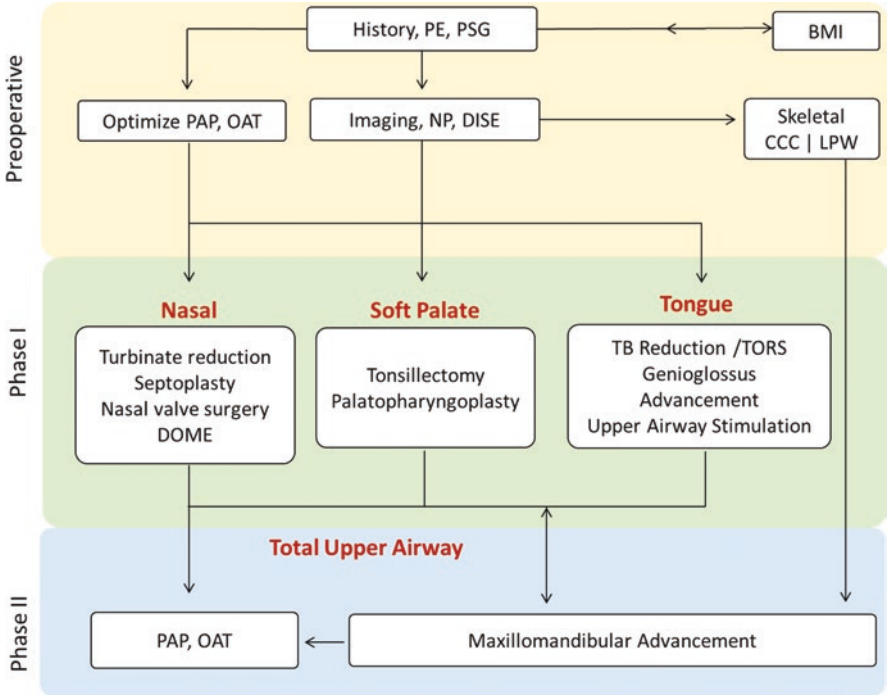

Fig. 29.1 Stanford protocol with medical and surgical interventions. *BMI* Body Mass Index, *PSG* Polysomnography, *PE* Physical examination, *PAP* Positive Airway pressure, *OAT* Oral appliance therapy, *CCC* Complete Concentric Collapse, *LPW* Lateral Pharyngeal wall, *TB* Tongue Base, *TORS* Trans Oral Robotic Surgery, *DOME* Distraction Osteogenesis Maxillary Expansion

29.1.2 Polysomnography

Polysomnography (PSG) is the gold standard for diagnosing and evaluating the severity of OSA, although it may not reflect the patient's condition over time [7]. Severity of OSA is defined using the apnea–hypopnea index (AHI). Studies have shown that the oxygen desaturation index (ODI) correlates more strongly with cardiovascular morbidity than AHI alone [8]. Ambulatory sleep study with cardiorespiratory monitoring (CRM) is easier to obtain than attended PSG in patients with a high risk of OSA, but it can underestimate OSA severity [9]. Surgical success can be evaluated using the same diagnostic sleep studies and hypopnea criteria before and after surgery [10]. It is important to note that AHI alone as an indicator of success is increasingly inadequate to characterize the complexity of OSA-related symptoms and comorbidity. As an index, it does not fully capture changes in sleep architecture and does not account for developmental and aging changes, or gender and ethnic differences [11]. The PSG offers a wealth of information, and the contemporary sleep surgeon needs to interpret the study beyond the AHI.

29.1.3 Clinical Examination

Clinical examination involves a comprehensive medical history with a meticulous sleep-specific history and a full head and neck examination including the nasal airway, velopharynx, pharyngeal wall, tongue base, epiglottis, and facial skeletal relationship [5].

Endoscopic examination of the nasal airway should identify all possible anatomic and functional causes of nasal obstruction [12]. The negative pressure maneuver (Muller's maneuver) can be performed simultaneously and is a quick method to assess upper airway collapsibility [13]. A mandibular protrusion maneuver can also be performed simultaneously to visualize the degree of lateral pharyngeal wall dilation and tongue base advancement. Examination of the facial skeletal relationship is essential for diagnosing dentofacial contributors to sleep-disordered breathing. Long-term nasal obstruction can often lead to facial changes, a long midface, anterior open bite, and retrognathic mandible. Examination of the mouth and dentition may reveal a high-arched and narrow maxilla with the appearance of a relatively large tongue and excessive soft palatal tissue.

29.1.4 Diagnostic Tools

Lateral cephalometric X-ray has been used since the early days of evaluating maxillofacial morphology in OSA patients. It allows for an easy and direct visual assessment of the anterior-posterior airway space [14, 15]. Compared to lateral cephalometric X-ray, computed tomography (CT) or cone beam computer tomography (CBCT) significantly improves soft tissue contrast and provides information regarding upper airway cross-sectional area at different levels. Image processing allows three-dimensional reconstruction and volumetric assessment [16].

For the evaluation of soft tissue structures, magnetic resonance imaging (MRI) provides advantages such as excellent soft tissue contrast, three-dimensional assessment of tissue structure, and lack of ionizing radiation. Dynamic sleep MRI is a diagnostic tool that allows simultaneous real-time evaluation of airway obstructions and respiratory events during natural sleep. Dynamic sleep MRI can characterize the actual site of dynamic airway obstruction and potentially improve predictions of successful surgical outcomes in OSAS patients [17]. It is important to note that while retropalatal and retrolingual collapse is common with OSA of all severity, lateral pharyngeal wall collapse during dynamic MRI with a low hyoid bone position have been shown to predict severe OSA [18].

Drug-induced sleep endoscopy (DISE) has shown to be important in optimizing surgical outcomes in OSA patients. With DISE, clinicians can visualize and phenotype pharyngeal muscle collapse that varies in morphology and degree at distinct levels of the upper airway [19] (Fig. 29.2). There is no consensus regarding standardized protocols for DISE. However, the procedure is usually performed in the supine position in an outpatient setting with monitoring of oxygen

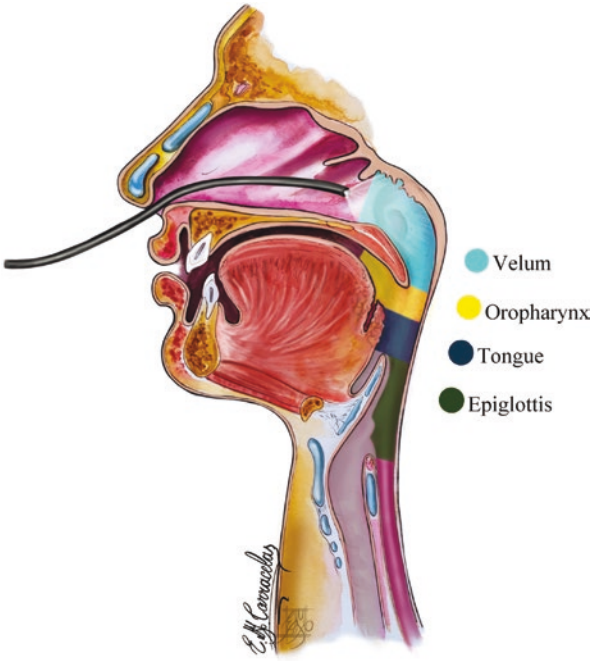

Fig. 29.2 DISE (Drug Induced Sleep Endoscopy): allows visualization and phenotype pharyngeal muscle collapse that varies in morphology and degree at distinct levels of the upper airway

saturation, heart rate, blood pressure, and sometimes bispectral index score. Sedation is commonly initiated with propofol, dexmedetomidine, and midazolam. The depth of sedation is crucial and is evaluated by the onset of the disordered breathing or the Bispectral index score [20]. Several classification systems have been introduced to characterize DISE findings in OSA patients [19, 21]. The VOTE classification system, which comprises the Velum, Oropharyngeal (lateral walls), Tongue, and Epiglottis, is widely used for DISE scoring [22]. Multilevel collapse is the most common finding from DISE, and patterns of complete concentric collapse, multilevel collapse, and tongue base collapse are associated with a higher AHI [23].

A complete concentric collapse has been associated with unfavorable surgical outcomes in multilevel surgery and is currently a contraindication for upper airway stimulation [24–26]. In the updated Stanford Sleep Surgery Protocol, patients presenting with both complete concentric collapse of the velum, and complete lateral pharyngeal wall collapse, may be recommended maxillomandibular advancement (MMA) as first-line surgical therapy. This is based on studies showing that MMA addresses these two collapse patterns more reliably than soft tissue or upper airway stimulation procedures [24, 25, 27, 28] (Fig. 29.3).

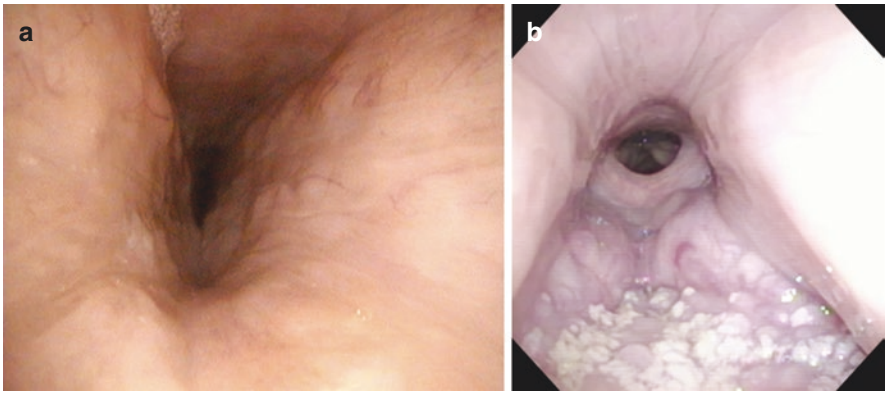

Fig. 29.3 DISE allows visualization of airway collapse sites. DISE before and after maxillomandibular advancement (MMA). (**a**) Pre MMA pharyngeal collapse. (**b**) An important improvement of airway is observed. Post MMA pharyngeal collapse

29.2 Genioglossus–Genioplasty Advancement

29.2.1 Introduction

Genioglossus advancement (GA) was first described in 1984 by Robert Riley and Nelson Powell to improve outcomes in patients with obstructive sleep apnea (OSA) who did not improve sufficiently with palatal surgery [29]. Their initial technique with a modified horizontal mandibular osteotomy was improved in 1986 to include a limited inferior parasagittal mandibular osteotomy (anterior mandibular osteotomy) [30]. Electromyographic studies have identified the genioglossus muscle as the major pharyngeal dilator musculature of the airway during sleep. Its role has been extensively implicated in the pathophysiology of OSA with the rationale that the upper airway collapse occurs with failure of the dilator muscle to sustain patency during the respiratory cycle [31]. The genioglossus muscle is attached to the genial tubercles of the mandible. By advancing the genial tubercles, the genioglossus muscle lengthens and strengthens over time to allow greater tongue advancement during sleep [3]. GA is usually performed in conjunction with other sleep surgery procedures (uvulopalatopharyngoplasty, maxillomandibular advancement) [32]. Variations to the GA procedure include the trephine osteotomy, genioplasty with genioglossus suspension sutures, and combining the GA with a genioplasty [33]. With the wide availability of CT scans and the development of virtual-surgical-planning (VSP), using 3-dimensional (3D) printing of medical-grade cutting guides has allowed the contemporary GA to be more precise and predictable [34]. GA and genioplasty can often be performed in conjunction to improve facial balance in mandibular hypoplastic OSA patients, which also exerts a strengthening effect on the suprahyoid muscles [35]. The surgical success rate of GA surgery as an isolated treatment of OSAS ranges from 43% to 53% [32, 36].

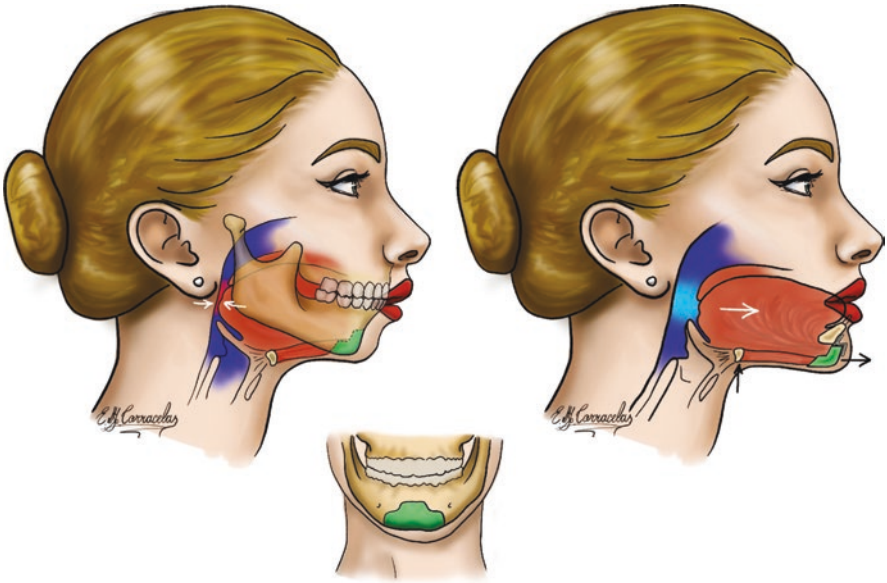

Fig. 29.4 Genioglossus advancement (GA). Improvement of the airway collapse at the level of the tongue base is seen with a mild modification of the chin area that has been displaced anteriorly at the level of insertion of the genioglossus muscle

29.2.2 Indications

Isolated GA, or combined with a genioplasty (GGA), is typically one component of multilevel sleep surgery for OSA. The primary indication for GA is airway obstruction at the hypopharyngeal level, especially in conjunction with a retruded position of the tongue base, in the absence of lingual tonsillar hypertrophy. OSA patients with mandibular retrognathism and microgenia will benefit from GA in combination with a genioplasty (GGA), as it addresses hypopharyngeal obstruction and dentofacial deformity (Fig. 29.4).

29.2.3 Surgical Technique

GA is performed under general anesthesia. A reinforced oral endotracheal tube is secured to either lip commissure allows adequate exposure of the surgical field. A vestibular incision is made 1.5 to 2.0 cm from the mucogingival junction, through the labial mucosa. At this point, the approach is perpendicular to the distended lower lip. Once the mentalis muscles are identified, the approach takes an oblique path toward the inferior border of the anterior mandible prior to subperiosteal dissection to access the bone. This detail during the approach is essential because, without it, there would often be inadequate muscle and mucosal cuff to close with the advanced bone graft.

Subperiosteal dissection is extended bilaterally along the inferior border until the mental nerve is identified on both sides. For an isolated GA (anterior mandibular osteotomy) only, identification of the genial tubercle can be made by palpating the floor of the mouth or measuring its position from the preoperative CT. However, with a preoperative CT scan, a 3-dimensional (3D) cutting guides can be made to direct osteotomy toward the exact location of the genial tubercle. A rectangular osteotomy is made through the outer cortex. The osteotomy is typically 10 mm by 20 mm and the superior osteotomy should be places a least 5 mm inferior to the root apices. To avoid mandibular fracture, the inferior osteotomy should be approximately 8 mm above the inferior border of the mandible. A bicortical screw is placed though the center of the rectangular osteotomy to allow manipulation of the bone fragment. The osteotomy cuts are then completed through the inner cortex. Maintaining parallel walls in the osteotomy cuts is important to prevent tapering on the inner cortex. By grasping the bicortical screw, the bone fragment can be gently advanced and rotated 90 degrees in either direction. The outer cortex and bone marrow is removed with a round cutting bur or electric piezo saw, and the fragment is fixated with a titanium screw at the inferior border. A round or pear-shaped cutting burr may be used to contour the advanced bone fragment.

For a genioglossus and genioplasty advancement (GGA) the osteotomy includes both the genial tubercle and the inferior border of the mandible. This is particularly useful in patients with mandibular retrognathism and low hyoid position or in patients with insufficient chin length for an isolated GA. Osteotomy guides and patient specific implants (PSI) can be designed by virtual-surgical-planning (VSP) and used intraoperatively to ensure precise location of the genial tubercle, avoidance of vital structures and accuracy and stability in the surgical procedure. In cases where the genial tubercles are in unfavorable positions, they should be avoided. When genial tubercles are superior and close to the dentoalveolar bone, capturing them would increase risk of dentoalveolar fracture. As stated earlier, the genioplasty advancement can still address dentofacial deformity, decrease possible mentalis strain, and still provide tension for the suprahyoid muscles (Fig. 29.5).

Sufficient hemostasis should be ensured before wound closure. Inadvertent injury to the sublingual artery and veins can easily occur with a reciprocating saw and lead to the formation of a postoperative sublingual hematoma. The surgical incision is closed in two layers with a suspension of the mentalist muscle with horizontal mattress sutures and by closing the mucosa with interrupted sutures. No other dressing is needed if the approach is performed correctly and there is adequate muscle for suspension and closure.

29.2.4 Postoperative Care

Overnight observation after GA or genioplasty surgery is highly recommended because of the risk of sublingual hematoma formation or tongue swelling that may lead to upper airway obstruction. When the patient undergoes multilevel surgery, including septoplasty, pharyngoplasty, and GGA, a higher level of overnight care

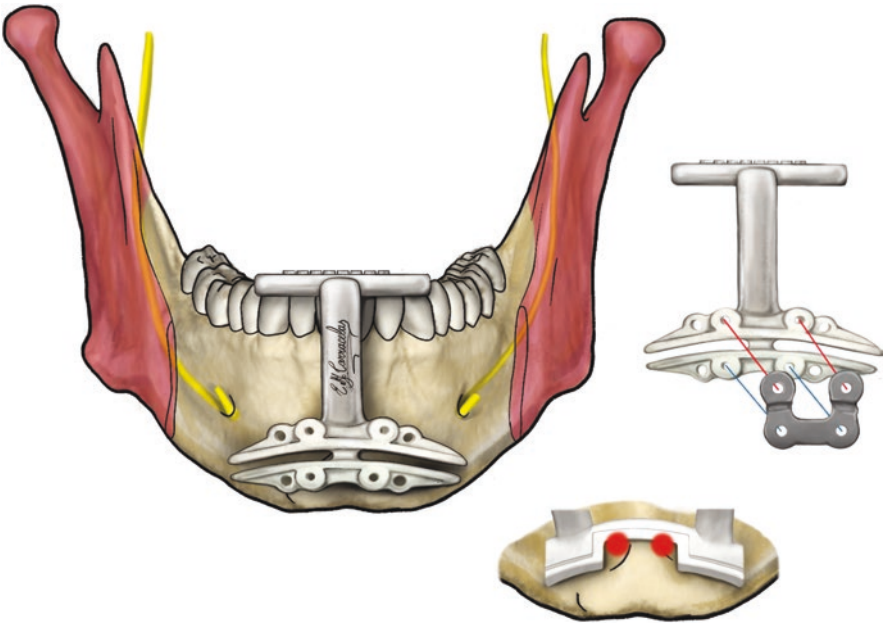

Fig. 29.5 Genioplasty advancement can address dentofacial deformity, decrease possible mentalis strain, and still provide tension for the suprahyoid muscles. Diverse types of plates may be used according to the case

may be needed. The decision depends on the type and length of surgery, perioperative complications, comorbidity of the patient, OSA severity, and the possibility of CPAP use. Postoperative pain control is managed with oral analgesia. Patients can begin with a mechanical soft diet for comfort but should not have restrictions after mucosal wound healing, which is most accurately assessed at 2 weeks postoperatively.

29.2.5 Complications

GA is associated with wound infections, persistent paresthesia of the anterior lower lip, and dental injury, with incidence rates of 2%, 6%, and 1%, respectively [37]. Mandibular fractures in the symphysis region can occur, particularly in the techniques that violate the inferior border of the mandible. Alternatively, if the osteotomy is superior to the alveolar bone, alveolar fractures can occur and are more challenging to address than inferior border fractures. The lower border fractures lend themselves to further open reduction and fixation. The superior border fracture can only be addressed with maxillomandibular fixation (arch bars) for several weeks. Intraoperatively avulsion of the genioglossus muscle from its attachment at the posterior mandibular border is the worst complication in GA surgery and is a serious airway risk.

29.3 Maxillomandibular Advancement

Maxillomandibular advancement (MMA) remains one of the most effective surgical interventions for patients with OSA. Riley and Powell pioneered the procedure at Stanford Hospital in the late 1980s The surgery addresses both skeletal support and soft tissue suspension of the upper airway, which treats OSA and airway collapsibility [38]. MMA enlarges the upper airway space at multiple anatomic locations, including the nasopharynx, oropharynx, and hypopharynx [39]. MMA involves Le Fort I maxillary and bilateral sagittal ramus split mandibular osteotomies with advancement of the maxilla and mandible, and frequently accompanied by counterclockwise rotation [40]. The counterclockwise rotation with an adequately selected rotation center allows for a more significant lower jaw advancement than the upper while maintaining proper occlusion and facial balance. The anatomic limit of counterclockwise rotation depends on (1) maxillary incisal show and (2) the length of mandible that is available for adequate fixation after rotation and advancement. Ultimately, the terminology of MMA, suggesting advancement only, is not entirely captive of the complexity of maxillary and mandibular movements (Fig. 29.6).

A meta-analysis by Holty and Guilleminault examined 22 studies involving 627 patients who underwent MMA and reported a mean AHI decrease from 63.9 to 9.5 events per hour [41]. The surgical success rate was 86%, and the cure rate (AHI <5) was 43.2%. Predictors of increased surgical success include younger age, lower preoperative AHI and BMI, and a greater degree of maxillary advancement. An updated meta-analysis with 45 studies and 528 patients reported a surgical success and cure rate of 85.5% and 38%, respectively [42]. In 40 patients who underwent MMA with an average follow-up of 4.2 years (range 1–12 years), 36 (90%) maintained a significant reduction in the respiratory disturbance index from 71.2 to 7.6 events per hour with improvement in daytime sleepiness [43]. Following MMA, most patients report improvements in health-related quality of life, depression, excessive daytime sleepiness, memory impairment, and hypertension [44]. It has also been shown to improve sleep architecture by increasing the percentage of rapid eye movement (REM) sleep and decreasing wakefulness after sleep onset (WASO) [45, 46].

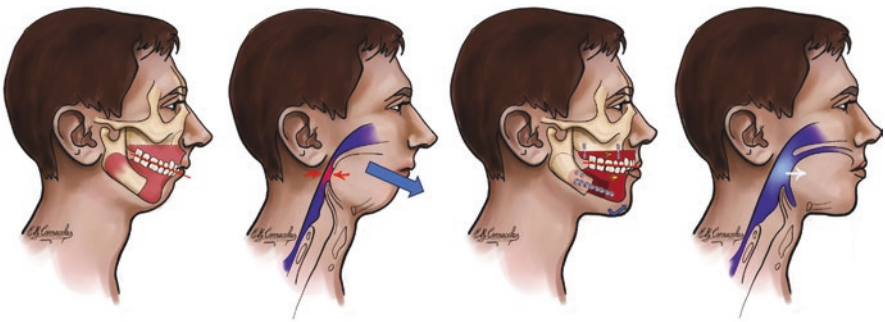

Fig. 29.6 Counterclockwise rotation depending on (1) maxillary incisal show and (2) the length of mandible that is available for adequate fixation after rotation and advancement. Improvement of airway is seen at the velum, oropharynx, and tongue base

29.3.1 Indications

MMA is recommended for: (1) patients with moderate to severe OSAS with or without a history of phase 1 surgery (tonsillectomy, uvulopalatopharyngoplasty with genioglossus advancement), (2) OSA patients of any severity with concurrent dentofacial deformity, and (3) concentric and lateral pharyngeal wall collapse seen in DISE [4–6, 47]. (Fig. 29.1).

29.3.2 Preoperative Planning

OSA patients planned to have MMA surgery may present with a normal class I occlusion or varying degrees of malocclusion. In patients with malocclusions or dental compensated class II or class III occlusion, orthodontic treatment in conjunction with MMA can facilitate more optimal skeletal advancement of the maxillofacial complex.

Preoperative surgical planning of MMA has changed dramatically with the introduction of virtual-surgical planning (VSP). With a computer tomography (CT) or cone beam computer tomography (CBCT) scan of the face, and dental or digital models in the desired occlusion, surgeons can use VSP to plan skeletal movements with versatility and precision. VSP also generates anatomical landmarks and information to be used intraoperatively: (1) distance from the mandibular cortex to the inferior alveolar nerve, (2) height of the lingula relative to the occlusal plane, (3) impact of occlusal plane changes associated with counterclockwise rotation, and (4) presence of anatomic anomalies.

Custom plating can increase precision and decrease operative time in MMA surgery. It is important to note, however, that, unlike classic orthognathic surgery, the exact position of the maxillomandibular complex is subject to alterations or adjustments intraoperatively, in which case the preplanned plates may not work. The senior author typically plans cases with two movements, where one usually has more rotation and less advancement, and the other has less rotation and more advancement. Since the surgeon intraoperatively controls the pitch, having these two plans and their associated intermediate splints allows for a wide range of movements to optimize breathing and beauty.

Classic orthognathic surgery is planned with the patient in the so-called “natural head position.” This is with the patient standing relaxed, facing forward, while the clinician assesses the patient from the side, profile view. As many patients with long-term OSA have an exaggerated forward head tilt, planning from this position will mask the degree of maxillomandibular deficiency. Therefore, it is important to gently guide the patient’s head position such that the neck is in a straight, neutral position, while the face maintains the Frankfort horizontal. It is important to remember that an OSA patient’s “natural head position” is frequently natural but not healthy. With maxillofacial surgical treatment, patients can frequently restore less strained neck and body posture with retraining.

29.3.3 Surgical Technique

Nasal RAE tubes are frequently used in orthognathic surgery. However, OSA patients often have longer airways, where RAE tubes tend to fall short. The cuff may come close to the vocal cord, resulting in trauma or inadequate seal, contributing to interoperative air leak or hypoventilation. To address this, the larger lumen RAE tubes tend to be used, severely distorting the nose. Strategy, including the use of a micro-laryngeal tube (MLT) positioned adequately with a 120-degree reverse metal connector, is described in our broader, overall strategy to optimize nasal function during MMA [48].

The sequencing of MMA surgery is based on the surgeon's experience and preference. Mandible-first approach has been recommended to remove potential condylar position errors in the interocclusal registration before surgery [49]. However, committing to the mandible first means that there is no room to adjust the maxilla if it is deemed during surgery that more advancement or rotation (both clockwise or counterclockwise), is desirable. As systematic reviews and meta-analyses have shown the maxilla to be the critical driver to surgical success, the maxilla first may be preferable for the airway. Fortunately, in the era of VSP, where custom maxillary plates can be designed, this may mitigate the classic issue of condylar registration preoperatively.

Patients who are not in orthodontic braces are initially equipped with arch bars or intermaxillary fixation (IMF) screws. To access the maxilla, a mucosal incision is made approximately 1 cm superior to the mucogingival junction from the premolar area to the premolar area perpendicular to the maxilla. Subperiosteal dissection is then performed with a periosteal elevator within the following boundaries: (1) medially to the piriform rims, (2) superiorly to the area of the infraorbital nerve foramen, (3) laterally to the inferior zygomatic and maxillary buttress, and (4) nasal floor posteriorly to the palatine bone. A curved freer elevator may assist with the dissection of the nasal mucosa, and it is easiest to begin the exposure from the lateral aspect of the perform aperture and proceed in an inferior-medical direction. A toe-out retractor is placed in the pterygomaxillary junction to expose the maxillary buttress. A periosteal elevator or malleable retractor is inserted medially to the piriform rim to protect the nasal mucosa.

The osteotomy is then initiated at the lateral maxillary buttress and extended through the piriform rim below the inferior turbinate utilizing a reciprocating saw. The osteotomy is then mirrored on the contralateral side, and the lateral maxillary buttress can then be "back cut" by reinserting the reciprocating saw into the lateral portion of the osteotomy and passing it in a medial to lateral direction.

Disjunction of the maxilla from the septum, medial nasal wall, and pterygomaxillary junction is completed with straight and curved osteotomes. Down-fracture of the maxilla is performed with gentle digital pressure at the anterior nasal spine region. Completing the down-fracture should be followed by careful inspection for any active bleeding, that needs to be controlled. Efforts should be made to preserve the descending palatine arteries by carefully removing the maxillary pyramidal

process that may lacerate the vessel during mobilization, advancement, and impaction of the maxilla. In addition, the removed bone pieces from the maxilla can be used for later bone grafting of the osteotomy sites.

A thorough mobilization of the maxilla important to allow a tension-free repositioning of the maxilla into the planned position. A 24-gauge wire with a Kocher clamp through the anterior nasal spine is used to perform simultaneous traction of the anterior maxilla toward the right and left while gently pushing the posterior maxilla anteriorly with a distractor. In large counterclockwise rotations, further mobilization is performed by pushing the posterior maxilla downward while holding the anterior maxilla upward. The use of Rowe's disimpaction forceps transmits excessive force and is strongly discouraged by the first author. The key to the mobilization of the maxilla is not in pulling it forward but in rocking it sideways. The excessive force with the Rowe forceps in older patients is especially problematic with the risk of unintended fractures.

A planned impaction will require bone reduction and reduction of the nasal septum to allow for appropriate repositioning and to prevent nasal septal deviation. The piriform aperture and nasal floor widening are performed with a pineapple burr. Septoplasty can also be performed with an exposure of the septum inferiorly. These modifications improve both form and function of the nasal structures after MMA [48]. In reality, to achieve an esthetic nose after MMA, the entire process includes pre-, peri-, and postoperative considerations. Our results from patient-reported outcome measures are favorable with the advent of these considerations [50].

With the maxilla and mandible secure in the intermediate splint, measurements are made to ensure movements planned for yaw, cant, and pitch are accurate. The maxilla can be fixated in various of ways, using the vertical pillars of strength (piriform and buttress). The suspension wiring technique is highly desirable especially with older patients and more significant movements. They are discussed in detail as part of the contemporary Stanford MMA, though it has been utilized since the procedure's earliest days [40].

Access to the mandible begins with a vestibular incision starting 10–15 mm posterior to the second molar and continues 1 cm inferior from the mucogingival junction to the second premolar. This incision should be through the buccinator muscles and allow a muscular cuff to close after mandibular advancement. The subperiosteal elevation is made buccally in the first and second molar, and the inferior border of the mandible is stripped. The anterior border of the ramus is elevated, and the temporalis muscle attachment is stripped to gain access to the medial ramus. The location of the lingula is either directly visualized or probed with a blunt nerve retractor. If the subperiosteal elevation at the medical ramus is performed correctly, one should obtain a "tent effect," in which a curved retractor reflects the entire soft tissue flap and exposes the medical surface of the ramus and protects the inferior alveolar nerve posterior to it.

To improve visibility and access to the medial ramus, a round oval bur can be used to trim a groove toward the lingula. The bony protuberance of the lingual should be removed for more predictable split that allows for the maximum area of contact after mandibular advancement. The sagittal ramus split osteotomy is made

with a reciprocating saw well seated in the groove created. Various ultrasonic cutting instruments have also become popular. To maximize bony overlap in significant advancement, the anterior vertical osteotomy is made just to the midline of the inferior cortex. A deeper osteotomy cut in a lingual direction beyond the midline of the inferior cortex results in a thin posterior lingual bone plate that can be insufficient for bicortical screw fixation in large advancements [51].

Splitting and separation of the tooth-bearing segment from the condylar segment begins with completion of the medical ramus osteotomy with a straight osteotome. Straight osteotomes are sequentially wedged together to widen the gap at the anterior part of the osteotomy until a complete separation is achieved. The separation and location of the inferior alveolar nerve is checked before the tooth-bearing segment is mobilized thoroughly. The tooth-bearing segment is then advanced and placed into the final splint. When movements are significant, the suspension wires described earlier are highly desirable to begin the process of wire maxillomandibular fixation prior to rigid plate fixation. The suspension wires, which are anchored to parts of the facial bone not involved in the osteotomies, confer stability to maxillomandibular fixation.

Fixation of the mandible begins with a trocar-assisted access for perpendicular placement of bicortical screws through the condylar and dentate segments. The assistant surgeon holds the condylar segment ensuring proper condylar seating. It is desirable to have the condylar segment placed slightly lower than the dentate segment at the inferior border. In essence, one is creating a longer ramus by using part of the body of the mandible. The biomechanics, in a significant advancement with such a placement, place less stress on the condyle and reduces the likelihood of a condylar sag. Typically, two bicortical screws are placed, followed by a 1.5 mm thick plate spanning the advancement gap. Therefore, the plate sits passively on the bone, and nonlocking screws are used.

After fixation, the wire MMF is released, and the mandible should be rotated in and out of the final occlusion to confirm a (1) stable rotation, (2) reproducible occlusion, and (3) bilateral canine excursion. The osteotomy gaps in the mandible and maxilla can be grafted to facilitate bone healing postoperatively. Prior to the closure of the vestibular incision, the septum is checked for passive seating along the maxillary crest. An alar cinch suture with 3-0 Vicryl is used to restore alar base width. The mucoperiosteal flap is closed with 3-0 chromic in a continuous fashion, and V-Y anterior lip lengthening may be considered. The sagittal split incisions are closed with 3-0 Vicryl in interrupted sutures. Guiding elastics are placed in a class II direction.

Final splints, commonly used postoperatively in classic orthognathic surgery, are an added burden for OSA patients. OSA patients are frequently anxious about breathing, and the placement of a final splint and expected postoperative nasal congestion make for a difficult initial postoperative period. Furthermore, without the final splint, dental remodeling can often work in the patient's favor as part of the accelerated orthodontics movement. Unless there are special considerations in surgery-first orthodontic set-up, where the occlusion is designed in a particular way, final splints are not recommended nor needed postoperatively.

29.3.4 Postoperative Care

OSA patients are predisposed to dynamic airway collapse, and prevention of airway obstruction after MMA surgery is the top priority. The level of care for MMA patients postoperatively is determined by patient, surgeon, and hospital system-related factors. Historically, patients at Stanford were extubated in the OR but kept overnight in the ICU for observation. Currently, with advances in anesthesia, surgical time, and postoperative care, patients are sent to a regular ward familiar with MMA patients postoperatively. The typical stay is two nights, which patients familiarize with a liquid diet and nasal irrigation and are comfortable with pain control.

A mean arterial pressure below 90 mm Hg is helpful to minimize the risk of epistaxis associated with the LeFort I osteotomy. To prevent postoperative edema, patients receive intravenous corticosteroids. Postoperative pain control is essential but excessive sedation of OSA patients should be avoided. Intravenous antibiotic is given in the beginning of surgery and an empiric prophylaxis is continued for a total of 5–7 days.

Nasal saline rinses are initiated on the first postoperative day to improve nasal patency. Patient requirements for discharge include reasonable pain control in oral medication, adequate oral intake, and a patent airway. The arch bars or suspension wires are removed 6–8 weeks after surgery, together with a postoperative DISE. Sleep studies are conducted 10–12 months after surgery to allow adequate time for airway muscle remodeling and neuroventilatory reflexes stabilization.

Paresthesia of the V_2 and V_3 nerves are known side effects from orthognathic or MMA surgery. MMA surgery, with its larger mandibular skeletal movement, the inferior alveolar (IA) branch of the V_3 nerve is the most affected (Fig. 29.7). Patients

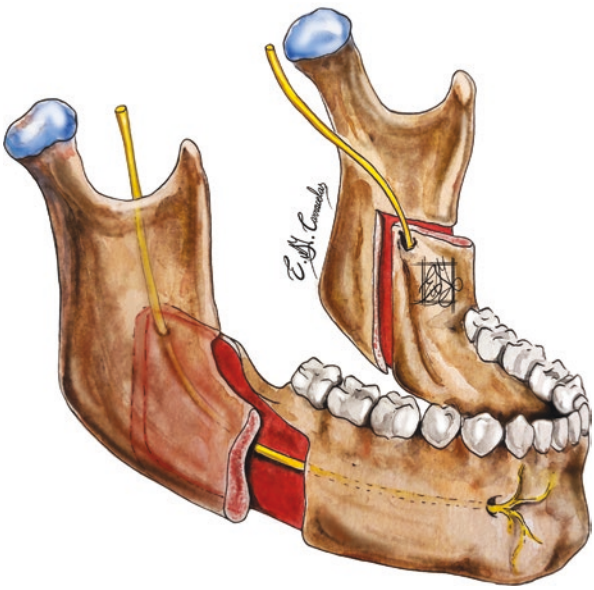

Fig. 29.7 In MMA surgery, the inferior alveolar (IA) branch of the V_3 nerve is the most affected

are counseled on the possibility of long-term or permanent numbness of the chin and lower lip region. Injury to the nerve occurs during the mandibular split, which is frequently performed in older patients without much marrow space in the mandible. When the condylar and dentate segments are fixated, the compression of the IA can also prolong paresthesia. Finally, the stretch of the nerve also contributes. From the Stanford team, we advise patients concerned about permanent numbness of the chin and lower lip, even in a small distribution, to reconsider MMA surgery very carefully. To minimize the impact of IA paresthesia, patients are recommended perioperative high dose of omega-3 supplementation. An aggressive neurobiofeedback exercise postoperatively has also been helpful for patients. Surgical techniques described above with regards to the wedging versus mandibular split technique pioneered by Riley and Powell are also essential for optimizing the osteotomy and protecting the IA nerve.

29.3.5 Complications

MMA confers higher rates of complications than orthognathic surgery in younger patients with dentofacial deformity [52]. There are significantly higher infection rates, hardware failure, and the need for reoperation. Compared to patients undergoing routine orthognathic surgery, OSA patients undergoing MMA have significantly more dysesthesia, infection, velopharyngeal insufficiency, need for hardware removal, and need for reoperation.

Avascular necrosis of the palate is a rare complication. If there is an indication that the blood supply to the maxilla is inadequate the surgeon should reposition the maxilla to its original position and suspend the procedure. Besides greater efficacy with single piece maxillary advancements, risk of avascular necrosis further discourages multipiece maxillary osteotomies for OSA patients.

Postoperative functional or cosmetic nasal problems that require surgical intervention affect up to 18% of patients undergoing MMA. However, techniques from Stanford have greatly improved this outcome, both objectively and patient-reported [48, 50].

Overall, MMA is a safe procedure regarding mortality rate, but OSA patients should be counseled preoperatively regarding the relative increased risk of complications known to similar maxillofacial procedures.

29.4 Maxillary Expansion Surgery

Maxillary morphology is an essential anatomic element for the obstructive sleep apnea (OSA) pathophysiology [53]. OSA patients with transverse maxillary hypoplasia and high-arched and narrow hard palate struggle with increased nasal airflow resistance and an inferior–posterior tongue resting position that worsens hypopharyngeal airway collapse [54] (Fig. 29.8). Healthy people breathe through the nose during sleep, generally, with a total sleep time of less than 4% reported as oral

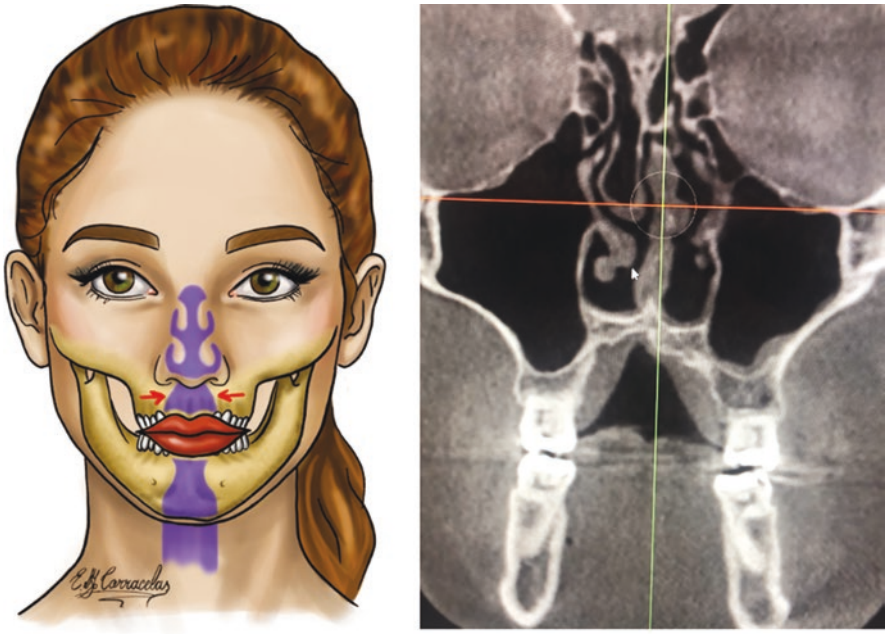

Fig. 29.8 OSA patients with transverse maxillary hypoplasia and high-arched and narrow hard palate struggle with increased nasal airflow resistance and an inferior–posterior tongue resting position that worsens hypopharyngeal airway collapse

breathing [55]. Nasal airflow stimulates ventilatory reflex with activation of nasal receptors leading to increased spontaneous ventilation and improved upper airway tone [56]. Improving nasal breathing during sleep is imperative to optimizing the treatment outcome of all patients with OSA. Moreover, to promote nasal breathing during sleep, the tongue needs to fit inside the oral cavity without collapsing into the oropharynx or mouth breathing (Fig. 29.9). It has already been shown that improving nasal breathing optimizes the outcome of most common forms of OSA treatment, including weight loss, positional therapy, positive airway therapy, oral appliance, and various forms of surgery [48, 50, 57–61].

First-line treatment for nasal obstruction includes medical treatment, and intranasal procedures such as septoplasty, inferior turbinate reduction, and various forms of nasal valve surgery (spreader grafts, upper lateral cartilage suspension). However, in the patient presenting with nasal obstruction and narrow maxilla, results from first-line nasal procedures tend to be worse [62]. For these patients, maxillary expansion has shown significant improvement in objective measures from polysomnography, and self-reported outcome measures such as the Epworth Sleepiness Scale and NOSE scores [63, 64].

Surgically assisted rapid palatal expansion (SARPE) is a common orthodontic procedure to correct dental crowding and to ensure a normal transverse maxillary-mandibular relationship [65]. Classic SARPE tends to bend the dentoalveolar ridges

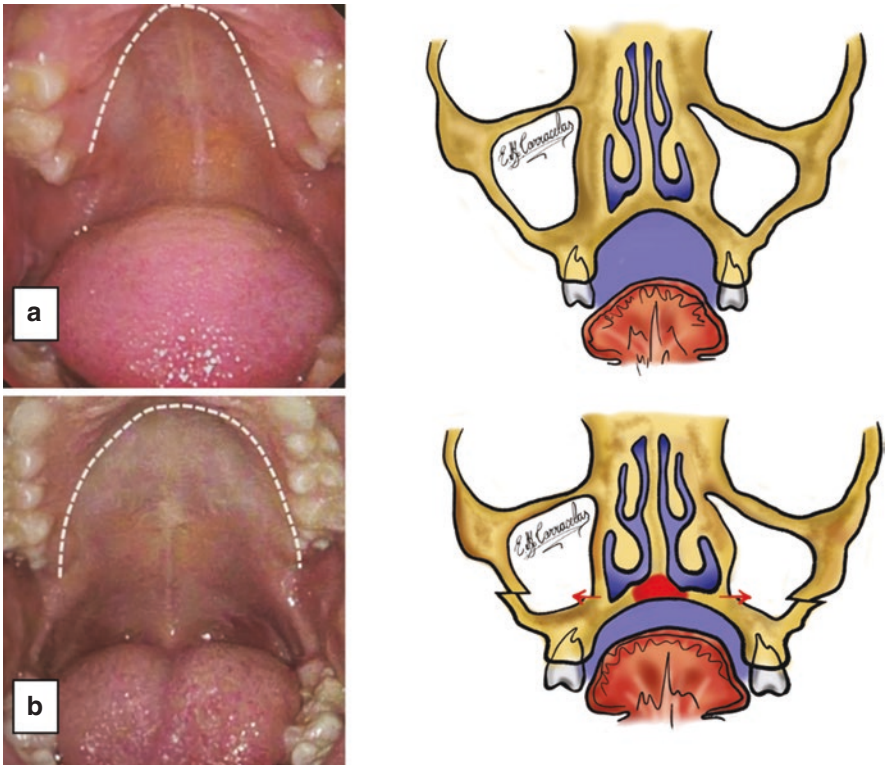

Fig. 29.9 (**a**) High arch palate, the nose is narrow, the tongue is at a lower level that the palate. The tongue adopts a different position which favors OSA. (**b**)After an expansion surgery the tongue can fit inside the mouth and within the palate, the nasal cavity is wider

but has more limited expansion at the nasal floor. It is also challenging to control unwanted dental movements since traditional expanders are only anchored to the dentition. This results in the need of aggressive osteotomies like a LeFort I procedure without active down-fracture. The key difference compared to pediatric OSA patients is the fusion of the mid-palatal suture in adults, which occurs before the pubertal growth spurt [66]. Nevertheless, the increased transverse dimension from SARPE allows the tongue to position superiorly and anteriorly, resulting in an increased hypopharyngeal airway [67]. Several studies have shown the efficacy of SARPE with improvement of AHI and lowest oxygen saturation (LSAT) [68].

To improve expansion at the nasal floor (or palatal vault), in addition to safely expanding adult maxilla of more advanced age while limiting the amount of surgical osteotomy needed, distraction osteogenesis maxillary expansion (DOME) has continued to evolve for patients with obstructive sleep apnea (OSA) [63, 69, 70]. The incorporation of endoscopic assistance and patient-specific osteotomy guides to DOME is consistent with the goals of precision surgery [69] (Fig. 29.10). DOME has been shown to expand the nasal floor, increase the surface area, and

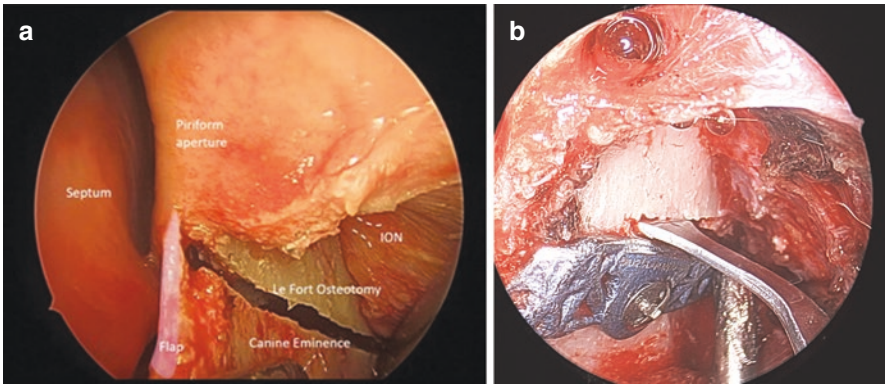

Fig. 29.10 Mini DOME with bone cuts performed endoscopically. ION: Infra orbital nerve

widen the internal nasal valve angle, resulting in reduced nasal resistance [71]. Skeletal-anchored expanders are used in DOME as they are more reliable for maxillary skeletal expansion [72]. Placement of the expander across the mid-palatal suture line inferior to the nasal floor enables a physiologic suture expansion with fewer adverse dentoalveolar effects and achieves more nasal expansion than earlier techniques [73].

29.4.1 Indications

Suggested indications for adult OSA patients to undergo DOME surgery include: (1) OSA patients with transverse maxillary hypoplasia, which in the most severe cases have an apparent crossbite, (2) patients with mild OSA demonstration persistent nasal obstruction accompanied by a high-arched and narrow hard palate who (2a) have previously undergone nasal surgery, or (2b) have not previously undergone nasal surgery and does not demonstrate significant septal deviation, inferior turbinate hypertrophy, or nasal valve collapse, and (3) patients with moderate to severe OSA planned for multilevel surgery, including uvulopalatopharyngoplasty, upper airway stimulation or MMA, presenting with transverse maxillary hypoplasia [74].

29.4.2 Surgical Technique

DOME surgery is performed under general anesthesia with an oral tube. Before surgery, a maxillary expander with four to six mini-screws is inserted along the mid-palatal suture into the hard palate by an orthodontist under local anesthesia. The surgical approach includes two 1 cm mucosal incisions superior to the maxillary mucogingival junction in the premolar area bilaterally. Subperiosteal dissection with a periosteal elevator is made toward the piriform rims medially and the

maxillary buttress laterally. The area of the infraorbital nerve foramen is the superior extent of the dissection. The LeFort I osteotomy is made with a reciprocating saw tunneling laterally from the maxillary buttress to the piriform rim medially. A vertical incision with subperiosteal dissection is made between the maxillary incisor roots. The primordial groove of the mid-palatal suture is deepened with a piezo electric saw and wedge opened with thin straight osteotomes, resulting in separation of the right and left hemimaxilla. A diastema between the maxillary incisors is seen immediately as the suture opens. The expander is then turned to ensure symmetric separation of the mid-palatal suture bilaterally until a 2 mm gap is seen between the maxillary incisors. The three small incisions are closed with 3-0 chromic suture.

29.4.3 Postoperative Care

After the advent of minimally invasive DOME techniques, patients are discharged on the day of surgery. Postoperative pain control with nonsteroidal anti-inflammatory drugs supplemented with opioids for a few days is sufficient. Limited epistaxis and nasal congestion in the early postoperative period are expected. Nasal irrigation is encouraged. Soft diet restrictions are continued 1 week after surgery. The patients begin their maxilla expansion 7–10 days postoperatively by turning the expander 0.25–0.5 mm daily. Most patients obtain an 8–10 mm expansion of the nasal floor within a month. Orthodontic treatment to close the diastema between the maxillary incisors and restoration of the occlusion is initiated after completing the maxillary expansion. In older adults, slowing down any part of this process can be of benefit from a dental perspective. The expander is left in place passively to prevent relapse during the consolidation period. The consolidation period is defined as the time between the cessation of traction forces and the removal of the expander. Normally, the consolidation period is 3 months for typical craniofacial distraction osteogenesis, but for adult OSA patients the period is extended to 6–9 months to ensure complete skeletal calcification [63, 75].

29.4.4 Complications

The most common post-DOME complications involve dental and occlusal restoration. Loss of central incisor vitality with discoloration is occasionally seen and can result in root canal treatment and internal bleaching. There is also the risk of asymmetric expansion, though, with VSP, surgeons are already alerted to patient anatomy where the maxilla itself is asymmetric, canted, or has significant yaw rotation. These can be corrected after expansion with double jaw surgery, which must be thoroughly discussed with patients at the beginning of the treatment process. Minor asymmetry can be corrected with orthodontic treatment. Temporary paresthesia of the infraorbital nerve in the anterior maxilla takes place but resolves within 1–6 months.

29.5 Summary

The common etiology of all treatments for OSA target collapsibility of the upper airway during sleep. The aim is to increase the negative pressure required to collapse the airway (P_{crit}) [76]. As the upper airway muscles are anchored to the maxillofacial skeleton, skeletal position and morphology contribute significantly to the stability of sleep breathing. In combination, maxillary expansion, maxillomandibular advancement, and genioglossus–genioplasty advancement can improve airway stability. Frequently, that maxillofacial and soft tissue procedures (uvulopalatopharyngoplasty, lingual tonsillectomy), or upper airway stimulation (hypoglossal nerve stimulation) can be sequenced for optimal results, as per the continuum presented in the updated Stanford Sleep Surgery Protocol [4–6, 47]. Restoring sleep-disordered breathing is the gateway to wellness, and as surgeons, having the entire repertoire of procedures in this contemporary era allows precision planning for treatment success [77].

Take-Home Messages

- Maxillofacial surgery has played a central role in the surgical management of obstructive sleep apnea (OSA).
- Single jaw advancement evolved to maxillomandibular advancement surgery (MMA) and genioglossus advancement (GA) with high surgical success rates.
- MMA and GA originated from the need for an effective multilevel sleep surgery as an alternative to tracheostomy in patients with severe OSA.
- Since then, the role of skeletal surgery has developed to include MMA, genioglossus advancement, and maxillary expansion.
- In the contemporary era, improved precision in patient phenotyping, surgical techniques, and peri-operative care have identified patients who will more likely respond to skeletal surgery, which can be offered earlier in the treatment paradigm.
- The combination of skeletal and soft tissue expansion stabilizes the upper airway during sleep.
- The combination of MMA and neurostimulation further addresses the needs of patients with very severe OSA and those who relapse from either procedure.

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Obstructive Sleep Apnea and Hematology Manifestations

30

María Marcos-Jubilar

30.1 Hemoglobin Structure and Function

30.1.1 Hemoglobin Structure

Hemoglobin is an intracellular protein that works as a two-way respiratory carrier, transporting oxygen from the lungs to the tissues and facilitating the return transport of carbon dioxide. In arterial circulation, hemoglobin has a high affinity for oxygen compared to venous circulation [1].

Hemoglobin is a protein constituted by four subunits, each having one polypeptide chain (globin molecules) and a heme group, conforming to a tetramer [1]. The heme group is formed by an iron ion held in a heterocyclic ring. This iron ion is where oxygen binds. In humans, hemoglobin is usually formed by two alpha globins and two non-alpha globins.

In the case of adults, the most common type of hemoglobin is hemoglobin A (HbA), which is formed by two alpha-globin and two-beta globin ($\alpha 2\beta 2$). However, most of the hemoglobin is made up of 2 alpha chains and two gamma chains ($\alpha 2\gamma 2$) in children. It is known as fetal hemoglobin (HbF). These gamma chains are replaced with beta-globin along with growth [1].

30.1.2 Hemoglobin Function: Oxygen Dissociation Curve

Red blood cells transport most of the oxygen in humans bonded to the hemoglobin. However, only 2% of oxygen in the bloodstream is directly dissolved in plasma compared to 98% of the oxygen that is transported in the protein-bound state to

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hemoglobin [2]. Oxygen binds reversibly to the ferrous iron atom (Fe2+) in each heme group.

Hemoglobin can be in a deoxygenated-tense state (T state) and an oxygenated-relaxed state (R state). These two conformations differ mainly in the affinity for binding oxygen. There is a low affinity for oxygen in the unbound state (T-state), so it requires a higher partial pressure of oxygen (pO_2) to facilitate the binding of an oxygen molecule. When oxygen binds to hemoglobin, its structure changes to a high-affinity R-state allowing more oxygen to get into hemoglobin, leading to a molecule that is more prone to get oxygen; in summary, oxygen-binding affinity is clearly influenced by the oxygen bound in the other heme groups of the same hemoglobin molecule, and it is represented in the oxygen fixation curve. The oxygen fixation/dissociation curve (Fig. 30.1) is plotted as the percentage of oxygen saturation against oxygen partial pressure; it has a sigmoid shape, reflecting this cooperative interaction between oxygen binding sites. It varies according to environment and species. P50 is defined as the oxygen partial pressure in which 50% of hemoglobin is saturated; in adult hemoglobin, it is at 26 mmhg (+/−1.6) [3]. At a partial pressure of oxygen of 100 mmHg, the hemoglobin in the red cell is fully saturated with oxygen [1, 2, 4].

As we mentioned before, the hemoglobin–oxygen affinity can be affected due to numerous situations, such as pH changes, temperature, and 2–3 diphosphoglycerol (DPG), which is reflected by shifting the curve to the right or the left [2]. Either a decrease in carbon dioxide (CO_2), temperature, and DPG or an increase in pH shifts the curve to the left (increased affinity). In contrast, an increase in CO_2, temperature, and DPG or a decrease in pH shifts the curve to the right (reduced affinity) [5, 6].

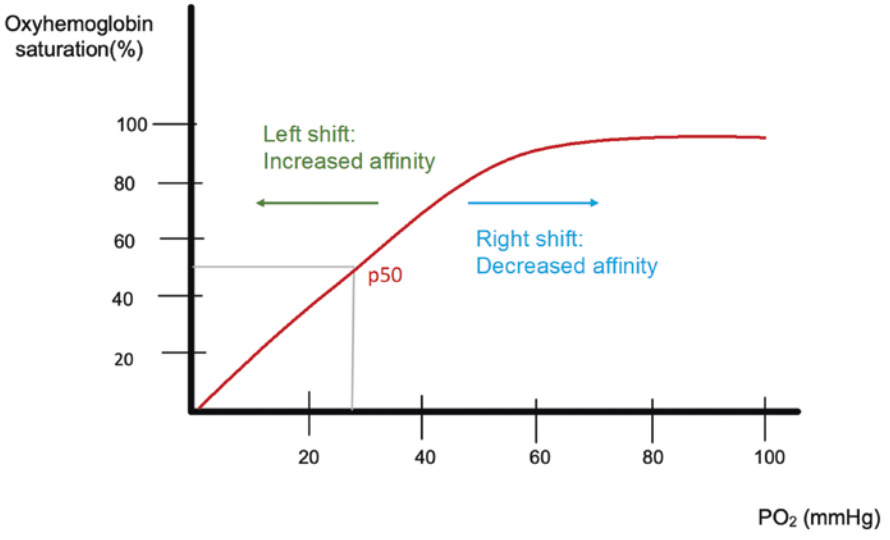

Fig. 30.1 Oxygen fixation curve. The horizontal axis shows the oxygen pressure plotted against the oxygen hemoglobin saturation. Adult hemoglobin has a P50 of 26 mmHg (+/− 1.6)

DPG, an intermediate product of glycolysis, is considered the major intracellular modulator of hemoglobin affinity; it binds strongly to the deoxygenated form of hemoglobin and poorly to the oxygenated state. It is present within the erythrocyte at concentrations equimolar to hemoglobin [6].

Bohr Effect explains the carbon dioxide (CO_2) transport in blood, showing an inverse relationship between the CO_2 concentration and the pH, so as the pH decreases, the CO_2 increases [2]. When CO_2 gets into red blood cells, it is converted to hydrogen ions and bicarbonate; this increase in hydrogen ions leads the unloading of oxygen stabilizing the hemoglobin in the T-state (deoxygenated state). In other words, the right shift (a decrease in pH and an increase in CO_2) can be considered a protective mechanism because, in this situation, more oxygen can be freed into the tissues.

In persistent hypoxia situations, mainly from nonpulmonary origin, a right shift in the oxygen affinity curve appears as a protective mechanism against hypoxia. However, when hypoxia is originated because of a pulmonary disorder, the role of 2,3 DPG is still controversial. Hypoxia in the pulmonary disorder is usually associated with alkalosis, and 2,3 DPG and respiratory alkalosis have opposite effects on oxygen affinity.

Additionally, depending on the hemoglobin structure, oxygen affinity varies. For example, HbF has a higher affinity for oxygen at lower partial pressure because of a poor DPG affinity, resulting in a leftward shift of the dissociation curve [2, 4].

30.1.3 Nocturnal Hemoglobin Desaturation

Nocturnal hemoglobin desaturation is characterized by prolonged episodes of decreased oxygen saturation of hemoglobin during sleep. It has been defined as having with <90% oxygen saturation during more than 30% of the time in bed. Independently of OSA, during sleep, there is a reduction in minute ventilation of around 15% of the physiologic CO_2 ventilatory response [7].

Due to hemoglobin dissociation curve shape in sleep apnea, cyclical changes in saturation and desaturations would be expected. During apnea and hypopnea, P_{CO2} increases, and pH lowers because of alveolar hypoventilation, which means a right shift in the hemoglobin dissociation curve predicting a decreased oxygen affinity. However, during acidosis, DPG falls, so the respiratory acidosis produced by apnea/hypopnea during sleep might neutralize the effect of the DPG decrement in the dissociation curve [8].

Maillard et al. described a right shift in the hemoglobin dissociation curve in untreated patients with OSA, observing higher p50 and DPG levels. In their study, these changes were reversible after a surgical intervention or CPAP treatment for OSA. However, later studies did not bear out these findings [9].

Clause et al. showed that intermittent arterial desaturation during sleep did not produce changes in the hemoglobin affinity during daytime. Therefore, they propose that several hours of maintained hypoxia are needed to induce DPG elevation because of hypoxia's opposite effect on hemoglobin dissociation curve and DPG half-life [8].

30.2 Most Common Hematological Alterations

30.2.1 Erythrocytosis

Erythrocytosis is characterized by an absolute increase in red cell mass, and it may be primary or secondary to another condition. Nowadays, diagnosis can be made related to a hematocrit level higher than 52% in males and 48% in females or hemoglobin higher than 18.5 g/dl in males and 16.5 g/dl in females, with levels associated with an increased erythroid mass [3].

An etiological study should rule out the cause of erythrocytosis as it is usually secondary to other conditions. Persistent hypoxemia is known to be an important cause of secondary erythrocytosis. However, the association between OSA and polyglobulia is still not clear. Even though several hematology guidelines recommend discarding OSA in patients with known secondary polyglobulia [7].

Many studies have tried to address this association, although they did not find an association between OSA severity and the hemoglobin or hematocrit levels [7]. Several explanations for hematocrit increase in OSA have been proposed from changes in the hemostasis volume to an increase in erythropoietin excretion [10].

To date, erythropoietin (EPO) increases, and the secondary polyglobulia produced are a response to the activation of hypoxia-inducible factor-1 (HIF-1). This HIF-1 activation happens in sustained hypoxemia. The EPO rise leads to higher hemoglobin and hematocrit levels, although it is thought to be associated with the duration and intensity of the hypoxic event. According to these hypotheses, several studies demonstrated that only those patients with severe OSA had increased EPO levels, and therefore, only this cohort of OSA patients developed polyglobulia [10, 11].

Some authors demonstrated that low nocturnal saturation and awake hypoxemia predict higher hematocrit and erythrocytosis. However, a study performed by Nguyen et al. showed that only 10.5% patients with nocturnal hypoxemia and erythrocytosis had hypoxemia while awake. In fact, nocturnal mean oxygen saturation is an independent factor of erythrocytosis. This association is stronger than the apnea/hypopnea index [7].

30.2.2 Procoagulant State in OSA

30.2.2.1 Platelets

Platelets play a central role in normal hemostasis and pathological bleeding. These cells act together with other cells not only in bleeding control but also in inflammation. Primary hemostasis consists of the interaction between platelets and the endothelial vessel wall. Several steps are necessary for a successful platelet function. It begins by the adhesion to the endothelium, the spreading and conformational change lead to the aggregation and granule release, exposing a procoagulant surface (Fig. 30.2); this process ends with the retraction of the clot [12]. Platelets can be activated by dysfunctional endothelium secondary to vascular inflammation and

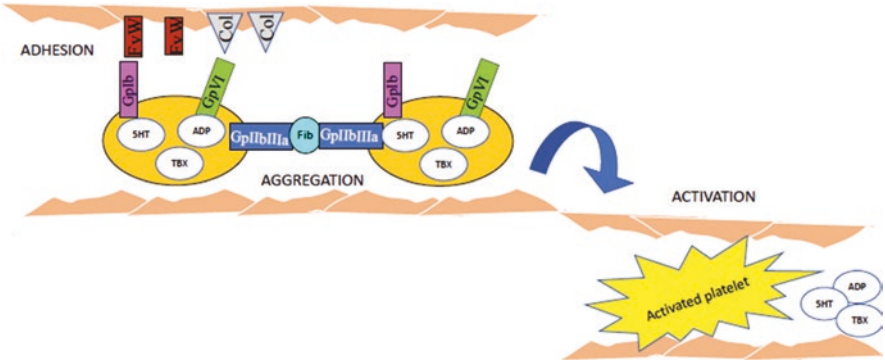

Fig. 30.2 Platelet activation process. The interaction between platelet and the damaged endothelium leads to conformational changes that make it more prone to aggregate with other by fibrinogen binding. Additionally, this conformational change makes platelets release their granules that produce a positive retrofeeding mechanism. *FvW* von Willebrand factor, *Col* Collagen, *5HT* Serotonin, *TBX* Thromboxane, *ADP* Adenosine diphosphate, *Fib* Fibrinogen

cellular damage due to oxidative stress. This activation may be secondary to many stimuli, with hypoxia being an important one among many other.

Several studies can be performed to evaluate platelets aggregation disorders, giving us different information. Some of these studies can address the conformational changes in platelet surface (flow cytometry) that give them a procoagulant state; and other studies assess platelet performance (platelet function test: aggregometry). Depending on the different techniques used, different results may be obtained. Most of the studies that used flow cytometry were able to find differences; however, results obtained with platelet aggregometry were not always concordant [11].

As it may be previously exposed in another chapter, OSA patients have increased blood levels of catecholamines (epinephrine and norepinephrine); these levels are said to correlate with OSA severity. This persistent rise in epinephrine levels may result in a desensitization of the α2-adrenergic platelet receptor that produces a decrease in the aggregation response, shown in aggregometry after epinephrine stimulation; this desensitization reflects an increased in vivo aggregation [11].

Additionally, platelets with intermittent nocturnal hypoxemia showed a decrease in vitro aggregation after stimulating with thrombin, related to platelet desensitization due to prior platelet activation as a consequence of nocturnal oxygen reduction.

Focusing on membrane ligands changes by flow cytometry, studies did not find differences in P-Selectin expression, although, CD40 ligand (CD40L) expression was reduced in patient with severe OSA, resulting in an increase platelet activation. This platelet activation, produces cleavage and release to circulation of CD40L [11, 13].

This increased platelet activation and aggregation may return to normal function after OSA treatment [13].

30.2.2.2 Clotting Factors

It is known that OSA produce a systemic inflammatory state, and inflammation is an important trigger for hypercoagulability states. Some OSA studies have demonstrated that the AHI level correlated with prothrombin time [14]. Moreover, some trials showed increase levels of factor VII and XII in patients with OSA [13].

Additionally, patients with moderate-severe OSA presented increased fibrinogen levels independently of other factors, such as body mass index, age, or smoking [15, 16].

The association between other hypercoagulability factors have been addressed demonstrating increased levels of thrombin-antithrombin (TAT) complex, metabolites of thromboxane A2 and prostacyclin in urine or increase levels of plasminogen activation inhibitor I (PAI-1) in blood [11, 13]. Higher levels of PAI-1 demonstrated not only a procoagulant state but also a dysregulation in fibrinolytic pathways [11].

30.3 Association to Other Hematologic Conditions

30.3.1 Hemoglobinopathies

30.3.1.1 Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive disorder produced by a single mutation of the β-globin gene provoking an abnormal hemoglobin S (HbS). It represents about 80%–90% of total hemoglobin of patients who suffer from this disease. Compared to HbA, HbS presents an increase instability, under deoxygenation it produces aggregates. This instability origins hemolytic anemia and may produce vaso-occlusive crises [17–19].

Different studies reported increase frequency of OSA in SCD patients, 22% in children and 40% in adults; however, this higher association in SCD patients compared to healthy population remains undiscovered [19]. Some authors proposed that SCD children might have adenotonsillar hypertrophy as a compensatory mechanism for the functional asplenia, and others suggest that craniofacial alterations due to extramedullary hematopoiesis may play a role [20].

As OSA may produce deoxygenation and hypoxemia, vaso-occlusive crisis may occur in SCD patients. It is crucial to rule out this disorder in SCD patients. However, a recent study by Stauffer et al. showed that nocturnal hypoxemia, but not OSA was associated with decreased red blood cell deformability and, therefore, hemolytic crises [17–19].

30.3.1.2 β-Thalassemia

β-thalassemia is produced due to a mutation or deletion in β-globin chain (11p15.5). This genetically alteration leads to a diminution or lack of β-globin synthesis. The globin chain reduction depends on the mutation or deletion nature. In intermediate or major cases, HbA is replaced by HbF with an increased in oxygen affinity. Anemia stimulates erythropoietin production with consequent increase but ineffective bone marrow expansion, leading to extramedullary production [21].

OSA disease is more frequent in children with β-thalassemia intermedia-major due to an extramedullary hematopoiesis that may obstruct the nasopharynx. Patient with OSA had a higher serum ferritin level compared to those without it. Moreover, thalassemia patients may have craniofacial alteration that may narrow airway space, facilitating obstructive sleep apnea [20, 22].

30.3.2 Lymphoma

Lymphoproliferative disorders are characterized by enlarged lymph nodes due to lymphocyte accumulation that can affect any lymphoid tissue. There are more than 80 entities with very different clinical phenotypes (from indolent forms to aggressive diseases). Sometimes, they can produce obstructive manifestations depending on enlarged adenopathies localization.

Some case reports showed that OSA might be the first disease manifestation of lymphoma, emphasizing the importance of the upper airway examination in patient with OSA, and in those with asymmetric tonsillar hypertrophy, especially in children, it is recommended to perform a histopathological evaluation [23–26].

Additionally, Choi et al. performed an extensive retrospective cohort analysis evaluating the association between OSA and lymphoma incidence. They showed that non-Hodgkin lymphoma was more frequent in OSA patients compared to the control group. Females were more affected than males (1.62 fold vs. 1.28 fold). There are no mechanical studies about this association, but obesity may be a potential link [27].

To date, there is some concern about long-term comorbidities in Hodgkin lymphoma (HL) patients. It is a pathology that frequently appears as a mediastinal mass that usually needs radiotherapy as part of its treatment. However, 90% of patients with this pathology are cured, so evaluating of long-term life quality is very important. Its treatment is associated with increased cardiovascular risk (due to chemotherapy and radiotherapy) that may be worsened by OSA. In fact, there is an ongoing trial (NCT 03361020) that try to address the prevalence of OSA in HL survivors treated with radiotherapy and the risk factors for its development.

Take-Home Messages

- Obstructive sleep apnea may be associated to several hematological conditions as a cause or as a consequence.
- Most of the oxygen in the blood is transported binded to hemoglobin in the red blood cells, so hypoxia is considered a leading cause of increased red cell mass.
- Additionally, airway obstruction can be produced due to extramedullary hematopoiesis secondary to hematological disorders; we should highlight hemoglobinopathies and lymphoproliferative disorders.
- Non-Hodgkin lymphoma seems to be more frequent in OSA patients

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Bariatric Surgery

31

Christel A. L. de Raaff, Nico de Vries,
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31.1 Obesity

Obesity represents a certain amount of excessive adipose tissue, negatively affecting health status, life expectancy, and medical outcomes. The exact definition is formulated with the body mass index (BMI), a weight ratio related to length. It can be calculated by dividing someone's weight in kilograms their height in square meters (kg/m^2) and enables us to categorize a person as underweight, normal weight, overweight, obese, morbidly obese, or super obese (Table 31.1). Obesity is defined as a BMI $\geq$30 kg/m^2. Morbid obesity is defined as a BMI $\geq$40 kg/m^2 or $\geq$35 kg/m^2 with obesity-related comorbidities. The basis of the BMI was formulated by Adolphe Quetelet between 1830 and 1850 when interest in an index measuring weight came with increasing obesity [1]. Due to its simplicity, BMI has become a universally used metric for weight.

The overall global population is progressively affected by obesity. Between 1975 and 2016, the prevalence nearly tripled. Worldwide, more than 1.9 billion and over 650 million adults were overweight and obese, respectively. This represents a prevalence of 39% and 13% of the worldwide population [2].

By the year 2030, the number of obese US adults is expected to rise to 40%–50% [2]. However, knowing that obesity causes multiorgan diseases and decreased life expectancy, it is a threatening perspective for global health.

Excessive adipose tissue negatively affects the function of organ systems. Anatomical, cardiovascular, metabolic, neuromuscular, and hormonal changes

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Table 31.1 Body mass index and weight categories

Body mass index (kg/m^2)	Weight category
<18	Underweight
18–24.9	Normal weight
25–29.9	Overweight
30–34.9	Obesity
35–49.9	Morbid obesity
≥50	Super obesity

occur due to obesity. Many of these changes are associated with obstructive sleep apnea (OSA), the most prevalent sleep-disordered breathing problem and affecting more obese individuals than type II diabetes, hypertension and dyslipidemia [3].

The pathogenesis of OSA is multifactorial and complex [4]. Local anatomy, obesity, gender, age, sleep position, and sedative drugs are examples of risk factors for OSA and its severity. One hypothesis explaining obesity as a significant risk factor for OSA is that fat deposition diminishes pharyngeal airway size, thereby increasing the risk of apneas.

OSA prevalence increases with BMI and age and is more common in men than women. Around 2% and 4% of middle-aged women and men, respectively, suffer from OSA in the general population [4]. In morbidly obese individuals, the prevalence rises to 70% [5, 6]. Nearly 90% of these patients were unaware of their OSA status before testing [6]. Patients associating symptoms of loud snoring and severe daytime sleepiness with their obesity rather than OSA could be an essential factor for this underdiagnosis.

31.2 Bariatric Surgery

Billions of dollars are spent on conservative weight loss programs to tackle the problem of obesity every year. Failure of long-term results has led to a more aggressive approach, including bariatric, also known as, metabolic surgery. This term has been derived from the Greek words baros (weight) and iatros (doctor) and refers to the surgical treatment of obesity.

The jejunoileal bypass, in which most of the intestines were bypassed and the stomach kept intact, was the first performed weight loss procedure in the 1950s. Adverse outcomes of diarrhea and severe vitamin deficiencies forced surgeons the search for alternatives. Observed weight loss among patients undergoing partial stomach removal from ulcers was the onset of a historical moment in bariatric surgery. In the 1960s, Dr. Mason and Dr. Ito performed the first gastric bypass, which was characterized by restricting the amount of food by reducing the stomach and causing malabsorption of nutrients by bypassing the small intestines. Over the past decades, the gastric bypass has been modified to its current form, the Roux-en-Y gastric bypass (Fig. 31.1). It is considered the gold standard and is competing in

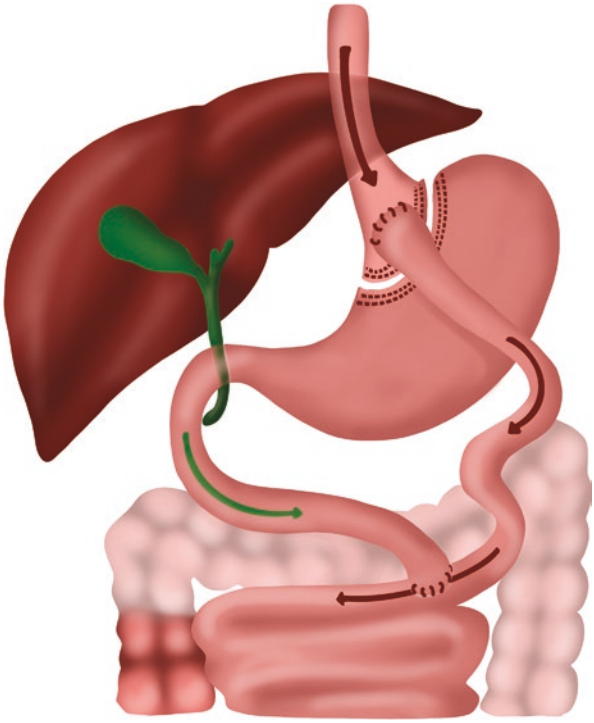

Fig. 31.1 Roux-en-Y gastric bypass. Illustrated by Zouzou Graphics ©

popularity with the stomach reducing sleeve gastrectomy (Fig. 31.2) and one anastomosis gastric bypass, also known as the mini gastric bypass.

Open bariatric surgical procedures have been converted to minimally invasive with the introduction of laparoscopic surgery. Improved perioperative recovery and outcomes in terms of complications, weight loss, comorbidities, quality of life, and life expectancy resulted in a growing interest in bariatric surgery [7]. Reimbursement by insurance companies allowed a growth from 150,000 procedures in 2002 to almost 700,000 in 2016 [8].

Criteria for bariatric surgery were set at the National Institutes of Health consensus conference in 1991 [9]. Patients are candidates for bariatric surgery if they are morbidly obese, have failed conservative therapies such as diets and exercise programs, are motivated to change their lifestyle, and have no significant psychological diseases. The International Federation for the Surgery of Obesity and metabolic disorders added the criteria age between 18 and 65 years, no drug dependency problems. and no pregnancy anticipation in the first 2 years after surgery [10]. In 2021, the European Respiratory Society guideline-recommended bariatric surgery for patients with a BMI $\geq$35 kg/m^2, OSA, and failed conservative weight reduction programs [11].

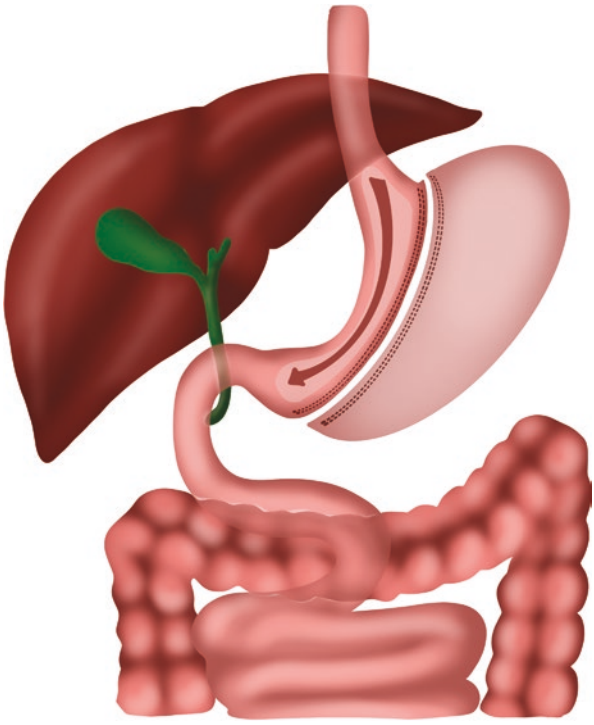

Fig. 31.2 Sleeve gastrectomy. Illustrated by Zouzou Graphics ©

31.3 Perioperative Risks

Bariatric surgery requires general anesthesia and intubation. Morbid obesity and OSA have shown to be independent risk factors for perioperative complications such as difficult intubation, desaturations, cardiac arrest, respiratory failure, and unexpected ICU admissions [6, 12]. Both suggest that special attention should be paid on to the recognition and anticipation of OSA in bariatric surgery to prevent disastrous perioperative complications.

Anesthesiologists should be aware of anatomical, physiological, metabolic, and pharmacological changes in obese patients. An essential physiologic characteristic is the time to desaturation. Benumof et al. illustrated the rapid desaturation in obese patients following 1 mg/kg intravenous succinylcholine [13]. The time to $SaO_2 = 80\%$ was reached after 3.1 min and was even shorter than the time to desaturation in a 10 kg child (3.7 min) or a moderately ill 70-kg adult (5.5 min). Other negatively affected respiratory components, including compliance, neuromuscular strength, and work of breathing, cause obese patients to be at risk of the development of perioperative cardiopulmonary complications [12].

Cardiac events within 30 days occur in around 0.1% of bariatric patients [14]. In the study of Mocanu et al. (n = 750,498), patients with a major cardiac event more often had OSA than the noncardiac event group (56.8% versus 38.2%), $p < 0.01$)

[14]. Also, in the long term, incident atrial fibrillation (AF) and stroke occurred more often in patients with OSA than without OSA during follow-up, despite similar weight loss [15]. In multivariate analysis, OSA (HR 2.88 95% CI 1.45–5.73), age, and hypertension were independent risk factors for new-onset AF, and OSA (HR 5.84 95% CI 3.02–11.3), depression, and BMI for stroke events [15].

Topics on OSA in combination with bariatric surgery have caught the attention of many researchers and clinicians over the last 30 years. Publication numbers on this subject have increased from less than 20 in 1990 to more than 1350 in 2021.

31.4 OSA Diagnosis in the Bariatric Population

The high prevalence of OSA in the morbidly obese population, and its perioperative risks have led to recommendations to screen for OSA before to bariatric surgery [6, 16]. The gold standard for diagnosis of OSA in overnight laboratory polysomnography (PSG) [6]. A less time-consuming and more patient-friendly sleep study than PSG is a portable study of a limited range of variables, known as type 3 portable sleep monitoring, e.g., polygraphy (PG). This can be used to screen for OSA in the bariatric population with high pretest probability [6]. Its use is most reliable when moderate to severe OSA (apnea–hypopnea index (AHI) $\geq$ 15/h) is suspected [6]. A PSG and type 3 PG generate two accurate measurements for OSA diagnosis in the bariatric population: the AHI and oxygen desaturation index (ODI) [6].

However, mandatory sleep studies before to bariatric surgery have not been accepted as the standard of care due to limited sleep laboratory capacity, costs, time management, and a lack of high-quality evidence showing the benefit of OSA screening and treatment in the bariatric population. An at-home continuous overnight pulse oximetry is a less accurate alternative to diagnose moderate or severe OSA. With a sensitivity and specificity of 80% and 92%, respectively, the optimal cutoff value for diagnosing moderate to severe OSA was an ODI of 23.9 [17].

As a portable monitor is considered a helpful adjunct to questionnaires in OSA screening, this has led to the development of several quick and costless screening questionnaires. A commonly used and validated questionnaire is the STOP-Bang, of which score can be used as a screening tool to stratify high-risk OSA in morbidly obese patients [6]. Additionally, with a sensitivity of 86% and specificity of 77%, the Berlin questionnaire can also be used to identify the risk of OSA [6]. In addition, the Epworth Sleepiness Scale should not be used as a screening tool for OSA. This is a symptom severity score and has a poor correlation in the bariatric population of OSA detection [6].

$PaCO_2$ is not an accurate indicator of the presence of OSA [6]. Elevated levels, however, are important for perioperative risk stratification and can be used as part of a diagnostic tool for obesity hypoventilation syndrome (OHS) in a patient with OSA [6]. OHS is a condition in which obese patients fail to maintain adequate ventilation levels, leading to oxygen desaturation and high CO_2 levels. OHS is a triad of components consisting of BMI above 30 kg/m^2, daytime hypoxemia, and CO_2 elevation. Sleep disorders such as OSA seem to play an important role in the pathophysiology

of OHS, as the prevalence of OHS is reported to be as high as 20% among obese OSA patients, and OSA treatment partly corrects the adverse effects of OHS [6]. The coexistence of OHS and OSA is associated with a higher morbidity and mortality rate after bariatric surgery. Therefore, OHS should be screened for in bariatric patients with OSA [6]. It is recommended to perform venous HCO_3 measurements as part of the routine screening [6]. An HCO_3 cutoff >27 mmol/L has a sensitivity and specificity of approximately 86% and 90%, respectively, for diagnosing OHS [6].

31.5 Ventilation Strategies

Ventilation strategies aim to minimize the risk of postoperative complications. Continuous positive airway pressure (CPAP) is the first treatment of choice for OSA and is recommended in all bariatric patients with moderate or severe OSA (AHI ≥15/h) [6]. CPAP significantly reduces the AHI, and data are available suggest a decreased risk of pulmonary complications, atelectasis, and reintubation when initiated in the postoperative period following major abdominal surgery [6, 18]. A systematic review of Tong et al. including 13 studies and 5465 patients reported that noninvasive pressure ventilation (NIPPV) in the immediate postoperative period decreased the risk of respiratory complications, incidence of postoperative hypertension, oxygen disturbances and prolonged stay in the postanesthesia care unit (PACU) [19]. However, NIPPV had no effect on the number of reintubations or unplanned ICU admissions [19].

Which ventilation strategy, that is, CPAP or bilevel PAP (BPAP), is superior in the bariatric population is not clear. Both CPAP and BPAP showed beneficial effects, but there is a lack of comparative studies. In 2017, a randomized controlled trial (RCT) found similar improvements in OHS with BPAP and CPAP [20]. These results align with the consensus paper's commendation to provide CPAP as standard treatment for OSA and OHS [6]. For those with inadequate alveolar ventilation, BPAP could be considered. Supplementary oxygen might be necessary for both ventilation strategies, those with desaturations despite PAP therapy.

As a specific period of time is necessary to get used to CPAP, patients should get acclimated to its use before surgery if possible [6]. This may take up to several weeks. On admission for surgery, patients should bring their CPAP machine and mask to the hospital for an optimal mask fit and pressure requirements [6]. Adequate observation of its efficacy is required, as pressure requirements may change in the postoperative setting. Its efficacy can be assessed during admission by continuously monitoring vital signs and SaO_2 [6]. After discharge, a more appropriate method is to determine airway efficacy and compliance from downloaded data from the CPAP device [6].

Choice of nasal versus full-face CPAP systems should be based on patient comfort and efficacy [6]. Besides CPAP, other treatment strategies are available. Positional therapy is recommended in patients with positional OSA who cannot tolerate CPAP. Another evidence-based non-CPAP device is a mandibular advancement device (MAD). If patients use MAD before surgery, it is recommended that they continue efficacious MAD usage postoperatively [6].

31.6 Intraoperative Management

Within the operating room, anesthesiologists should take precautions to ensure patient safety and provide optimal anesthetic care. Special attention is paid to the optimal positioning of the patient. Optimal preoxygenation is achieved by placing patients in a sitting position (90°) [21]. This extends the time to apnea by 1 min when compared with supine position [21]. The ramped position is the preferred position for induction and intubation [6]. This position improves oxygenation and the laryngoscopic view during intubation. Other positions, such as the flat supine position should be avoided in the morbidly obese patients, as they may desaturate rapidly if there are difficulties with mask ventilation or intubation, because of obesity on lung volumes, oxygen stores, and gas exchange [6]. Videolaryngoscopy should be available for patients concerned about a problematic intubation [6].

Providing CPAP and PEEP during induction avoids airway collapse and increases end-expiratory lung volume [6, 21]. This combination extends the time to hypoxic apnea by 1 min, prolonging the time for intubation [21]. High-flow oxygen could be considered as an adjuvant strategy to decrease the time to desaturation during induction. During the surgical procedure, maintenance of low tidal volumes reduces the risk of postoperative pulmonary complications [21].

Anesthesia and analgesia play an additional role in risk reduction and improvement of postoperative outcomes. Early and complete recovery of neuromuscular reflexes is an essential aspect of anesthesia and can be achieved by administering short-acting agents [22]. Sedatives as premedication should be avoided in patients with OSA [6]. Opioids should be avoided or used with caution by slow titration and careful monitoring, as this induces respiratory depression and relaxation in the upper airway dilator muscle [6]. At the same time, pain management is needed to avoid a negative impact of pain on recovery, hemodynamics, respiratory status, and length of hospital stay.

Multimodal anesthesia and analgesia include the usage of several low-risk drugs and play a vital role in reducing opioid administration and improving postoperative analgesia and outcome [6, 22]. In an observational study of 412 bariatric patients, multimodal analgesia resulted in shorter PACU stay, lower postoperative opioid requirements, less postoperative vomiting, earliest oral intake, and shorter hospital stay than with unimodal morphine analgesia [23]. Therefore, the choice of drugs and appropriate dosing strategies are essential considerations in this approach.

Pain management of bariatric patients with OSA is in line with the WHO pain ladder starting with paracetamol and nonsteroidal anti-inflammatory drugs. Tramadol and opioids should be minimized and replaced by adjuvants to core analgesics, including magnesium, ketamine, dexamethasone and clonidine, or dexmedetomidine [6, 24, 25]. Regional anesthesia, for example, with lidocaine, has shown positive results and is recommended for all bariatric patients [6].

At the end of the surgical procedure, patients should be close to fully awake, e.g., opening their eyes and coughing well, with reversed neuromuscular blockade before extubation [6].

CPAP usage in the direct postoperative period reduces the AHI and ODI by 69% and results in a higher oxygen saturation [26]. CPAP also seems to mitigate the respiratory depressant effects of opioids after bariatric surgery [26]. In a group receiving oxygen with atmospheric pressure, opioids increased the AHI by 13%, from 28 ± 32 to 32 ± 58/h. CPAP seemed to decrease this effect. With CPAP, the AHI increased from 6 ± 11/h by 4%, without affecting hemodynamics [26].

31.7 Postoperative Monitoring

Observation and monitoring are essential during and after surgery to decrease perioperative risks. Requirements depend on the type of surgery and patients' comorbidities. Patients who undergo minor surgery and those without comorbidities are often transferred to the general surgical ward in the postoperative setting. These wards generally only have the capability for intermittent vital parameter measurements. In a recent cohort of 1450 bariatric patients, 752 received continuous, noninvasive monitoring (intervention group) and 698 intermittent vital sign checks (control group) [27]. The intervention group experienced fewer cardiorespiratory complications, even after adjusting for confounders (OR 0.64, 95% CI 0.46–0.88, $p < 0.01$) [27].

In another retrospective cohort of 5682 bariatric patients without preoperative OSA screening, all patients were postoperatively monitored with continuous pulse oximetry [28]. Patients with no known history of OSA (n = 5089, 89.6%) were compared to patients with adequately treated OSA patients (n = 593, 10.4%). Cardiorespiratory complications occurred in 31 (0.6%) and 5 (0.8%) patients, respectively, $p = 0.171$ [28]. No mortality occurred. These data highlight the value of continuously monitoring bariatric patients, especially those with undiagnosed OSA.

Bariatric patients with OSA are at increased risk of complications and should be continuously monitored in the early postoperative period until they are no longer at risk of respiratory depression [6]. The minimum required monitoring is a pulse oximeter. Still, there may be a role for additional monitoring such as heart rate, blood pressure, respiratory rate, and end-tidal carbon dioxide, especially in patients receiving postoperative narcotics [6]. The risk of postoperative complications is even more significant in male patients with a BMI $\geq$ 60 kg/m^2 and 50 years or older [6].

To identify high-risk patients and to determine subsequent appropriate management, there is a role for a prolonged stay in the PACU. A designated surgical ward with continuous oxygen saturation measurements or medium care unit (MCU) should be present to accomplish adequate postoperative care [6]. Routine admission of OSA patients to the intensive care unit (ICU) is not necessary [6]. However, these monitoring recommendations are independent of CPAP usage, as CPAP compliance is not guaranteed. Length of stay in the monitored environment is dependent on several factors, including opioid requirements, and generally varies between the day of surgery and 2 days postoperatively.

Postoperative care should not be different for patients based on the choice of bariatric procedures. However, the type of surgery does not influence on OSA-related outcomes. In contrast, the length of the operation, the approach (open or laparoscopic) and level of expertise of the center may influence outcomes [6].

Described strategies all fit the enhanced recovery after bariatric surgery protocols, which have become standard practice in most bariatric clinics.

31.8 Follow-Up

Whereas OSA increases the perioperative risk in bariatric surgery, bariatric surgery induces weight loss and decreases OSA severity in the long term. Two years after surgery, BMI falls to 14.3–14.5 points following gastric bypass and 12.1–16.2 points following sleeve gastrectomy [29]. This equals an excess weight loss of 74.3–80.1% and around 46.7%, respectively [29].

The majority of OSA patients (77%–99%) show improved disease with weight loss [30]. Mean AHI significantly decreases in the mild, moderate, and severe OSA group [30], from 9.6 (SD 2.6)/hour to 4.8 (SD 3.2)/hour in the mild OSA group, 21.2 (SD 4.4)/hour to 8.9 (SD 6.5)/hour in the moderate OSA group and 66.1 (SD 26.9)/hour to 25.4 (SD 20.8)/hour in the severe OSA group [31]. The curation of OSA (AHI <5/h) is reached in 54% in mild and 18% of severe OSA patients [31] (Fig. 31.3).

Moreover, in at least three-quarters of patients with a preoperative AHI ≥ 15/hour, the AHI is reduced below 15/h during follow-up [32]. This implies that a mere

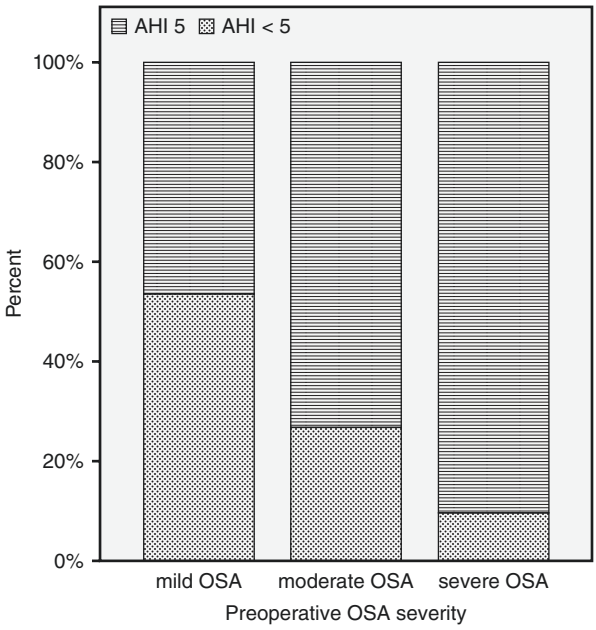

Fig. 31.3 Percentage of patients with a postoperative AHI <5, stratified per preoperative OSA severity group Patients with preoperative mild disease were more likely to be "cured" than those with a preoperative severe disease (53.6% vs. 17.9%). Source: Ravesloot et al. Assessment of the effect of bariatric surgery on obstructive sleep apnea at two postoperative intervals. Obes Surg. 2014 Jan;24 (1):22–31

75% of the preoperatively CPAP dependent OSA patients become CPAP independent after bariatric surgery.

Prior to the decision to discontinue CPAP, a patient should be re-evaluated [6]. There are no reliable screening tools to assess for residual disease in the postoperative setting. Therefore, a formal sleep study is recommended [6]. Optimal timing of this re-evaluation is unknown and should be dependent on weight loss and patient symptoms [6]. Therefore, a reduction of required CPAP pressure might be helpful in timing postoperative PSG.

Compliance is known to be a challenge in these patients. It has been reported that up to 50% of moderate and severe OSA patients do not attend postoperative PSG or PG [33]. In addition to the low compliance in follow-up, up to 50% of patients are noncompliant with their CPAP therapy in the long-term [34].

To increase adherence, counseling on the importance of compliance, follow-up testing, and information regarding alternative OSA therapies to CPAP should begin before bariatric surgery. In addition, adequate education of caregivers and preoperative counseling for patients should address this matter and align patient expectations with realistic outcomes.

An important note to bariatric surgeons is that CPAP can be safely used without damaging the anastomosis or staple line. Some surgeons believe that the positive pressure insufflated into the upper airways can cause an increase in intragastric pressure with an increased risk of anastomotic or staple line leakage. However, this was evaluated in a large cohort of 4052 patients, of which 970 (24%) used CPAP after bariatric surgery. In multivariable analysis, CPAP usage was not an independent risk factor for anastomotic leakage (OR 1.40, 95% CI 0.60–3.28, $p = 0.44$) [35].

Take-Home Messages

- When conservative weight loss programs fail, bariatric surgery might be an option.
- Worldwide, more than 700,000 bariatric surgical procedures are performed on an annual basis.
- As morbid obesity and OSA are independent risk factors for perioperative cardiopulmonary complications, a combination of both suggests that special attention should be paid on the recognition and anticipation of OSA in bariatric surgery to prevent disastrous outcomes.
- The chapter aims to provide information derived from guidelines and literature on the perioperative management of OSA in bariatric surgery.

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Burden of Disease

32

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"*In the modern health-care climate of rising costs and limited budgets, the disease burden of obstructive sleep apnea (OSA) is highly underestimated by policy-makers. This chapter serves as a call for action. Firstly, to awaken public health decision makers that the high burden of disease of OSA is a serious concern affecting health care cost directly and society tremendously. Considering OSA as a risk factor for other costly conditions and with evidence suggesting that the treatment of OSA is economically beneficial, more budget must be dedicated to the diagnosis and treatment of OSA. Secondly, this call for action must bring awareness amongst physicians and patients in order to address the underdiagnosis and undertreatment of OSA. Emphasizing the symptoms of OSA like disturbing snoring and no restorative sleep should be taken seriously, diagnosed and treated by a multidisciplinary team.*"

With health costs rising yearly, public health decision-makers—like governments and other payers—balance the best possible healthcare outcomes for their citizens at an affordable cost. As a result, the science and practice of health economics serve as a tool to make optimized decisions in this complex world. Since the late twentieth century, institutional bodies like the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) was established with the vision to improve healthcare decision-making. As a result, the field of Health Economics and Outcomes Research (HEOR) has grown substantially in importance and developed exponentially. In writing a contemporary book describing

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obstructive sleep apnea (OSA) and the adverse health consequences, devoting a chapter to the latest health economic insights is inevitable.

In 2007, Al Ghanim et al. [11] analyzed the economic impact of untreated OSA and concluded that it increases healthcare utilization and is comparable to other costs of chronic diseases. They conclude that, among others, governments and insurance companies need to be better informed about the economic impact of untreated OSA and the benefits of therapy.

Over the years, Wickwire and colleagues published extensively on the value of health economic aspects of OSA. In 2021, they state that OSA, as a consequence of the negative direct and indirect health-related outcomes, is associated with significant economic costs borne by multiple stakeholders, including patients, payers, employers, and society [1]. Previously, in 2019, the prestigious Italian Management School Bocconi by Armeni et al. 2019 published in the "Cost-of-illness study of Obstructive Sleep Apnea Syndrome (OSAS) in Italy" that the impact of OSA, and its syndrome (OSAS), is highly underestimated by policy-makers, clinicians and general population. Their study was the first social-economic study assessing the burden of this disease in Italy [44].

Previous chapters of this book describe the pathophysiology, the variety of direct symptoms resulting from sleep fragmentation and repetitive hypoxemia, and the personal toll of OSA patients. Subsequent chapters describe OSA as a risk factor for several cardiovascular, neurologic, and metabolic conditions such as hypertension, diabetes mellitus type 2, coronary artery disease, congestive heart failure, stroke, and arrhythmias [2] and correlated with other non-medical consequences. The importance of this book is to highlight OSA as a risk factor for comorbidities and not to see OSA as a more or less "stand-alone" medical condition. The purpose of this chapter, on the other hand, is to analyze the impact of this holistic approach and how this impacts the perspective of the burden of the disease of OSA. Also, it renders a burning question: How should this latest holistic perspective on OSA influence public health decision-making and priority setting? How can decisions be made optimal and healthcare ensured for OSA patients in a world with numerous diseases, illnesses, and disabilities?

Let us start with the question: "What is the definition of burden of disease?" Although it might sound like a simple question, it has a variety of meanings depending on who is asked. In our definition, we follow the backgrounder "Exploring the concept of disease burden" published by the National Collaborating Centres for Public Health (NCCPH) in 2016. It describes two main ways of thinking about and measuring the burden of disease: the biomedical and the economic burden of disease. More important is why we look at the burden of the disease. Understanding which diseases pose the greatest threat to health and well-being helps public health practitioners and policy-makers decide how to use limited resources for maximum benefit. We expect that analyzing the burden of disease of OSA with the latest holistic perspective and the expected adverse health consequences increases the burden of disease from a biomedical

and economic definition. Consequently, increasing the urgency for devoting healthcare budgets to diagnosing and treating OSA.

32.1 The Biomedical Burden of Disease

First, the most common approach to the burden of disease published by NCCPH, has been labeled "biomedical." It involves gauging the impact of disease and disability on bodies, from the onset of illness to the outcome—sickness or disability, recovery, or death.

Public health interventions aim to reduce the disease burden and increase populations' quality of life. To enable evaluation and comparison of treatments and healthcare innovations, research economists have summarized since the 1970s the burden of disease in a measure of Health-Adjusted Life Years (HALYs). These measures calculate the combined effects of mortality and morbidity in populations, allowing for comparison across illnesses or interventions and between populations [3]. Two common approaches to measure HALYs are quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs).

A QALY is the arithmetic product of life expectancy combined with a measure of the quality of life-years remaining. QALYs are internationally accepted for cost-effectiveness analysis, where "1" equates to perfect health, and "0" equates to death. It enables decision-makers to compare return-on-investment decisions across diverse disease states. Quality of life (QoL) is measured by different QoL questionnaires, both generic (e.g., SF-36, EQ-5D) and disease-specific (for OSA: e.g., SAQLI—Sleep Apnea Quality of Life Index). Cost-effectiveness is determined based on the ratio of quality to cost, known as the incremental cost-effectiveness ratio (ICER). As a measure of value, ICERs reflect the cost per QALY. A given health system or payer determines a willingness to pay (WTP) for a QALY [4]. For example, in the United States, $50,000 per QALY is a generally accepted threshold for cost-effectiveness. The National Institute for Health and Clinical Excellence (NICE), the UK Health Technology Assessment Center, holds a threshold between £ 20.000/30.000.

The DALY is an alternative tool that emerged in the early 90s to quantify the burden of disease. For DALYs, the scale used to measure health state is inverted to a "severity scale," whereby "0" equates perfect health and "1" equates death. DALYs are based on the assumption that time is the most appropriate gauge of disease burden. The greater the time lived with the disability of an illness or the more time lost due to premature death, the greater the burden of disease is considered. It is a non-financial approach, where pain, suffering, and premature mortality are measured in terms of DALYs.

Nowadays, what illnesses are impacting society most and should be on top of the minds of healthcare decision-makers? The World Health Organization (WHO)

publishes available data on causes of death and disability globally, per region and country, by age, sex, and income group [5].

The top 3 global causes of DALYs in 2019 are neonatal conditions, ischemic heart disease, and stroke.

Due to economic and demographic heterogeneity between continents, the ranking changes when we focus on the EU and the Regions of the Americas (North and South Americas). When specifying these regions, the top 3 for 2019 ranking changed to ischemic heart disease, stroke, and diabetes mellitus (DM) and were responsible for a total of 55.606 DALYs, 28.953 DALYs, 22.332 DALYs, respectively. This means a total of 106.891 years of life are lost due to premature mortality and disability for people living in less than good health resulting from ischemic heart disease, stroke, and DM in Europe and North and South America. Needless to mention that OSA is not reported in this table. Applying our holistic perspective—realizing that OSA is a scientifically proven risk factor for the top three illnesses—consequently leads us to call for action for decision-makers: the burden of disease of OSA is higher and the indirect health consequences should be prioritized.

At the same time, what can stakeholders in the OSA society do to show this higher burden of disease decision-makers? Today's and future public healthcare decision-makers want to make evidence-based decisions. Analyzing current literature on the effect of OSA on mortality—mainly investigated using observational cohort studies [6]—public healthcare decision-makers will find ambiguous results.

Marin et al. found in a Spanish cohort that patients with mild OSA or those undergoing treatment with CPAP did not have a significantly increased odds ratio for mortality compared with a group of subjects without OSA. In the same Spanish cohort, the authors found that severe untreated OSA (AHI >30) is associated with an increased risk of cardiovascular mortality, defined by fatal myocardial infarction (MI) or stroke [7]. Young et al. established the risk of mortality with untreated Sleep-disordered breathing (SDB), determined by polysomnography screening, in the general population in a 18-year mortality follow-up that was conducted in the population-based Wisconsin Sleep Cohort [8]. In the patient group with moderate to severe OSA (AHI >15), first-line CPAP therapy failed, either by the inability or unwillingness to use CPAP, and who were left untreated, which led to a significant decrease in survival compared to the treated population. Furthermore, Pietzsch et al. considered indirect factors influencing mortality. OSA-related Excessive Daytime Sleepiness (EDS) has shown to be associated with increased risks of motor vehicle collisions (MVCs) and other accidents [9].

Interpreting these ambiguous results might be complex for healthcare decision-makers due to miscellaneous reasons. First of all, mortality rates reflect patients with different severity levels of the syndrome. A clear definition of patient population and the corresponding parameters toward public healthcare decision-makers is necessary.

Pervernagie et al. summarize the historical evolution of the apnea–hypopnea index. This index has been subject to many changes and criticized for not capturing relevant clinical features of obstructive sleep apnea. They prompt a reconsideration of the role of the apnea–hypopnea index as the prime diagnostic metric of clinically

relevant obstructive sleep apnea [10]. Alignment within the OSA society on these parameters and clear communication toward the financial decision-makers would improve the situation.

Another point of attention is the level of evidence presented. The effect of coexisting cardiovascular diseases on survival strongly suggests that OSA is an independent risk factor for the development of cardiovascular disease and death. Still, it lacks randomized control trials to investigate the effect of CPAP in preventing the potential cardiovascular risk. Furthermore, the low compliance level of CPAP patients, the gold standard in first-line treatment of the OSA patients, might be a bias taken into account in analyzing results.

In conclusion, there is a mutual responsibility for physicians and healthcare decision-makers to align on the mortality and morbidity results in the OSA patient population to understand the exact biomedical burden of disease for a country. The in-depth cost of illness analysis of Armeni and colleagues in Italy can be taken as an example on an assessment on mortality and morbidity rate. After an in-depth systematic literature review, clinicians from different disciplines involved in a consensus board validated and integrated the results. Despite heterogeneous opinions, it resulted in an extensive list of adverse health consequences of OSA and/or OSA as a risk factor, which can be used as a guideline for future analysis.

32.2 The Economic Burden of Disease

"Exploring the burden of disease" by the NCCPH describes the second approach defining the burden of disease as "economic." It focuses on the financial costs of illnesses for individuals, households, healthcare systems, and societies.

Researchers and policy-makers measuring the economic burden of disease are interested in the direct cost of diagnosing, treating, and curing the illness. Direct costs refer to the consumption of healthcare and nonhealthcare resources directly attributable to disease. Direct healthcare costs include costs due to hospitalizations, consultations, laboratory testing, drug or medical device consumption, etc. [14].

In addition, a broader society perspective can be taken, where the impact of the disease burden on nonhealthcare costs and indirect social costs, like productivity losses on society, are taken into account. The knowledge and evidence on the later mentioned topic for OSA is scarce since indirect cost information is generally not available. The following paragraph elaborates on publications assessing both direct and indirect costs.

Although the exact costs are difficult to gauge, OSA appears to cause a huge economic burden (billions of dollars per year) and is comparable to other chronic diseases [11]. The report "Hidden Health Crisis Costing America Billions" from the American Academy of Sleep Medicine (AASM) estimates that approximately a direct cost of $12.4 billion was spent in 2015 diagnosing and treating OSA for the 5.9 million US adults diagnosed with the condition—a $2105 per patient per year [13]. A case–control analysis in the United Kingdom found that the use of

CPAP increased the total NHS cost of patient management by £4141 over 5 years [12].

In the same white paper commissioned by Frost and Sullivan of the AASM it was estimated that total societal-level costs of OSA exceeded $150 billion per year in the United States alone [13]. The greatest costs associated were lost workplace productivity ($86.9 billion), increased Health Care Utilization ($30 billion), Motor Vehicle Collisions ($26.2 billion), and workplace accidents and injuries ($6.5 billion).

Mentioned earlier, Armeni et al. 2019 (SDA Bocconi) report in—one of the scare—cost of illness studies that the economic burden due to conditions associated with OSA in Italy is substantial and is approximately equal to 31 billion Euros per year. The main drivers of economic burden are direct healthcare costs, which account for 60% of the total cost, followed by indirect costs due to morbidity (36%) and direct nonhealthcare costs (4%). The mean annual cost per moderate-severe OSA patient is approximately 2500 Euros. Productivity losses due to premature death related to OSA amount to more than 17 million Euros per year, around 1570 Euros per dead patient. Literature suggests that the burden of OSA in terms of quality-adjusted life-years (QALYs) lost due to OSA is substantial. Three scenarios based on a Willingness to Pay (WTP) factor are analyzed on both living as in dead untreated OSA population. In the most conservative analysis, it is estimated that the cost for the society of impaired quality of life (QoL) due to OSA undertreatment is approximately 9 billion for Italy.

Apart from the perspective of the cost of illness, other studies have analyzed the isolated effect on the workforce. A substantial proportion of patients with OSA participate in the workforce. Given that sleepiness negatively affects cognitive function, one would expect that patients with OSA would suffer from impaired work performance.14 In Denmark, patients with sleep disorders incur a significant socioeconomic burden because of their lower employment rates, lower earning potential among those who are employed, higher social transfer expenses made to patients, and direct costs of the disease [15, 16].

Another perspective that gives substantial relevance to the economic burden discussion is OSA being a highly underdiagnosed illness. Based on a sample of 4925 employed adults in the United States, Young et al. (1997) estimated that 93% of women and 82% of men with moderate-to-severe OSA were not diagnosed [17]. Several studies in various countries have shown that untreated patients with sleep apnea consume a disproportionate amount of healthcare resources and that healthcare expenditures decrease after treatment [18]. Taraskiuka reports an accrue about two-fold more medical expenses due to CVD morbidity [19]. Furthermore, untreated and undiagnosed OSA is associated with reduced work performance and occupational injuries and to be associated with reduced quality of life (QoL) and depression [20, 21].

The total yearly economic burden of a disease result from multiplying the direct and indirect cost per patient times the prevalent (or incident cases). Like the heterogenetic data on mortality and morbidity on OSA, public healthcare decision-makers can again face the challenge in their need to determine updated epidemiological data of OSA for their population.

The Forum of International Respiratory Societies (FIRS) report on chronic respiratory disease recently published global epidemiological estimates for the most prevalent chronic respiratory diseases. In the FIRS report, sleep apnea is estimated to affect approximately 100 million people globally [22]. Benjafield and colleagues report a global prevalence of OSA (AHI ≥5 events per h) varied between 711 million and 961 million individuals, depending on which American Academy of Sleep Medicine (AASM) scoring criteria was used, of which an estimated 272–458 million had moderate to severe sleep apnea (AHI ≥15 events per h) [23]. These estimates are in line with the findings of Lyons et al., estimating one-seventh of the world's adult population, or approximately one billion people to have OSA [24].

The global increase in obesity drives the development in prevalence of OSA [25–29]. We conclude the same as Neyjef (2007) does: "Given the high prevalence of this disease, the economic costs of OSA have substantial relevance" Consequently, OSA should be a higher priority on the list of public health decision-makers when analyzing the economic burden.

Coming back to the hypothesis defined in the beginning, "analyzing the burden of disease of OSA with the latest holistic perspective and the expected adverse health consequences increases the burden of disease from both a biomedical and economic definition" it seems inevitable to confirm and commit urgently to increasing healthcare budgets for the diagnosis and treatment of OSA. What are next steps to consider?

Multidisciplinary collaboration toward public healthcare decision-makers is a crucial element and is increasingly seen for the development of clinical guidelines. The publication of Linz (2021), supported by de German Cardiology Society (DGTHK), associates OSA with atrial fibrillation (AF). It concludes that intensive management is needed to prevent the progression of AF substrates, not only in severe OSA, but also in mild-to-moderate cases especially when there is a high night-to-night variability deserves [30]. These multidisciplinary collaborations on guidelines can be an example of how forces can be joined in the communication toward healthcare decision-makers in emphasizing the burden of disease of OSA both clinically and economically.

Part of the communication should not only be about the negative economic impact but instead emphasize the potential economic benefit of OSA treatment from a payer perspective. Wickwire and colleagues published a systematic review of the impact of OSA treatments on monetized economic outcomes. Results demonstrated that 17 of 19 comparisons reported a positive economic benefit from OSA treatment [4, 31]. The primary favorable economic outcomes were: accepted ranges of cost-effectiveness, reduced healthcare utilization (HCU), increased workplace productivity, and diminished accident risk [32]. Another example is a recent study conducted within Union Pacific Railroad Employees Health Systems found that a focused educational campaign on sleep-disordered breathing improved health outcomes and led to a measurable reduction of medical expenses [33].

The Cost-effectiveness of health interventions is an essential guide for public health decision-makers in priority settings [34, 35]. One study we would like to highlight specifically was done by Streatfeild et al. 2019, who determined

cost-effectiveness of continuous positive airway pressure (CPAP) treatment for OSA in Australia for 2017–2018 to facilitate public health decision-making. They examined the cost-effectiveness of CPAP therapy for OSA. From the healthcare system perspective, they found that its estimated net cost was $381 per person affected per year, which equated to an ICER of $12,495 per DALY averted. From a societal perspective (where other financial costs associated with the untreated condition, such as productivity losses and nonmedical accident costs, are also taken into account) the estimated net cost of treatment was −$326 per person affected per year and the ICER value for it was correspondingly negative (−$10,688), indicative of a dominant effect. A dominant effect means that it costs society more not to treat the problem than to treat it. The uniqueness of this study is the holistic approach instead of the other cost effectiveness studies undertaken with a limited scope, considering health expenditures but not additional costs (or a limited array of them) [36–41]. Where this chapter only "states verbally" that the loss of DALYs caused by OSA as "a stand-alone condition" is lower than the loss of DALYs caused by OSA approached holistically, Deloitte Access Economics 2017 calculated this relationship [42]. They gave a disability weight for comorbid conditions. For example, they estimated that the disability weight for OSA and coronary artery disease is 0.18 and the weight for OSA and stroke 0.24. Streatfeild used these weights as a base in his cost effectiveness analysis, and they calculated the DALYs lost per OSA patient when not treated. For OSA and coronary artery disease, this is 0.53 DALYs per case, and OSA and stroke 0.66 DALYs per case, which resulted in an annual average health system cost of $1650 and $1688 respectively per case in 2017–2018 [43].

Lastly, we want to emphasize that not only the proven cost-effectiveness of the first line of treatment (CPAP) is essential to public healthcare decision-makers but also the scientific proven clinical- and cost-effectiveness of innovative treatments or therapies. Depending on the patient's situation the current therapy spectrum of OSA includes CPAP, positional therapy and mandibular advancement devices (MAD). To complete the portfolio of treatment, there are many surgical therapies like tonsillectomy (TE), breath-synchronized upper airway stimulation (UAS), uvulopalatopharyngoplasty (UPPP), and newer modifications of the technique, that can be combined with multilevel-surgery and skeletal frame surgery.

Publications of cost-effectiveness studies on these new OSA treatments, preferably with holistic approaches like Streatfeild and colleagues did, is the key to convince public healthcare decision-makers. By translating the burden of disease of OSA and the economic benefit for societies in an optimized way, it is inevitable that public health decision-makers conclude that diagnosis and treatment of OSA patients in a multidisciplinary setting is urgent and must be prioritized.

Take-Home Messages

- The burden of disease of obstructive sleep apnea (OSA) is highly underestimated by policy-makers. Therefore, diagnosis and treatment of OSA are often not prioritized in healthcare budget decision making.

- OSA is a risk factor for comorbidities such as ischemic heart disease, stroke, and diabetes mellitus which, are listed in the top three World Health Organization (WHO) global causes of Disability- Adjusted Life Years (DALYs).
- With a broader society perspective, cost of illness studies of OSA concludes that the disease produces a substantial economic burden, with indirect costs due to morbidity as one of the main cost drivers.
- Instead of focusing on direct treatment costs of OSA, publications emphasizing the potential economic benefit from a payer perspective are increasing and with positive results.
- Cost-effectiveness analysis defining OSA as a risk factor for comorbidities concludes positively; society benefits from treating OSA.

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Sleep Apnea Syndrome in Elderly

33

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33.1 Sleep Apnea Syndrome in Elderly

Sleep apnea syndrome (SAS) is a disease characterized by breathing pauses during sleep, causing intermittent phenomena of hypoxia, which are repeated over time [1]. As resumed in previous chapters, OSA could be due to recurrent/partial or complete obstructions (hypopnea/apnea) of the upper airway during sleep [2], which takes the name of obstructive sleep apnea (OSA) and/or due to recurrent abnormal breathing pauses of central origin, without the evidence of upper respiratory obstruction, defined "Central Sleep Apnea" (CSA) [3]. Understanding the genesis of these disorders is essential to make up a complete overview, at least for what concerns fragile subjects, such as elderly patients.

Although the geriatric population has the same risk factor as the adult population for the development of OSA, such as obesity, male sex, smoking, upper airway abnormalities, family history, insulin resistance, current smoking, craniofacial abnormalities, excessive alcohol intake, and chronic drug therapy (e.g., muscle relaxants) [4], in this category of patients, the presence of associated risk factors is linked to more significant mortality and a major incidence of cardiovascular accidents [5].

Literature data suggest a higher incidence of this disorder in subjects over 65 years old [6], with an estimated prevalence between 13% and 32% [7]. This prevalence is two times higher in men than in women (over the age of 65), probably because of hormonal differences [8]. It is closely related to dietary habits, lifestyle, and population's general health status.

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Differently from young/adult subjects, there are a higher percentage of apnea episodes of central origin (CSAS) in the elderly; in particular, it constitutes almost one-third of the cases and may be connected to the different duration and structure of sleep with age. In particular, apneas and hypopneas are present and seem to be proportionately distributed in both rapid eye movement (REM) and non-REM (NREM) phases of sleep architecture [9]. On the contrary, obstructive events in the elderly are often related to the loss of elasticity and tone of tissues, the loss of pharyngeal dilator muscle tone, and the increased extraluminal pressure during sleep. Furthermore, geriatric patients have anatomical peculiarities which promote airway narrowing, such as a physiological descent of the hyoid bone [10] and a reduction of the upper airway lumen, which may further contribute to obstructive phenomena.

According to scientific contributions, the increase in respiratory efforts secondary to breathing pauses during apnea episodes is deeply connected to a chronic sympathetic activation and systemic inflammation [11]. This condition could further contribute to the developing and/or worsening cardiovascular (arterial hypertension and diabetes mellitus) and neurological problems. In addition, the sympathetic activation secondary to recurrent breathing pauses leads to chronic vascular stress repeated over time, contributing to the worsening of cardiovascular disease, which represents the leading chronic cause of death in geriatric patients [12]. Among the possible mechanisms of development and/or worsening of cardiovascular disorders, oxidative stress, systemic inflammation, endothelial dysfunction, insulin resistance, and coagulopathies also contribute to increase the possibility of a cardiovascular accident.

Regarding the relationship between OSA and hypertension, Wang et al. [13] described a high incidence of OSA in middle-aged and elderly and high body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) as independent risk factors for developing OSAS. As demonstrated by Unal et al. [14], a high value of BMI, waist-to-height ratio, and waist circumference are linked with the severity of OSAS. However, considering the crucial correlation between obesity and all-cause mortality [15], it is rare for an elderly subject to reach our attention for apneic complications exclusively linked to a state of overweight and/or obesity. They usually die earlier due to health complications related to excessive body weight and bad dietary habits.

Different authors have analyzed the correlation between apnea–hypopnea index (AHI) and mortality [16, 17], highlighting that OSAS represents an independent risk factor for all-cause mortality (1.9-times increased risk in all-cause mortality and 2.65-times increased risk of cardiovascular mortality) [18]. Between the main predictor risk factors related to OSAS mortality, we find existing coronary artery disease, poor adherence to CPAP therapy, type II diabetes mellitus (DMII), and chronic obstructive pulmonary disease [19]. A deep overview of mortality and morbidity in OSAS is presented in the article by Dodds et al. [20].

Moreover, patients affected by OSA also have a higher mortality risk due to other causes, such as the significant risk of traffic accidents [3] linked to daytime symptoms and sleep deprivation. Alongside cardiovascular disorders, the elderly patient

suffering from a sleep apnea disorder has a greater risk of developing neurodegenerative diseases [21] due to hypoxic events and the increase in daytime sleepiness, as highlighted by Cohen-Zion et al. [22].

Considering one of the most used models for neurodegenerative disease represented by Alzheimer's disease (AD), some authors analyzed the association between OSA and Alzheimer's disease (AD) [23], revealing that OSA is associated with intrathoracic and hemodynamic changes, anomalies in sleep architecture. Therefore, OSA treatment may represent a potentially modifiable target for AD prevention. Treatment of OSA appears to be a reversible cause of cognitive impairment in the elderly.

33.1.1 Clinical Evaluation

A thorough medical history anamnesis should be collected concerning systemic diseases, cardiovascular risks, and nervous system disorders. Also, it includes medical documents concerning previous evaluations and questionnaires to assess anxiety disorders, irritability, quality of life, cognitive impairment, quality of sleep, and daytime sleepiness. Remember that, especially in the female sex, sleep disorders could present through nonspecific symptoms such as insomnia and depression [24].

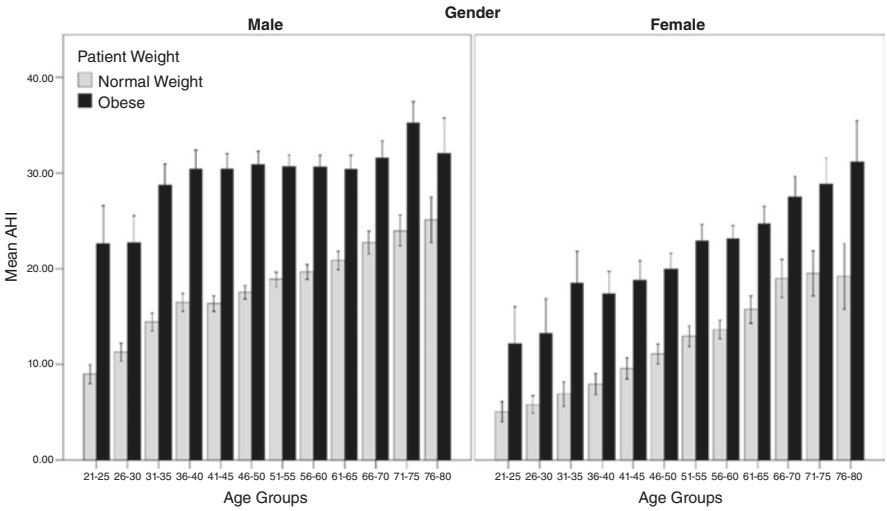
Each patient should be subjected to an accurate physical examination, with particular reference to the collection of anthropometric parameters, such as BMI, waist-to-height ratio, and neck and waist circumference [14] even though geriatric subjects may often seem to have a lower neck circumference and body mass index (BMI) [25]. Although there are very few data correlating the incidence of OSA in concerning age, sex, and BMI, Gabbay et al. [9] highlighted a linear increase in AHI with age and correlation with body weight (Table 33.1).

The ENT evaluation should include a fiberoptic endoscopy and a polysomnography (PSG) (the current gold-standard diagnostic tool for all age groups). As reported in previous chapters, PSG provides essential information, including the AHI value, which represents the total number of apneas and hypopneas during sleep-time. It is expressed in the number of episodes per hour.

Sleep apnea diagnosis in the elderly follows the same diagnostic parameters of young/adult subjects; patients with an AHI value of equal to or greater than 5 were diagnosed as having OSA. Moreover, according to AHI values, we distinguish between mild ($5 \leq \text{AHI} \leq 15$), moderate ($15 < \text{AHI} < 30$), and severe ($\text{AHI} \geq 30$) OSA, according to AHI value. PSG represents a valuable tool in defining OSA, which may depend on the assumption of a supine or lateral decubitus, described as "position-dependent obstructive sleep apnea (POSA)" [26], which represents an important portion of OSAS in the elderly.

Differently from young/adult subjects, drug-induced sleep endoscopy (DISE) should be reserved in selected cases, considering the greater number of possible anesthetic complications related to the procedure, especially in fragile subjects.

Table 33.1 Table resumed by the article of Gabbay IE et al.[9] which highlighted Mean AHI vs. age for obese and normal-weight patients of both genders



33.1.2 Therapeutic Approach

POSA in elderly patients could be considered treatable with positional therapy in many cases [26]. Still, little is known about the outcomes of positional therapy in subjects over 65 years old suffering from positional apnea.

As in the adult population, the treatment of choice for symptomatic or severe forms of OSA is represented by continuous positive airway pressure (CPAP); according to Labarca et al., CPAP therapy in elderly patients improves cognition, sleepiness, and quality of life [27]. Moreover, several studies which consider cognitive outcomes in patients suffering from degenerative diseases under CPAP therapy show the treatment of OSA as a reversible cause of cognitive impairment in the elderly.

The effectiveness of CPAP in patients affected by AD and suffering from OSAS was analyzed by Wang et al. [28], which revealed that the duration of CPAP is crucial for its therapeutic effects on improving cognitive performance. In addition, surgical strategies in elderly patients are limited, mostly because of comorbidities that give the elderly patient a greater anesthetic risk, which can be associated with a longer period of postoperative hospitalization time and the possibility of poor tissue healing.

33.2 Conclusions

Sleep apnea is an important disorder in elderly patient, often accompanied by cardiovascular comorbidities and neurological disorders, including a greater probability of developing degenerative diseases. The presence of sleep disturbances in elderly patients with associated comorbidities cannot be underestimated, as it correlates with higher mortality and a general worsening of the quality of life.

Furthermore, the elderly patient is less suitable for surgical treatment than the young/adult patient, because of greater anesthesiologic risk and potential major postoperative complications. For these reasons, the gold-standard treatment in moderate-to-severe sleep apnea disorders is represented by CPAP therapy, which also correlates with an improvement in cognitive performance and quality of life.

Take-Home Messages

- Geriatric population has the same risk factor as the adult population for the development of OSA; however, due to associated risk factors there is more significant mortality and incidence of cardiovascular disease
- Literature data suggest a higher incidence of this disorder in subjects over 65 years old, with an estimated prevalence between 13% and 32%. This prevalence is two times higher in men than in women (over the age of 65), probably because of hormonal differences. It is closely related to dietary habits, lifestyle and population's general health status.
- Differently from young/adult subjects, there is a higher percentage of apnea episodes of central origin (CSAS) in the elderly.
- The elderly patient is less suitable for surgical treatment than the young/adult patient, because of greater anaesthesiologic risk and potential major postoperative complications.
- For these reasons, the gold-standard treatment in moderate to severe sleep apnea disorders is represented by CPAP therapy, which also correlates with an improvement in cognitive performance and quality of life.

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Artificial Intelligence in Sleep Medicine: A New Epoch Dawns

34

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34.1 The Digitization of Sleep Medicine: A Living Memory

When I began training in sleep medicine 26 years ago, we recorded the polysomnography on paper and ink. In the quiet of the control room, I could hear when the patient was going into stage two sleep by the sound of the ink scratching out dense sleep spindles. Equally, I could tell when the patient was going into REM sleep by the sound of wide sweeping motions of the EOG signal as the ink swiped across and back on the moving paper roll. Those paper data on Grass machines are now akin to museum artifacts, and since then, the field has become fully digitalized capturing the complex electrophysiologic signals of polysomnography across almost a dozen channels fully into computerized platforms [1]. Today, over 7500 board-certified sleep specialists are credentialed in the United States practicing at 2500 sleep centers in the nation [2]. All sleep centers in the United States are now fully digitalized, and many computer programs exist to acquire, score, interpret, and archive polysomnographic data.

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This massive amount of data collection occurring nightly across thousands of sleep centers is a natural stratum to benefit from advances in digital medicine, computer and data science, and the latest field to interface with sleep medicine, artificial intelligence.

Alan Turing first articulated the challenge between computing and intelligence in his 1950 paper "Computing Machinery and Intelligence," and soon after, the enigmatic term Artificial Intelligence was first coined by John McCarthy in 1955 when submitting a grant proposal to fund a workshop that he and other computer scientists wanted to hold at Dartmouth College that summer [3, 4]. In the 70 years since, we have been captivated by the prospect of machine intelligence in competition with human intelligence. Human imagination has only fueled this race since its conception.

While artificial intelligence is canonized as futuristic in our imagination—by movies such as Stanley Kubrick's "Space Odyssey: 2001" where a renegade onboard computer HAL 9000 commandeers control of a spaceship, or more recent movie anthologies such as "The Terminator" brought the world the iconic character of a cyborg assassin played by Hollywood actor Arnold Schwarzenegger (who went on to become the future "Gubernator" of California), artificial intelligence today is not only part of our present day reality but has long eclipsed any fictional future portrayed decades earlier. The extraordinary movie trilogy "The Matrix" envisioned a technological revolution enslaving human beings in virtual realities, succeeding in embedding both the allure and fears of virtual reality which gripped global audiences 20 years ago and yet now, when viewed in our contemporary era of lives lived on Social Media, relationships are conducted more through virtual messaging platforms WhatsApp, Signal, and Telegram than real connection and ubiquitous video conferencing, 4D movies, Oculus Rift gaming, autonomous drone warfare, and Iron Dome Missile Defense Systems. The Matrix narrative, while certainly prescient, is entirely outdone by reality today where artificial intelligence is already deeply woven into the fabric of our everyday lives, in both peace and war [5].

Netflix started learning our preferences using algorithms to generate new viewing recommendations—informed through machine learning—since 2006 [6, 7]. The motor cars we drive now have computer vision. We use computer-assisted radar to park in an empty spot. The Tesla company—the world's most valuable company—far from being a carmaker, or even a battery marker, is at essence a data company acquiring billions of miles of data to build global insights into human drivers and driving in pursuit of enhanced, safer, more efficient driving and practices and the future of fully autonomous driving. Less known is that Tesla uses big data analysis to inform perhaps a more ominous future of monetizing our insurance risks, recording our telephone and text messages inside the vehicle, and predicting our consumer habits. Unquestionably digitalization, vast amounts of real-time-generated data and artificial intelligence and machine learning are deeply embedded in our daily lives.

Corporations are increasingly embedding artificial intelligence into the consumer interface with their products, services, digital processes and decision-making, evolving algorithms, whether for self-driving cars, approving mortgages and loans, issuing credit and, to return to our field, in diagnosing disease.

The use of artificial intelligence is becoming so widespread that there are now efforts for legislation toward regulation of artificial intelligence which is considered vital to develop artificial intelligence tools that we as consumers feel our trustworthy [8].

Artificial Intelligence Ethics is now in sharp focus within corporations which must codify key AI principles with the balance between humans and machines and decide whether.

Artificial intelligence systems are used in approval for Apple's new credit card quickly bringing it under investigation for discrimination against women by New York State Department of financial services [9]. (The alarm was raised by a wife of an Apple cofounder who was offered a line of credit 20-fold *less* than that offered to her husband despite holding joint assets). Elsewhere, in 2018 Amazon used artificial intelligence algorithms for screening resumes which discriminated against women, leading Amazon to eventually axe the algorithm [10].

Recent investigations published in Science have uncovered that algorithmic risk prediction tools impacting millions of people in the United States annually are already demonstrating significant bias in terms of race [11]. Race multiplier algorithms used by hospitals prioritized kidney transplant candidates at the expense of race, discriminating against African-American transplant recipients on transplant waiting lists [12]. The investigators identified the bias was caused by predictive algorithms focused on healthcare expenditure rather than comorbidities. Yet, these algorithms failed to account for disparate healthcare access—we spend fewer healthcare dollars on Black patients compared to equivalently sick White patients. Thus, when the algorithm determined healthcare cost as an appropriate proxy for health by some measures of predictive accuracy, significant racial biases followed. These algorithms made black patients less likely to be listed for renal replacement transplantation.

These flaws are not deliberate but merely reflect the original data set that might have been used to teach the computer, and when it is expanded to scale, that bias is amplified.

Most recently the world was ignited by the launch of OpenAI's Chat GPT app unleashing AI capabilities to the public in November 2022. The app allows people to type in questions and watch the generated responses using seemingly human like language in text which may be sophisticated essays, a letter in response to a parking ticket, or even poetry. The reaction has been so intense, leaders in the world of technology have just penned an Open Letter calling for a halt to the race for development of such AI systems, and Italy has already outlawed the app—all in less than 6 months from its release. The intense reaction underlines how unprepared humanity feels it is for the rapid advances in AI and specifically generative AI. Former NASA Jet Propulsion Laboratory Roboticist and Founder of Caspian Autonomy, Dr. Reza Ahmadi Gilani cautions generative AI is not true AI—it is not intelligent in a cognitive sense even if it seems—from its responses—it might be. If you embed generative AI on a humanoid robot it cannot learn to walk as a child can—the robot can only perform tasks it is trained to—human intelligence has a cognitive dimension—generative AI of the kind in Chat GPT can only "generate" sentences based on its scope of training (personal communication March 29th, 2023, Dr. Reza Ahmadi Gilani, Pasadena California). In other words, these systems are, unlike

humans, far from creative and unless they are constantly learning on advancing knowledge platforms they will perpetuate and even amplify biases.

34.2 Sleep Medicine Is Big Data

For those of us practicing sleep medicine, even though we have adjusted to the digital acquisition of biometric data from our patients, whether it is acquired in the sleep center or out of the sleep center with portable technology, we need to be aware of how artificial intelligence is entering our field and indeed how it can enhance our capabilities as long as we understand its limitations and reinforce the perpetual need for human input and physician oversight.

During every sleep study we acquire significant quantities of electrophysiological signals of EEG and EMG activity, respiration signals of effort and flow, EKG signaling cardiac function and additional signals of body position, snoring in parallel with video and audio data. These large amounts of labeled data are acquired every day for thousands of patients around the nation sleeping in thousands of sleep centers around the country. Even more data is gathered in "out-of-center" (OOC) portable acquisitions which are now increasingly used in part accelerated by the pandemic and also out of necessity due to the expanding awareness of the field and the paucity (and prohibitive cost) of Level I attended sleep centers.

Over 25 million EEG studies are performed annually in the United States for seizure disorder or altered consciousness [6]. Over 40 million EKGs are performed annually in doctors' offices in the United States [6]. With the expansion of out of center sleep studies and the vast population at risk of sleep disorders, the volume of sleep medicine data being acquired dwarves other data sets. At present the majority of this data is scored once, interpreted and archived without being leveraged further. This represents an immense reservoir of knowledge which could be used to enhance artificial intelligence insights of the sleep disorders patient and indeed the sleeping person.

Given the advances in big data that identifies patterns within huge data sets, sleep medicine is well positioned to benefit from big data analysis which often involves data engineering with data scientists and ultimately applications of artificial intelligence. Artificially intelligent computer programs can already score sleep stages, identify abnormal breathing events and even identify certain sleep phenotypes or sleep endotypes predicting characterization of disease. The hope is artificial intelligence can vastly expand access, facilitate optimization and personalization of treatment strategies centered around each individual patient.

34.3 Artificial Intelligence and Machine Learning

The term artificial intelligence connotes computer systems' ability to perform tasks that normally would require human intelligence—for instance, classifying stages of sleep or types of sleep-disordered breathing. AI relies on computer programs,

algorithms, and software systems. Commonly, we use artificial intelligence for speech recognition applications, patterns of decision-making, and recognition of patterns and objects. While writing this chapter, the coauthors rely on artificial intelligence to voice dictated much of the text with apps that recognizes our speech, surprisingly accurately, despite distinctive international accents reflecting our origins from different continents.

Machine learning is a separate concept bookended between the two categories of computer learning—supervised learning and unsupervised learning—but has become used interchangeably with artificial intelligence as more and more machine learning is occurring.

By machine learning we refer to the computer's ability to improve performance with experience and exposure to prior data. Algorithms inside the computer programs that are machine learning algorithms continuously improve because of preprogrammed commands so the machine learns without supervision and without human intervention—this is called unsupervised machine learning. For instance, a computer pattern could be trained to learn to recognize cyclic alternating pattern in the background EEG signal of a sleep study. Similarly, machine learning algorithms can also be programmed to respond to supervised learning when the computer is educated to relate one input to a different output, for instance learning to distinguish stage N3 slow wave sleep in non-REM sleep from stage N1 non-REM sleep.

The machine learns against the basis of training data sets which have been previously established by human beings as gold standard measurements such as a cohort of 1000 patients with documented obstructive sleep apnea syndrome. The machine can learn only in comparison to the training data set, so if the data set is heterogeneous and diverse and includes other kinds of sleep disorders breathing, different ages, different genders then its ability to learn and recognize may be impaired compared to learning from a homogenous data set in the training stage.

Of course when training the computer, we recognize we do not seek 100% correlation because even in normal gold standard scoring of human being technicians to human being technicians or human being physicians to human being physicians there is a degree of variation between even the most seasoned scorers and so an adequate target for the automated machine learning program would be to achieve the same level of variation and the same level of agreement which will be less than 100% correlate.

At this moment, the most rapid developments and game-changing advances in Artificial Intelligence have come in an area known as "Deep Learning" through "Neural Networks," including convolutional neural networks. These computer networks do not rely on rules of probability, and computer scientists who develop them, note these networks do not deal with uncertainty in a predictable manner. Instead, the neural network evolves, learns, and extends its intelligence independently. Turing Prize Winner and legendary computer scientist Professor Judea Pearl of UCLA writes about this truly unknowable intelligence in his book—*The Book of Why*—surmising that when the programmer has finished training a new neural network, they cannot know what computations the network is performing or if the network fails, they are not able to repair it. Also, Pearl cites the prototype of

convolutional neural network AI "AlphaGo" developed by Google subsidiary DeepMind which defeated Lee Sedol 4–1 (for years the global human champion of the computer game) within months of launch [3].

Pearl notes that systems like economics and medicine, which are impacted by multiple variables influenced by overlapping webs of causal factors, truly can only be mined and understood by "Strong AI" systems—neural networked AI systems that can learn, reflect, and evolve based on their mistakes [3]. Sleep medicine may be particularly suited to applications for Strong AI systems since almost every system of health is impacted by both sleep as a state compared to wake, as well as an array of sleep disorders, acute and chronic combined with sleep deprivation and circadian timing. They all add up to impact of disease and treatment.

34.4 The Use of Machine Learning in Medicine to Date

Algorithms are used when assessing vast quantities of data repeatedly. AI has been used for skin cancer classification from dermascopic and photographic images; myocardial infarction diagnosis from EKGs; macular degeneration from a neural network trained on physician labeled fundoscopic images; brain tumor subtyping using AI neural networks trained on DNA methylation patterns; neurobiological signatures from EEG data predicting response to antidepressants; deep neural network learning has identified malignant pulmonary nodules from tens of thousands of chest x-rays with greater accuracy than board-certified radiologists; Artificial intelligence can de facto change the practice of medicine [6].

Artificial intelligence looking at 25 million pathologic specimens came to light when Memorial Sloan Kettering was found to have sold its 60 years of archives of pathology tissue specimens to commercial AI startup "PaigeAI," in exchange for equity for key stakeholders, bringing the use of artificial intelligence into sharp focus and raising questions about data sovereignty, patient consent, even clinician consent, and financial compliance laws [13, 14].

34.5 Artificial Intelligence and the Staging and Scoring of Sleep

Presently most of us in the field score sleep manually and by eye when reviewing electrophysiologic data, which we divide into 30-second intervals known as "epochs." A typical sleep study may comprise over 1000 epochs which are artificial slices of electrophysiologic data upon which we decide if the patient is awake or asleep, if the patient is asleep, what stage of sleep we see, and if there are any abnormal events during that slice of staged sleep. This process is labor-intensive and time-consuming and requires inspection by sleep technicians and the sleep medicine physician. Some automated scoring is also integral to the sleep software platforms used to acquire and host the data but is always subjugated to human scoring.

Certainly, stages of sleep are distinctive. Perhaps because they are so unique and largely reproducible when scoring many patients with homogenous demographics, machine learning, and artificial intelligence can succeed quite well at identifying stages of sleep. In addition, excellent data sets can be used to form the basis for machine learning. In fact, the most researched aspect of artificial intelligence in sleep medicine is examining the use of artificial intelligence and machine learning in classifying sleep stages.

Commercial entities now exist that provide artificial intelligence scoring at high speed, and they have been evaluated as a tool to augment the performance of the sleep technologist. These programs rely on examining, for instance, the ability to detect sleep spindles that define stage N2 sleep to look at the percentage of Delta waves that will determine stage N3 sleep. When used in conjunction with a seasoned sleep technician, these technologies can significantly reduce the time taken to stage and score a sleep study. These technologies are increasingly seen as valuable within the industry revealed by the recent 10-million-dollar minority equity investment made by Inspire Medical Systems—manufacturer of upper airway nerve stimulation for obstructive sleep apnea—into EnsoData, an FDA approved, commercial AI sleep study analysis platform. The investment (made public April 28th, 2022) is a clear sign that AI platforms will be increasingly used to identify patient candidates for interventions developed for obstructive sleep apnea.

The most common disorder examined in the sleep laboratory setting is still sleep-disordered breathing. Even though so many out-of-center sleep study devices are available and many home sleep apnea tests are being performed, there is still a very high number of patients who present to the sleep center with sleep-disordered breathing because they have many complex comorbidities requiring in-laboratory measurement.

Usually, the abnormal breathing events in sleep are scored manually by the sleep technician and validated and confirmed by the sleep medicine specialist. In my sleep center, I have worked for over a decade with the same sleep technologists, so we get very accustomed to each other's strengths and weaknesses and often cross consult with additional colleagues if we are unsure of how to interpret certain unusual events. Artificial intelligence now has been able to show automated scoring of similar accuracy to detect, for instance, obstructive sleep apnea and obstructive hypopnea comparable to the existing standard, which, is manual scoring.

Some of these data sets involve the examination of over 10,000 polysomnography acquisitions. One of the strengths of sleep medicine is that enormous quantities of data are being generated every night at every sleep center, making it highly applicable to big data algorithms, artificial intelligence, and machine learning. This is both a strength and a weakness. It means that the widespread application of machine learning and artificial intelligence to interpret polysomnography will be inevitable. While that can shorten the times to diagnose and finalize sleep studies and accelerate diagnosis, much of the interpretation of sleep studies also relies on the clinical judgment of the treating sleep specialist and knowledge about the patient being studied. Sleep physicians, however, continue to advocate for the best diagnoses to be made informed by their knowledge of the patient—vital clinical insights enhance the outcome of artificial intelligence measurements of polysomnography.

AI is increasingly being used to survey EEG data on massive scales to identify EEG signatures of obstructive sleep apnea, including some quantitative EEG measures that we do not currently recognize but are correlated with AHI and nocturnal hypoxemia [15]. Unlike human beings, the AI program does not have to be restricted to assessing sleep in artificial slices of 30-s epochs allowing these programs to see patterns we have not yet found. These EEG microstructure assessments are being correlated with neurobehavioral performance both in untreated disease and in the setting of resolved disease following CPAP use. These EEG approaches, which go beyond our ability to recognize Respiratory-Event Related EEG arousals against the background EEG, are already creating novel health metrics, including the Brain Age Index (BAI), which varies in relation to the presence or absence of cardiovascular disease [16]. Brain age increases with the increasing severity of sleep disorders.

Similarly, artificial intelligence has been used to assist with scoring of periodic limb movements, which tend to be repetitive and archetypal, and relatively predictable to recognize.

EnsoData Research, in conjunction with the University of Washington School of Medicine, advanced a large-scale machine learning analysis to train an artificial intelligence program to recognize sleep-disordered breathing events for classification [17]. There is a wide spectrum of sleep disorder breathing events including obstructive apneas, obstructive hypopneas, respiratory event related arousals, central apneas and the newly classified central hypopneas, which many sleep centers are finding difficult to define and recognize yet are very important in the central sleep apnea syndrome patient.

Using a data set that was obtained from the sleep heart health study, containing polysomnographic records of 5530 patients aged 40 years and older from 11 separate institutions the researchers developed a scoring framework using supervised machine learning to identify these different events (other than central hypopneas that have only just come into classification).

Previous researchers had used the same data set to develop automated scoring, and some used a combination of clinical features and polysomnographic features derived from the same data set. This formed the basis for a learning framework where every patient was described a binary classification as having either high AHI or high RDI or low AHI or low RDI. They used the presence or absence of these binary indicators as the basis for further analysis.

It is apparent that the researchers were building on an existing interpretation of established data sets and refining computer programs to become more precise. A high AHI index or low AHI index becomes apparent, but it can also become generalizable and reproducible, and accurate. The investigators pursued this line of inquiry because they sought to demonstrate gold standard sleep disorder-breathing classification on foundational data sets that have driven much of artificial intelligence beginnings in scoring sleep-disordered breathing.

Artificial intelligence itself is advancing as computing continues its own exponential evolution. High-performance cloud computing, deep machine learning, and strong AI techniques are advancing all the time because of the AI systems' ability to evolve its own intelligence—though cause and effect relationships are not clear, as

Judea Pearl detailed. This means that there is also a need for a new gold standard database against which to measure emerging artificial intelligence programs. These new databases will be interrogated more rigorously to provide a better and more reproducible baseline against which to compare new computer programs that are fast emerging.

Medicine is increasingly interfacing with computer programming, computer analytics, data science, and other fields traditionally outside of the realm of even very advanced medical education. One institute recognized this trend many years ago. Medical students at the Institute of Science and Technology studying at the Technion in Haifa, Israel, offer its most outstanding candidates dual degree studies in computer science in parallel to studying medicine to understand that these two fields are increasingly going to cross-pollinate and develop in parallel [18]. Similarly, Robson Capasso's Real World 4 Sleep Lab at Stanford University in California, offers future innovators an interface with data-science to identify challenges in need of solutions, seeking to improve translation of data-based solutions into clinical practice.

34.6 Use of Electronic Medical Records in Artificial Intelligence and Sleep Medicine

As dedicated sleep disorders specialists, we have always learned and continue to teach that the data we gather on patients only has the best value when we know the patient's history, clinical presentation, and examination findings. Knowing these features in advance influences our interpretation of the data, hopefully positively, to make the correct diagnosis and relevant treatment planning. The increasing explosion of out-of-center sleep testing, consumer wearable technology, and commercial digital apps seek to measure some form of sleep or offer clinical diagnosis. These tools will also only be of value if the patient's history is known. Particularly relevant to sleep-disordered breathing is knowledge of the patient's comorbidities which greatly increases the likelihood of clinically significant sleep-disordered breathing and clinical impacts.

Now that electronic medical records have been largely mandated by government decree and are becoming widespread in the use of medical schools, residency programs, fellowships, and day-to-day delivery of clinical medicine, healthcare institutions are in possession of a vital and valuable tool to identify patients that might be at risk of certain conditions particularly sleep-disordered breathing which is either undiagnosed or in genesis.

Investigators are now evaluating the electronic medical record with built-in artificial intelligence screening tools for undiagnosed obstructive sleep apnea. A small study conducted at the University of Washington school of medicine collaborated with the commercial entity of automated scoring EnsoData [17]. It published a small yet revealing study, underlining the future role of artificial intelligence in the practice of sleep medicine. It could undoubtedly expand the recognition of patients needing evaluation, diagnosis, and treatment.

They described modifying a well-known self-administered screening tool known as the STOP-BANG questionnaire, which can predict individuals at risk of sleep-disordered breathing. Because it is, self-reported, it is, of course, subject to reporter bias. The investigators considered this tool and combined it with data already populated in the electronic medical record to create a potential new screening tool and facilitate exposure or discovery of obstructive sleep apnea syndrome candidates or phenotypes before presenting clinically. Essentially the investigators used a combination of an existing screening questionnaire combined with data already documented in the electronic medical record to identify sleep-disordered breathing candidates.

They used two independent retrospective sleep study data sets. One relied on home sleep apnea tests for the first group of 5583 acquisitions. A smaller group contained data from sleep center polysomnography of 1037 patients. Raw sleep study waveforms manually scored events and generated standard indices (the apnea-hypopnea and the arousal indices) were all available. The study data sets looking at-home sleep apnea tests combined 90 separates electronic medical record metadata variables. When looking at the second data set using acquisition from within the sleep center, they combined 54 electronic medical record metadata variables. Presumably, they included fewer variables with the gold standard sleep study because diagnosis is more definitive in the sleep center, particularly for more complex patients.

They trained the computer program to detect the usual threshold of mild, moderate, and severe obstructive sleep apnea. They combined this across three different screening tools including the Stop BANG questionnaire, the "P bang" (Which includes blood pressure, body mass, age neck size and gender but no knowledge of snoring) and a separate index termed the common clinical data set (Containing metadata variables routinely recorded in the electronic medical record common clinical data set standard).

Investigators found that combining meta-data variables from the electronic medical record with the conventional self-reported subjective score in conjunction with data from both study groups, which were patients studied in the home setting or patient studied in the sleep center setting, provided the highest predicted value of obstructive sleep apnea syndrome. They also found that the top five features were STOP-BANG physiologic features including self-reported snoring, blood pressure, body mass index, age, neck size, and gender. Other relevant features were EMR-based physiologic measurements, including HDL, triglycerides, systolic blood pressure, diabetes hypertension, and depression.

The investigators concluded that using artificial intelligence programs to identify EMR based parameters can help uncover obstructive sleep apnea (OSA) patients before they have a clinical manifestations, leading to a systematic widespread, accurate screening for patients who may not have considered themselves or their doctor the diagnosis.

This has enormous and widespread applications, particularly for major healthcare systems managing tens of thousands, if not hundreds of thousands of patients. As an example, the AHI as a surrogate endpoint to assess disease presence and/or

severity has a limited correlation with cardiovascular, neuropsychiatric and/or other clinically relevant end-points. But considering the process in reverse—rather than seeking out a particular AHI to treat, but instead—from the outset—seeking out targeted populations carrying a high burden of cardiovascular or neuropsychiatric disease could help accelerate diagnosis and treatment to the most impacted sub-population and change trajectory of disease. Not only in a patient but a population [19, 20].

It would be easy to see how the combination of algorithmic assessment of sleep testing combined with a detailed analysis of data generated by the interaction of patients with the healthcare system. Sources of patients' generated data could have the potential for earlier identification and mitigation of developing comorbidities. These include metabolic syndrome, drug-resistant hypertension, myocardial infarction, congestive heart failure, cerebrovascular accident, obesity, complications of excessive daytime sleepiness (including motor vehicle collisions, employment loss, and other catastrophes) [21].

Using artificial intelligence and knowledge of sleep medicine could enormously impact the prevalence of noncommunicable disease, which remains the leading cause of death in the United States and much of the first world. Understanding the broader implications of combining the power of vast databases in existing electronic medical record platforms that already document the leading risk factors associated with sleep-disordered breathing, means that sleep medicine, artificial intelligence and population health will become increasingly relevant. In an environment where populations are booming, the obesity pandemic shows no sign of retreating, and higher and higher proportions of the GDP are being expended on healthcare. This will become an area of great interest clinicians, researchers, academicians, policy-makers, and legislators seeking to control exploding costs to society of generations of unhealthy populations.

Some institutes already recognize this, and in October 2021, Mount Sinai Health System announced the establishment of a new department of artificial intelligence and human health. The department's mission is stated to lead an artificial intelligence-driven transformation of healthcare through innovative research, clinical translation, and personalization of healthcare delivery for each patient with the view that these efforts would have a wide-reaching impact on human health.

Mount Sinai described achieving the creation of an "artificial intelligence fabric" to infuse machine learning and artificial intelligence-driven decision-making throughout the Mount Sinai medical center to inform decisions and outcomes. This nexus, of course, is deeply specialized and is being led by a pioneering researcher in the emerging field of computational pathology and this person Dr. Thomas Fuchs who became the inaugural chair of the department. His research was in the background of developing novel methods for analyzing digital microscopy slides to reveal genetic mutations and their influence on changes at the tissue level. His work created large-scale systems for mapping pathology origins and progress of cancer. By creating a special division dedicated to artificial intelligence and human health, this New York-based healthcare system hopes to lead scientists and clinicians to develop novel diagnostic approaches and treatments for acute and chronic diseases.

Interestingly this physician came to Mount Sinai as the Dean of Artificial Intelligence and Human Health from the center of digital and computational pathology at Memorial Sloan Kettering Cancer Center, which was the site of the previous controversy concerning data sovereignty over pathological specimens, which in fact brought the nexus of artificial intelligence and healthcare into sharp focus for many of us practicing in the field.

In the future, one can envision the need for a department of artificial intelligence and sleep health—because of the unparalleled scale of data collected in sleep studies both in the center and out of center and because of the impact of sleep disorders on leading noncommunicable disease, including hypertension, diabetes, cerebrovascular disease obesity, aging, and malignancy.

34.7 Population Health, Sleep, and Artificial Intelligence

If we focus on population health, it is apparent, and natural development of sleep medicine is to move toward the population health space simply because so many comorbidities are driven by pathology in sleep. There is increasing recognition, for instance, that Sleep is the new cardiovascular frontier. While that was editorialized in the New England Journal of Medicine almost 20 years ago it is only now, in February 2022, that the American Academy of Sleep Medicine has recommended cardiology based accredited sleep centers [22, 23].

It has long been identified that sleep duration and mortality demonstrate a U-shaped relationship meaning short sleep and long sleep times are associated with pathology. Still, the mechanism and cause are not recognized. This is also because sleep is not monolithic; it is highly variable. It is dynamic in each sleep opportunity and across time in individual patients and highly faceted and highly diverse across individuals.

In this era of wearable data, many Americans use wearables. Almost everyone has a smartphone with vast reservoirs of data that might potentially be interpreted as sleep predictors, including the duration of sleep, circadian timing of sleep, fragmentation of sleep and other findings which are now untapped in terms of understanding our own population. Applying machine learning and artificial intelligence to this ocean of digital information will probably reveal new outcomes between sleep and public health.

We can only answer these questions and requirements if the big data collected every night, whether in sleep centers or by ubiquitous devices that we now wear, are analyzed for previously unrecognized information, and correlated with our clinical knowledge. Unfortunately, the data is so vast that it is also very difficult to it assess manually. It requires computer-based analysis. Archiving vast quantities of data requires cloud-based methods that focus on the challenge of privacy protection, data sovereignty, and digital ethics.

We must never marginalize the role of the treating physician and clinical team because even copious amounts of sleep medicine data do not give us a true window into the diagnosis, absent clinical information and clinical knowledge of the patient being studied.

In my own practice (QA), I have been traditionally viscerally opposed to patients' immediate desire to open their smartphones and show me the findings on their favorite commercial "app du jour." This typically happens in the first moment or two that I enter the patient's room and try to begin gathering a traditional history. Inevitably, the patient would reach for the cell phone to show me for instance the findings on a Snore app, or a smartphone video that their family member had recorded, or their data on their Fitbit or Apple Watch, or "Oura ring" or compliance app data synced to their CPAP device. I found it enormously disruptive to my interaction with the patient, and it would often break my train of thought. Inevitably, the patient would also see an alert or notification from some other app on the smartphone and be distracted.

Indeed, there is evidence that proximity to a smartphone has an impact on cognitive ability and produces cognitive deficits [24]. But it was not until I met with my co-author (RC) that I decided to change my attitude after describing my frustrations with these daily digital interruptions in my many consultations with patients.

Robson explained that such technology was "here to stay," and patients were not going to be separated from wearable tech. In fact, it was time for physicians to embrace this. Certainly, wearable tech does not replace a seasoned clinicians history taking abilities or clinically standardized testing instruments which have been validated and FDA approved. But they may give us a helpful window into the patient's routine, concern, own assessment of their sleep, challenge, and successes after diagnosis and treatment.

After this discussion, changing my frame of mind changed my interactions with patients, who almost universally become extremely excited when I take an interest in their devices when we follow their progress by the consumer apps they have chosen to download. I am particularly struck by the impact on patients when they relate to their positive airway pressure devices using the software apps that correlate on their smartphone. It was only when I became a patient myself and began to adopt my own wearable technology that I realized how much it helped me feel healthier and gave me a sense of personal digital empowerment. I have entirely changed my view of the interface of digital technology, wearable tech, the future of remote monitoring, and the role of data science in managing both my patients and my health.

34.8 A Word on Digital Sleep Medicine

While this chapter is not focusing on home sleep testing, we must acknowledge the role of remote monitoring in accelerating digital sleep medicine, telehealth, sleep medicine, and the interface of artificial intelligence and sleep medicine.

Most of sleep breathing disorders are inevitably going to be diagnosed outside of the sleep center. The volume of patients is simply too high. Initial estimates of the prevalence of sleep-disordered breathing in 1993 by the sentinel study by Young et al. in the New England Journal of Medicine predicted 24% of men and 9% of women to have sleep-disordered breathing [25]. This is now widely recognized to be marked underestimation, and by some measures, one and four Americans is

likely to have sleep-disordered breathing [26, 27]. Others estimate over 1 billion human beings on the planet may have sleep-disordered breathing [28]. There will never be an adequate amount of sleep center beds, as the cost and labor are prohibitive to evaluate everybody in that setting.

While much of the sleep medicine field has long been apprehensive of remote sleep medicine measurement, it offers an incredible opportunity for patients and sleep specialists to drive the field forward and meet the needs of large populations of patients who require a diagnosis.

Migration of the evaluation of sleep patients outside the sleep center will have other impacts. Current guidelines recognize that patients who have a high pretest probability of sleep disorder breathing are safely evaluated initially by home sleep study. In recent years there has been a 400-fold increase home sleep studies [29]. However, patients who have complex sleep disorders in the form of central sleep apnea, hyperventilation, developmental disorders, neurological disorders, and congestive heart failure are more likely to require level one attended polysomnography. They are now gravitating and concentrating on the sleep center. This means that the complexity of patients undergoing testing in the sleep center setting is escalating and becoming more demanding and intensive. At the moment, most sleep centers are designed around relatively independent patients of low disease complexity attending for polysomnography, and even as more complicated patients with greater needs, including the cumulative burden of physical and more significant psychological needs are presenting to the sleep center, staffing requirements have not changed in many decades and technologist to patient ratios have not been adjusted.

This past month, at my sleep center, I performed two polysomnographies to activate the transvenous phrenic nerve stimulator, which required six individuals during one polysomnography, including my presence as the attending sleep disorder specialist. Alongside three members of the device company, one technologist to attend to the patient, and later three technologists to facilitate scoring this study and additional remote support from the sleep software program purveyor. This technology represents the cutting edge of interventions in sleep disorders medicine. Still, it gives an insight into the increasing demands on sleep centers both in handling very complex data which required interfacing of a nerve stimulator and a cardiac pacemaker and the polysomnography.

Investigators have documented that the complexity of patients undergoing attended level one polysomnography in American sleep centers has increased by 28–36% in the last 10 years [29]. This was done by calculating complexity based on validated indices and measuring comorbidities that correlate with a level of rendered care while performing the polysomnography. This means while many patients are being directed to low-cost, ambulatory home sleep studies, the sleep centers are increasingly burdened with more challenging, more labor-intensive, more complex patients with more comorbidities. Indeed, this is an added pressure to sleep centers. Still, it is also an opportunity for machine learning and artificial intelligence to accelerate scoring, support sleep technicians, relieve sleep technicians from manual scoring to be more patient-focused but also to provide data to support changes in staffing policies, reimbursement and laboratory workforce directed at the evaluation

of these highly complex patients. It can also liberate sleep personnel to participate in the burgeoning field of remote patient monitoring and virtual sleep patient navigation care pathways.

The investigators show that comorbidity indices in patients presenting to the sleep center for in-lab polysomnography have grown by 30% in the last decade. This is data gathered preceding the Covid 19 global pandemic, which I suspect will lead to further comorbidities, particularly in terms of cardiovascular and neurological diseases and sleep disorders.

Investigators importantly also showed that the complexity of patient's comorbidities meant a higher demand on care requirements during the investigation, more technologists needed, more time with more complex monitoring was required, and stretched demands for existing staffing ratios.

Machine learning and artificial intelligence can help identify the growing needs of very pressured sleep centers facing a tsunami of patients with these conditions. At our sleep center, it is very common to take care of medically complex patients with implanted devices, complex sleep disorders breathing, parasomnias or seizures and patients with developmental delay, intellectual disability, language barriers, and physical disabilities. In addition, we are a 911 World Trade Center Monitoring Center; our patients often carry complex psychological limitations and comorbidities such as posttraumatic stress disorder, which require a high degree of psychological support during the study.

34.9 Global Pandemic as a Driver for Artificial Intelligence in Sleep Medicine

We continued to practice sleep disorders medicine during the pandemic. In response to the global epicenter of the pandemic in NY, our center at NYU remained open throughout, even when most of New York State was locked down and all elective medical procedures were canceled by the Governor statewide.

Our chairman of medicine left it to the leadership of the sleep center to decide if we would continue investigating patients. We decided to continue diagnosing patients but discontinued the application of positive airway pressure in the sleep center because there were fears concerning aerosolization of the COVID-19 viral load before we knew more about the pathogen and before they were available treatments and vaccines.

We continued diagnosing patients in the sleep center and treating them with empiric positive airway pressure in their home settings. As the pandemic progressed, we developed air filtration capabilities and UVC light sterilization for reducing airborne bioburden and eventual return to in laboratory positive airway pressure titrations by late 2020. We also directed much of our investigations to the home setting and commenced a telemedicine sleep medicine service which continues for some of my colleagues even today.

The COVID-19 pandemic has impacted every aspect of healthcare, shifting resources dramatically, and these changes are here to stay even as we are entering

the third year of the pandemic. It also reveals the immense need to be able to pivot quickly away from an in lab setting to an at-home remote setting to provide care for enormous numbers of patients.

To put this into perspective, the impact of the pandemic on sleep medicine was particularly severe. Analyzing the impact of the COVID-19 pandemic on sleep medicine services, investigators reviewed survey data in Europe, the United States, China, and New York states [30].

Looking at 19 European countries and examining 40 sleep centers, diagnostic procedures were reduced by 70% at the time of the initial lockdown, which is March and April 2020. Staffing levels were reduced to 25% of baseline, and telemedicine was not being used. In the same time frame in 297 Members of the American Academy of Sleep Medicine centers (of which 90% were in the United States), there was a 90% reduction in activity for 90.4% of sleep center studies and, surprisingly, a 60.3% reduction for home sleep apnea testing. Sleep centers discontinued mask fitting procedures, introduced mitigation strategies, temperature testing, and PCR testing, and provided over 70% of their visits in a telemedicine setting.

In the first 6 months of 2020, surveying 56 sleep centers in China. 90% of diagnostic polysomnographies were discontinued, and 95% of CPAP titration studies were canceled—no staffing information is available. Data of sleep medicine services in New York State during the COVID-19 outbreak in spring 2020 show polysomnography studies and sleep centers came almost entirely to a stop. However, our sleep center was an extraordinary outlier continuing these investigations.

This considerably brought into focus the need for **remote** testing, monitoring, and managing huge patient populations and has ushered in the concept of the virtual sleep center with a broader reach and greater span than mere out-of-center testing.

While we are successfully back to normal operations, a future disaster could impact our ability to deliver sleep center centered sleep medicine services. There has never been a more opportune time to look at how artificial intelligence machine learning combined with the human health needs could be rapidly combined to be better prepared for the next unforeseen calamity as well as address the tens of millions of people yet to be diagnosed and treated.

We also discovered new limitations of which we were unaware. I learned new terms such as “digital desert” which surprisingly impacted my own patients in New York when I found my patients did not have access to the Internet at all, let alone high-speed Internet. Patient lacked smartphones, computers and essentially some of our patients were utterly cut off from care. I also learned this from my own patients who were attempting to provide their professional roles via the Internet, such as teachers, physical education coaches, and other doctors. We were shocked to learn of the challenges we shared in serving our patients, clients and students. To our surprise, the internet infrastructure in New York and much of the United States is still lacking. Many areas are devoid of true high-speed Internet access, which often impacts the most vulnerable demographics who also have the most comorbidities. The pandemic brought into sharp focus the connectivity gap and is being addressed by the US government [31]. Many areas of the nation lack broadband access, and often, this gap correlates with lack of access to doctors and healthcare [32].

34.10 A Word of Caution

There is intense interest in examining the role of artificial intelligence and machine learning in the setting of sleep medicine, and Goldstein and colleagues make a very worthy observation of the increasing number of data requests made of the National sleep research resource, which is a data repository financed by the National Institute of health comprising of 30,000 sleep studies including raw physiologic data annotated in summary files and clinical outcome data and other variables [33]. Goldstein reports over 40 Terabytes of data have been shared with 400 users worldwide, almost half of which is for a request to look at machine learning impacts on improved sleep staging and better outcome prediction. We are at the pioneering frontier of sleep and artificial intelligence interface.

However, analyzing the computationally extensive data that can be derived from electrophysiologic signals recorded in the average polysomnography means there is an infinite number of measures that can be calculated, few of which will have clinical meaning, and an almost infinite number of quantitative outcomes that could be extracted that might have a little clinical utility. Certainly, the conclusions drawn by artificial intelligence and machine learning will only be as good as the initial data sets used to train the AI programs and those data are still subject to artifact and other challenges that could corrupt or make the data less precise—and it's something that we as manual interpreters of sleep studies and manual scorers can easily extract when we review data on one patient at a time.

While much of the deeper trepidation in our field toward AI, is the fear of being supplanted as a physician by machine intelligence. Much of the hesitation among practicing clinicians is also due to a lack of transparency. We are increasingly encountering the tyranny of algorithms we as physicians cannot understand and algorithms that consider deep learning vital or AI programs even the programmers cannot know. Similarly, patients present concerns to sleep specialists from information generated by consumer wearable technology that makes assessments about the patient's sleep utilizing their own proprietary algorithms which we also cannot assess independently and are also not independently approved by the FDA. While the quantified self is already here in the commercial market, medicine retains its traditionally conservative ethos and will be reticent to adopt changes for some time.

In sum, doctors tend to be fearful not of what we do not know—the best doctor acknowledges the limits of his or her knowledge—but more fearful what we cannot ever know. Thus, the mystery of the strong AI-generated by the computer programmer who develops a convolutional neural network for example, that continues to create its own intelligence. When it succeeds, the programmer does not know how or even why.

Further hesitation confronts the physician because artificial intelligence algorithms are also subject to proprietary ownership with commercial goals. These closely guarded algorithms also represent barriers to scientific validation through reproducibility, making clinicians more reluctant to utilize this technology. Technology developers are recognizing this and may offer their technologies to be initially released to a sleep center to be used in tandem with gold standard

acquisition methods until the individual sleep center faculty becomes comfortable even with FDA-approved advanced technology. The Zoll Itamar WatchPat device measures sleep in the portable setting with validated measures and is FDA approved. Still, many new adopters will first use the technology alongside a traditional PSG to gain personal confidence in their patient's data on the new technological platforms (personal communication Andrey Afrin Zoll Itamar). As they build their confidence, faculty becomes increasingly comfortable with the new platform.

For such a broad research agenda to be effective, we need to think beyond academic prowess in AI and consider workforce preparedness, implementation readiness, strategies to scale innovation, and novel ways to fund the underlying efforts. Innovation requires both technology as well as business process transformation; and often there is a mismatch between the promise of a technology and existing business strategies [34].

One opportunity that is very well identified by Goldstein and worthy of repetition is that almost 2500 sleep centers in the United States are producing enormous quantities of raw data every day [33]. At the moment, most of that data is being used only for clinical interpretation and is not being subject to big data analysis and for formulating new foundational "Ground Zero" data sets that could drive future advances in evolutionary artificial intelligence development.

There is no infrastructure to support or collect or archive this clinical data, nor is there financial incentive to do so though certainly, this is an unrealized asset of significant equity value. A very common challenge in the working sleep center is running out of space to archive our own clinical studies. With the rise of the new era in cyber warfare, concerns about data sovereignty and data protection, these challenges, have become even more acute. This is a lot for an individual sleep center director to manage.

But there is a need in our field to gather all the accumulated data to analyze it with machine learning artificial intelligence to advance our knowledge about the role of artificial intelligence and machine learning in the management of millions of patients who are in need of evaluation.

When we consider that the National Institute of Health, a national sleep research resource contains only 30,000 sleep studies seems an incredibly small sample when my own sleep center studies almost 4200 patients annually—the output of one regional sleep center serving two or three counties in the United States which is made of almost 4000 counties. In sum, we are sampling a tiny tip of a huge iceberg.

Suppose we are to develop advanced, reliable, sophisticated, helpful artificial intelligence programs. In that case, we are going to need to collate enormous quantities of data that perhaps will rival even the military in scale. We will face the same dilemmas our military currently confronts—the struggle between the interface of artificial intelligence and human intelligence and concepts of autonomy or semiautonomy depending on the type of artificial intelligence involved.

Consider drone warfare. In this definition, artificial intelligence can be assisted, augmented, or autonomous. The distinction is important: when artificial intelligence is assisted, the machine will be executing the action (for instance, a drone), but it is human beings making the decision. When artificial intelligence is augmented,

machines are again executing actions—for example, firing weapons from a drone—but there is a collaboration between human intelligence and machine intelligence in the decision-making. Finally, in autonomous systems, artificial intelligence ensures the machine makes and executes both the action and the decision—human intelligence is not participating. Similar barriers and boundaries need definition in the field of artificial intelligence in sleep medicine.

Another concept to consider is the migration of sleep medicine into the consumer sector where eventually some sleep health can be driven by the patient, also known as the consumer. As the quantified self becomes more and more prevalent, *The Economist* reports one in four Americans wears a smartwatch to track activity–sleep interventions that are increasingly sought out by the consumer, such as downloading a digital app to treat insomnia with committed behavioral therapy or maintaining a food or exercise diary. In due course, purchasing and automatically adjusting a positive air pressure device may become possible. More complex challenges are driven by demand back to the clinical sleep specialist. This is much like the distinction between an ophthalmologist and an optometrist and a purveyor of Eyewear.

34.11 Conclusion

Sleep medicine is an incredibly ripe field for advancing the interface of artificial intelligence, machine learning, public health, and personalized medicine. Regulation is trailing these advances, and the FDA has embarked on a digital health innovation action plan to help facilitate advances in technology while protecting patient safety. It is crucial when we meet our patients that they understand that consumable wearable technology has not yet met the FDA standards. Unfortunately, most of that technology has not gone through the exhaustive and expensive process of being studied against a validated gold standard. Therefore, the FDA's regulatory strategies to evaluate such technologies are evolving, so there is a difference between consumer measures of sleep and accurate measures of sleep via validated polysomnographic data acquisition.

We should embrace artificial intelligence and innovation in sleep medicine in a systematic, structured, and gradual manner, perhaps beginning by allowing automated Scoring of Sleep and automated staging of sleep and automating scoring of certain events marking during sleep. These data sets will still need human beings to review, correct, and modify them, particularly with knowledge of the patient being studied at the sleep technician and the sleep physician level. Sleep centers considering engaging artificial intelligence commercially available products must verify data security and data sovereignty. In addition, massive healthcare systems with major health resources should consider acquiring with patient consent derived data gathered by in-center and out-center monitoring for ownership of their databases to learn about the population they are serving. Data registries across institutions and data consortia shared by institutions must be developed to maximize insights into our patient populations and the trajectory of their comorbidities, and the impacts of

our interventions. Electronic medical records should be rapidly integrated with artificial intelligence to identify target populations for rapid diagnosis and evaluation, providing knowledge of advancing outcomes for people with sleep-disordered breathing, ultimately avoiding complicating comorbidities of untreated disease.

The largest data consortia could represent entire populations by fully incorporating demographics, age, body mass, gender, race, ethnicity, and many other variables forming a more accurate basis for artificial intelligence programs to embark on unsupervised and supervise machine learning to advance our insights on specific disease. By pooling the sleep studies performed in such populations, AI scoring could become truly intelligent and representative.

The healthcare system will become responsible for storing even more massive quantities of patient related data in secure servers or clouds impenetrable to cyber warfare, ransomware hacking or other vulnerabilities. One of the challenges we have in our sleep center is that the computer software used to gather sleep study data has changed over time. Those data sets are incompatible and so accommodation must be made for this kind of diversity. Massive data consortia will need to be similarly flexible.

We must begin talking to our patients about this technology and its imminent arrival. With many of my patients, particularly if they have more complex findings, I open the sleep study and orient them on a computer screen, showing them what I see with my eye and why it is abnormal. I have found this extraordinarily empowering for the patients. It benefits my relationship with the patient when we want to pursue intervention. Similarly, they will need to know if their data has been read by only a machine or by a human being, and at the moment of course, it will always be a hybrid effort.

We must always lead with the philosophy that the data belongs to the patient, and the patients are in control of their data. This is something that I constantly visit with my patients and patients should have a choice of whether their data would be participating in big data analysis—interestingly this option is not yet offered to patients being seen in the United States on electronic medical record systems—there is no "opt out of Big Data" option when a digital medical record is initiated. Thus when documenting, my patients guide me as to what we should record in the electronic medical record if there is something of particular sensitivity that they would like me to know but prefer that I do not document on the computer interface.

Following patients' wishes regarding these deeply sensitive issues only ensure we have the greater trust of our patients. The more artificial intelligence will begin to interface with sleep medicine, the more important it is that we maintain and preserve our patient's trust.

At the same time, the more we understand the evolving trends impacting the practice of sleep and AI, the more confidence and measured trust we can begin to place in the artificial intelligence systems. So, we are starting to interface with the data we acquire from our patients and those technological innovators driving the field forward.

Take-Home Messages

- Sleep medicine is being digitalized
- Sleep medicine is well positioned to benefit from big data analysis which often involves data engineering with data scientists and ultimately applications of artificial intelligence.
- Artificial intelligence programs to identify EMR based parameters can help uncover obstructive sleep apnea (OSA) patients before they have clinical manifestations, leading to a systematic widespread, accurate screening for patients who may not have considered themselves or their doctor the diagnosis
- Combining the power of vast databases in existing electronic medical record platforms that already document the leading risk factors associated with sleep-disordered breathing means that sleep medicine, artificial intelligence and population health will become increasingly relevant.
- Sleep medicine is an incredibly ripe field for advancing the interface of artificial intelligence, machine learning, public health, and personalized medicine.
- Regulation is trailing these advances, and the FDA has embarked on a digital health innovation action plan to help facilitate advances in technology while protecting patient safety.
- It is crucial when we meet our patients and make them understand that consumable wearable technology has not yet met the FDA standards.
- Unfortunately, most of that technology has not gone through the exhaustive and expensive process of being studied against a validated gold standard.
- FDA's regulatory strategies to evaluate such technologies are evolving, so there is a difference between consumer measures of sleep and accurate measures of sleep via validated polysomnographic data acquisition.

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