



Association between Periodontitis and Obstructive Sleep Apnea

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ABSTRACT:- Stress is necessary for life. We need stress for creativity, learning and for survival. Unfortunately overwhelming stress has become an increasingly common characteristic of contemporary life. When stressors throw your nervous system out of balance, relaxation techniques can bring it back into a balanced state by producing the relaxation response. Body's natural response to stress is sleep. Sleep is a period of rest for the body and mind, during which volition and consciousness are in abeyance and bodily functions are partially suspended. Sleep is vital for human well being. Sleep deprivation is a well known form of torture. A sleep disorder or somniphobia is a medical disorder of the sleep patterns of a person. Among which obstructive sleep apnea is the most common form of sleep-disordered breathing characterized by repetitive full or partial collapse of the upper airway during sleep resulting in hypopnea or apnea. Serum levels of the inflammatory markers C-reactive protein and serum amyloid A appear to be increased in persons with sleep apnea and may be path physiologically related to sleep deprivation or intermittent hypoxemia. These inflammatory pathways are thought to play a role in the development and progression of periodontitis. Periodontitis is a chronic inflammatory disease of the gingival and supporting tissues of the teeth. Since OSA and periodontitis share an inflammatory basis, a common biological pathway for the association was possible. Hence this article reviews on types of sleep patterns, sleep disorders, sleep apnea, its symptoms, path physiology and its association with periodontitis and its treatment.

Keywords:- apnea, hypoxemia, inflammation, inflammatory mediators

I. INTRODUCTION

In mammals and birds sleep is divided into two broad types: rapid eye movement (REM) and non rapid eye movement (NREM). Each type has a distinct set of physiological and neurological features associated with it.[1] Sleep is prompted by natural cycles of activity in the brain and consists of REM and NREM sleep which consists of stages 1 through 4[2]. During sleep, the body cycles between non REM and REM sleep. Typically people begin the sleep cycle with a period of non-REM sleep followed by a very short period of REM sleep. Dreams generally occur in the REM stage of sleep.[3] A variety of respiratory disorders affect sleep or are affected by sleep. One such is Obstructive sleep apnea/hyperpnoea syndrome. It is now recognized that 2-4% of the middle aged population suffer from recurrent upper airway obstruction during sleep.[4] OSA is a chronic disorder characterized by the repeated collapse or narrowing of the pharyngeal walls during sleep, interrupting normal sleep.[5] It is a public health problem and potentially life threatening condition[6] in which a person temporarily stops breathing during night, perhaps hundreds of times. These gaps in breathing are called as apneas. The word apnea means absence of breath. An obstructive apnea episode is defined as the absence of airflow for at least 10 seconds.[7] A higher prevalence of periodontal disease has been reported in patients with obstructive sleep apnea syndrome[8] The various diseases of the periodontium is termed as periodontal diseases. The Periodontal diseases includes gingivitis, periodontitis[9] Gingivitis refers to inflammation of gingival and Periodontitis is an chronic inflammatory disease of the supporting tissues of the teeth characterized by progressive destruction of periodontal ligament and alveolar bone with increased probing depth formation, recession or both[10] The basic etiology of periodontal disease is dental plaque and calculus, acting as nidus evoking inflammatory response to bacterial plaque biofilm [11] The infection and host response begins with colonization and growth of periodontal pathogens.[12] These periodontal pathogens enter the blood stream by invading the epithelial cells and connective tissues and travel through human body.[13] Among which A.actinomycetemcomitans, P.gingivalis has a significant correlation with systemic diseases like coronary heart disease, diabetes, osteoporosis, malignancy.[14][15] Furthermore certain systemic disorders can have a direct effect on the periodontal tissues and these represent the periodontal manifestations of systemic diseases. In

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general these diseases do not initiate chronic destructive periodontitis but may accelerate its progression and increase tissue destruction.[16][17]However shared risk factors for periodontitis and OSA includes male sex, older age, obesity, oral breathing, cigarette smoking and alcohol consumption.[18]Hence these two chronic conditions may be linked via inflammatory pathways.[19]

II. STAGES OF SLEEP

The American Academy of Sleep Medicine divides sleep into REM and NREM. Three stages of NREM sleep includes N1,N2,N3,the last of which is also called delta sleep or slow-wave sleep[20]

2.1NREM stage 1-This is a stage between sleep and wakefulness. The muscles are active, and the eyes roll slowly, opening and closing moderately.

NREM stage2-In this stage theta activity is observed and the sleepers become gradually harder to awaken; the alpha waves of the previous stage are interrupted by abrupt activity called sleep spindles and K-complexes [21]

NREM stage 3-Formerly divided into stages 3 and 4,this stages is called slow-wave sleep. It is initiated in the peptic area and consists of delta activity. The sleeper is less responsive to the environment; many environmental stimuli no longer produce any reactions.

2.2REM:The sleeper now enters rapid eye movement where most muscles are paralyzed.REM sleep is turned on by acetylcholine secretion and is inhibited by neurons that secrete serotonin. This level is also referred to as paradoxical sleep because the sleep is harder to arouse than at any other sleep stage. Vital signs indicate arousal and oxygen consumption by the brain is higher than when the sleeper is awake.[22]An adult reaches REM approximately every 90 minutes with the latter half of sleep being more dominated by this stage.REM sleep occurs as a person returns to stage 1 from a deep sleep.[23]

III. SLEEP DISORDERS

Sleep disorders are among the most common clinical problems encountered in medicine and psychiatry. Inadequate or no restorative sleep can markedly impair a patients quality of life[24]Sleep disorders may be primary or secondary. Primary sleep disorders result from endogenous disturbances in sleep-wake generating or timing mechanisms, often complicated by behavioral conditioning. They may divide into 2 broad categories:[25]

3.1Parasomnias:These are unusual experiences or behaviors that occur during sleep;they include sleep terror disorder and sleepwalking and nightmare disorder.

3.2Dyssomnias:These are characterized by abnormalities in the amount,quality or timing of sleep.They include primary insomnia,hypersomnia,narcolepsy,breathing-related sleep disorder like obstructive sleep apnea and circadian rhythm sleep disorder.

IV. ETIOLOGY OF SLEEP DISORDERS.

The major causes includes medical conditions,psychological conditions and environmental problems.[26][27]

4.1MEDICAL CONDITIONS- Cardiac conditions include congestive cardiac failure,ischemia.Neurological conditions include stroke,dementia,peripheral nerve damage.Pulmonary conditions include COPD,asthma,OSA,Hematological conditions include paroxysmal nocturnal hemoglobinuria.

4.2PSYCHIATRIC CONDITIONS-Depression,anxiety disorders.

4.3ENVIRONMENTAL CONDITIONS-Stressful or life threatening events,environmental noise.

V. SIGNS &SYMPTOMS OF SLEEP DISORDERS[28]

Feel irritable,sleepy during day time,reacts slowly,difficulty in concentrating,tiredness,headache

VI. BREATHING DISORDERS IN SLEEP

Sleep related breathing disorders are group of disorders that affect breathing while we are asleep,and are characterized by disruptions of normal breathing patterns that only occur during sleep.[29]Sleep disorders are classified into dyssomnias,parasomnias,cardiac rythm sleep disorders.[30]However breathing disorders in sleep have emerged in recent years as an independant risk factors for cardiovascular morbidity and mortality.[31]It includes Sleep apnea,Snoring,Upper airway resistance syndrome.[32]Among which snoring & sleep apnea is the most common sleep related breathing disorders.[33]

VII. SLEEP APNEA

It is a common sleep disorder in which breathing temporarily stops during sleep due to the blockage of the upper airways.[34]

VIII. TYPES OF SLEEP APNEA

8.1 OBSTRUCTIVE SLEEP APNEA: It is the most common type of sleep apnea. It occurs when the soft tissue in the throat relaxes during sleep and blocks the airway, often causing to snore. [35]

8.2 CENTRAL SLEEP APNEA: It is a much less common type of sleep apnea that involves the central nervous system, occurring when the brain fails to signal the muscles that control breathing. People with central sleep apnea seldom snore. [36]

8.3 COMPLEX SLEEP APNEA: It is the combination of obstructive and central sleep apnea. [37]

IX. OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea is defined as five or more episodes of apnea or hypopnea per hour of sleep in individuals who have excessive day time sleepiness. Patients with 15 or more episodes of apnea or hypopnea per hour of sleep are considered to have moderate sleep apnea. [38] Obstructive sleep apnea is a chronic sleep disordered breathing [39] characterized by intermittent and recurrent pauses in respiration during sleep resulting in a decreased oxygen saturation and sleep fragmentation. There is accumulated evidence that hypoxia/reoxygenation such that is characteristic of sleep apnea. [40] OSA is caused by repetitive obstruction of the upper airway during sleep, resulting in hypopnea or apnea. [41] Persons with OSA may experience loud snoring, oxygen desaturation, frequent arousals and disruption of sleep. [42] Obstructive sleep apnea syndrome is an increasing major health concern affecting at least up to 5% of middle aged subjects in the general population. The main pathophysiologic feature in OSAS is the repetitive nature of partial or complete collapse of the upper airway leading to oxyhemoglobin desaturation of various severity [43]

X. AETIOLOGY

Sleep apnea results from recurrent occlusion of the pharynx during sleep, usually at the level of the soft palate. [44] OSA occurs when tissues in the upper throat relax and come together during sleep, temporarily blocking the passage of air. [45] Under normal conditions, the back of the throat is soft and tends to collapse inward as a person breathes. Dilator muscles work against this collapse to keep the airway open. Interference or abnormalities in this process cause air turbulence. If the tissues at the back of the throat collapse and momentarily block the airway, apnea occurs. [46] At this point breath is temporarily stopped and the person may gasp for breath. When the interference is incomplete (called obstructive hypopnea) and causes slow and shallow breathing. In patients with obstructive sleep apnea, the airways do become temporarily blocked or narrowed during sleep, reducing air pressure and preventing air from flowing normally into the lungs. [47] In response, the throat vibrates and makes the sound of snoring. Apnea decreases the amount of oxygen in the blood which triggers the lungs to suck in air. At this point the patient may make a gasping or snorting sound. [48] [49]

XI. AIRWAY CONTROL IN NORMAL SLEEP AND IN OSA

During normal sleep, stage dependent modulation of cardiac and vascular physiologic processes occurs. In OSA, this homeostatic control is severely disrupted. [50] During normal sleep, various protective mechanisms maintain partial patency of the upper airway. Tonic and phasic activity of more than 20 skeletal muscles that underlie the pharyngeal mucosa play a role in dilation and wall stiffening [51] Chemoreceptor responses to blood oxygen [52] and carbon dioxide [53] tensions, as well as local reflex mechanisms, such as negative airway pressure associated with forceful inspiration, also modulate muscle activity in the upper airway. [54] [55] Imaging [56] and endoscopic [57] studies have shown that during wakefulness and sleep, patients with OSA have a smaller-caliber upper airway lumen. Volumetric magnetic resonance imaging suggests that most of the responsible soft tissue originates from the tongue and lateral pharyngeal walls. [58] It appears that this tissue and the narrowing that results render the upper airway of persons with sleep apnea vulnerable to collapse. As a possible compensatory mechanism for this anatomically compromised airway, patients with obstructive sleep apnea have increased electromyographic activity of the pharyngeal dilator muscles during wakefulness. [59] [60]

XII. PATHOPHYSIOLOGIC MECHANISMS DURING SLEEP IN OSA

In healthy persons, there are interactions between the chemoreflex and baroreflex responses. Activation of the baro-reflex attenuates ventilatory [61] sympathetic [62] and bradycardiac [63] responses to peripheral chemoreflex excitation. [64]

12.1 Chemoreflex Sensitivity and Response to Hypercapnia, Hypoxia and Apnea.

Chemoreflexes mediate the ventilatory response to hypercapnia and hypoxia. Peripheral chemoreceptors are located in the carotid bodies of the internal carotid arteries, primarily respond to blood oxygen tension [65] whereas brainstem central chemoreceptors are most sensitive to carbon dioxide and acid base balance. [66] In healthy persons, the chemoreceptor response is blunted during sleep compared with wakefulness, leading to modest changes in blood gas tensions [67] Patients with obstructive sleep apnea have

heightened peripheral chemoreflex sensitivity resulting in an increased ventilatory response to hypoxemia[68] A physiologic hallmark of OSA is marked reductions in pleural pressure that are related to respiratory efforts against a narrowed or collapsed airway.[69] In healthy persons there are interactions between the chemoreflex and baroreflex responses. Activation of the baroreflex attenuates ventilator [70] sympathetic [71] bradycardiac [72] responses to peripheral chemoreflex excitation. In some persons hypoxemic stimulation of the peripheral chemoreceptors simultaneously increases sympathetic output to muscle and other vascular beds while activation of cardiac vagal activity results in bradycardia. This phenomenon is called the diving reflex [73]

XIII. PATHOPHYSIOLOGIC MECHANISMS DURING WAKEFULNESS IN OBSTRUCTIVE SLEEP APNEA

13.1 Sympathetic Activity and Impaired Cardiovascular Variability.

In addition to heightened daytime levels of sympathetic drive, other abnormalities in cardiovascular regulation are observed during resting normoxic daytime wakefulness in patients with obstructive sleep apnea. Patients with OSA have faster heart rates, blunted heart rate variability, and increased blood pressure variability [74]. Large studies have shown them to be markers of increased cardiovascular risk in the general population. [75]

13.2 Vascular Dysfunction

Increased endothelial-leucocyte adhesion mediated by increased production of adhesion molecules and upregulation of proinflammatory cytokines that predispose to endothelial dysfunction has been demonstrated in OSA. [76] The physiologic stressors associated with apneas cause elaboration of endogenous vasoactive substances of which the most important may be endothelin, a potent, long lasting vasoconstrictor. After 4 hours of disordered breathing events during sleep, endothelin levels and blood pressure increases. Levels of nitric oxide, a powerful vasodilator, may be decreased in OSA. [77]

13.3 Systemic inflammation.

Serum levels of the inflammatory markers C-reactive protein [78] and serum amyloid A [79] appear to be increased in persons with sleep apnea and may be pathophysiologically related to sleep deprivation or hypoxemia. [80] Moreover, there is evidence of oxidative stress in OSA. [81] These inflammatory pathways are thought to play a role in the development and progression of CVS. [82] and may be important mediators of disease in OSA.

13.4 Hypoxia/reoxygenation and Oxidative stress in Sleep apnea.

Oxidative stress represents a common threat and a hazard to all aerobic organisms. It is characterized by an imbalance between oxidant producing system and anti-oxidant defense mechanisms, resulting in excessive formation of reactive oxygen species. [83] Excessive ROS formation was documented in conditions such as hypoxia/reoxygenation or hypoxia/reperfusion, inflammatory diseases. [84] Increased ROS molecules such as superoxide, hydrogen peroxide and hydroxyl radical induce a plethora of signaling pathways that activate transcriptional factors responsible for the regulation of proper responses to the oxidative insults, by inducing redox adaptive gene expression [85] The primary source of altered redox balance in patients with OSA stems from their unique pathophysiology—the IH these patients undergo through sleep—which results in repetitive episodes of hypoxia/reoxygenation [86] Oxidative stress is a prominent feature of ischemia/reperfusion or hypoxia/reoxygenation and is manifested by increased ROS production and altered metabolic and molecular processes, resulting in cellular and tissue injury [87] Yet due to their pivotal role, ROS and oxidative stress in OSA may activate redox-sensitive signalling pathways which initiate adaptive responses to hypoxia and/or inflammatory pathways [88] Consequently, endothelial cells, leukocytes, platelets are activated [89] These activated cells can further contribute to oxidative stress through a further release of ROS and increased expression of adhesion molecules on leukocytes, platelets and endothelial cells thereby facilitating endothelial cell-leukocyte interactions that in turn further amplify inflammatory responses [90]

13.5 Inflammatory responses in OSA

Activation of redox-sensitive transcription factors can initiate and propagate inflammatory responses by subjecting a cell, a tissue, or the whole organism to IH. Some of the gene products upregulated by NF κ B and AP-1 induce adhesion molecules and proinflammatory cytokines. These have been shown to participate and aggravate inflammatory responses at the vasculature [91] [92] Proinflammatory cytokines are also gene products of redox-sensitive transcription factor activation which participate and amplify inflammatory responses. These pleiotropic molecules function to regulate macrophage activation, scavenger receptor expression and metalloproteinase secretion, modulate smooth muscle cell proliferation, nitric oxide production and apoptosis, and induce endothelial cell activation. The most investigated proinflammatory cytokines tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and interleukin-8 (IL-8), are regulated by oxygen tension and free radicals via

activation of NF κ B and AP-1 and possibly via HIF-1 α as well.[93]Apparently,once the inflammatory response is initiated,these cytokines can in turn activate NF κ B further exacerbating the inflammatory cytokines were found in the circulation[94][95]and in various cytotoxic T lymphocytes[96][97]Importantly,the balance between pro-inflammatory and anti-inflammatory cytokines is disrupted in patients with OSA.In lymphocytes for instance,while the levels of proinflammatory cytokine TNF- α were increased,the levels of the anti-inflammatory cytokine interleukin-10(IL-10) were also increased.A cytokine imbalance between the levels of TNF- α and IL-10 was suggested to be involved in the pathogenesis of several vascular morbidities[98]which further supports increased inflammatory-atherogenic processes in patients with OSA.

XIV. SYMPTOMS OF OSA [99]

- Excessive daytime sleepiness
- Morning headaches
- Impaired emotional or mental functioning
- Snoring

XV. RISK FACTORS ASSOCIATED WITH OSA[100]

Overweight
Gender
Age
Smokers
Alcohol/Smoking
Socioeconomic status

XVI. SNORING IN OSA

Snoring and OSA are on a continuum of sleep disturbed breathing that is a result of an airway supported by muscle tone that is reduced during sleep.Snoring and OSA are caused by repetitive dynamic obstruction of the oropharangeal airway[101]The oropharaynx is not supported by bone or cartilage,but by muscle tone.The physiological functions such as heart rate,respiratory rate decrease with each stage as sleep deepens[102]This decrease in neuromuscular activity,resulting in decreased muscle tone along with pharyngeal anatomy,can contribute to airway thresholds that lead to decreased oxygen levels during sleep.The smaller airway created by a combination of the anatomy and normal neuromuscular changes during sleep lead to a decrease in luminal pressure.When these pressure decrease to a critical level during inspiration,a collapse can occur causing ann obstruction,thereby preventing the passage of air resulting in snoring[103]

XVII. PERIODONTITIS

The tissues investing and supporting the teeth are known as periodontium.The periodontium is composed of tissues namely alveolar bone,root cementum,periodontal ligament ang gingiva.[104]The various diseases of the periodontium is termed as periodontal diseases.Their treatment is reffered to as periodontal therapy.The periodontal diseases includes gingivitis,periodontitis[105]Gingivitis refers to the inflammation of gingiva and periodontitis is an chronic inflammatory disease of periodontium characterized by alveolar bone loss,clinical attachment loss or both.The basic etiology of periodontal disease is dental plaque and calculus,acting as nidus evoking inflammatory response to bacterial plaque biofilm.The plaque microorganisms can exert its effect by releasing collagenase,hyaluronidase,protease,chondroitin sulfatase which can cause damage to the epithelial and connective tissue constituents.The intercellular spaces between the junctional epithelial cells are destroyed and may permit the bacteria and its products to gain access into connective tissue.[106]Gingivitis is characterized by vasculitis,release of inflammatory mediators,damage to junctional epithelium,loss of collagen fibre network,cytotoxic alteration of fibroblast[107]The pathogenesis of periodontal disease can be caused by subgingival bacteria and by evasion of immunological response.[108]characterized by bacterial invasion,production of exotoxins,role of cell constituents,production of various enzymes and inflammatory cells.Evasion of junctional epithelium by microbial mass and detachment of collagen fibers results in periodontal pocket.[109]The keratinocytes respond to the bacterial products by releasing cytokines and proinflammatory mediators[110]The periodontal destruction occurs as a result of infection by periodontal pathogens such as Porphyromonas gingivalis,Prevotella intermedia,Tannerella forsythia and Aggregatibacter actinomycetemocomintants[111][112]

XVIII. ROLE OF INFLAMMATION IN PERIODONTITIS

The consequences of periodontal infection is the synthesis of inflammatory cytokines and chemokines by local periodontal tissue or circulating inflammatory cells.The inflammatory cytokines such as interleukin-6,Tumour necrosis factor- α ,elevated C-reactive protein levels[113][114]evokes systemic inflammation.

XIX. ASSOCIATION BETWEEN OSA AND PERIODONTITIS

Gunaratnam et al suggested that the increased prevalence of periodontitis in OSA patients could be due to true association between OSA and periodontitis: OSA could act as an inflammatory mediator for periodontitis or vice versa.[115] Associative studies demonstrated that 60% of periodontitis cases (n=30) screened high risk of OSA compared with only 28% of controls (n=29). Cases were 4.1 times more likely (95% CI: 1.9, 11.4) to be at risk for OSA than controls (p=0.007) after adjustment for potential confounders [116]. It is also possible that increased prevalence of mouth breathing in patients with OSA could exacerbate periodontitis and underlie the association.[117] Of most relevance to the present study is a report suggesting that OSA is a risk factor for periodontitis [118]. Many factors associated with periodontitis are likewise associated with OSA. Those factors include Gender, Age, BMI, Cigarette smoking status, Alcohol/Sedative use before bedtime, Diabetes, Nasal breathing difficulty, Dry mouth, Educational attainment, Socioeconomic status. [119][120] Associative study suggested that old age, male gender, current smoking status, mouth breathing during sleep and high AHI were identified as risk factors for periodontitis. OSA was positively associated with periodontitis. [odds ratio=1.84, 95% CI=1.30-3.77] and CAL (OR=1.86, 95% CI=1.07-3.21) in a dose response manner. Additionally, OSA was positively associated with periodontitis (OR=2.51, 95% CI=1.37-4.62) in subjects \geq 55 years of age, but not in subjects less than 55 years of age. [121]

XX. TREATMENT

Periodontal therapy refers to the treatment of periodontal disease which mainly aims at removal of etiology of the disease and restoring the lost periodontal tissues. [122] Proper treatment planning followed by maintenance of oral hygiene results in good prognosis. However treating periodontitis is not only sufficient but on other hand its associative disease has to be treated. [123] The treatment of OSA depends in part on the severity of the condition. Treatment options include breathing device, dental devices, surgery. [124]

20.1 BREATHING DEVICES: Continuous positive airway pressure (CPAP) devices are the most common treatment for moderate to severe obstructive sleep apnea. It is safe and effective for people of all ages. Patients with obstructive sleep apnea who use CPAP feel better rested, have less daytime sleepiness, and have improved memory and concentration. For maximum use CPAP should be used for at least 6-7 hours each night. [125][126]

20.2 CPAP works in the following way:

The device itself is a machine and it has a mask containing a tube which connects to the device and fits over just the nose. The machine supplies a steady stream of air through a tube and applies sufficient air pressure to prevent the tissues from collapsing during sleep. [127]

The standard CPAP machine delivers a fixed, constant flow of air. Variations on CPAP include: [128]

Autotitrating positive airway pressure: These devices automatically respond to changes in the sleepers breathing patterns by adjusting and varying the air pressure flow throughout the night.

Bilevel positive airway pressure: This system delivers two different pressures, a higher one for inhalation and a lower one for exhalation

20.3 DENTAL DEVICES: They are also called oral appliances, are custom-made mouth pieces that help position the lower jaw and tongue during sleep. Dental devices may be helpful for mild cases of obstructive sleep apnea. It is indicated for patients who are not appropriate candidates for CPAP. [129]

DENTAL DEVICES INCLUDE: [130]

Mandibular advancement device: This is most widely used dental device for sleep apnea. It is similar in appearance to a sports mouth guard. MAD forces the lower jaw forward and down slightly which keeps the airway open.

Tongue retraining device: This is a splint that holds tongue in place to keep the airway as open as possible.

20.4 SURGERY: Various surgical procedures may be recommended for very severe cases of OSA but there is limited evidence for their effectiveness. Surgery is sometimes recommended by ear, nose, throat specialists, for severe obstructive sleep apnea. Uvulopalatopharyngoplasty, Pillar palatal implant, Tracheostomy are common surgical procedures indicated. [131]

XXI. CONCLUSION

Various studies have demonstrated a significant association between OSA and periodontitis. It has been suggested that OSA may be a risk factor for periodontal disease and that the treatment of OSA may prevent progression of periodontal disease. However diagnosis and treatment planning of OSA has to be done by a qualified physician. Oral appliance therapy can be considered as first line treatment in cases when CPAP has failed. There are many challenges facing the dentist who will be providing oral appliance therapy. The dentist should be knowledgeable in the science of OSA and oral appliance therapy. However further research is needed to establish the causal relationship between the two conditions.

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