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PERIODONTITIS AND SLEEP APNEA

Association Between Periodontal Disease and Obstructive Sleep Apnea: What the Periodontist Should Know

Ryan Price, DDS; and Philip Kang, DDS

Abstract: In recent years, studies have revealed a possible link between periodontitis and obstructive sleep apnea (OSA). Chronic periodontitis is characterized by the destruction of the supporting tissues of the teeth through complex cascades of inflammatory responses, and OSA seems to share common pathways, acting synergistically. This review article summarizes the literature on the potential association between a chronic oral infection such as periodontitis and OSA and discusses how clinicians can benefit their patients by understanding the commonalities and interplay that may exist between these two disorders.

LEARNING OBJECTIVES

- Describe the possible link between chronic oral infection and obstructive sleep apnea (OSA)
- Review what the literature says regarding the association between periodontitis and OSA
- Discuss the role periodontists can play in the diagnosis and treatment of OSA

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Periodontal disease and obstructive sleep apnea (OSA) are two conditions that plague society today. In recent years, the correlation between these two disorders has been evaluated. Numerous similarities and/or cofactors appear to overlap between them. When assessing periodontal disease and OSA, one needs to consider if there is an occurrence relationship within populations. If it is established that an occurrence relationship, whether direct or inverse, does exist between the two conditions within a population, the next question becomes whether a causal relationship in either direction or both directions can be proven. Will an increase in OSA lead to an increase in periodontal disease, or vice versa? Do the two conditions share a common biologic mechanism? It may be beneficial for clinicians to understand the commonalities and interplay that might exist between these two disorders.

Defining the Two Conditions

Periodontitis is characterized by the destruction of the supporting tissues of the teeth, including the alveolar bone, periodontal ligament, and cementum.[1] Periodontitis is one of the most prevalent illnesses, affecting 46% of the adult population; 9% of this is severe periodontitis.[2] The scientific and dental communities now understand that most often there is a microbiologic component that instigates the inflammatory cascade causing this destruction. Socransky et al outlined the most virulent strains of bacteria most often associated with advanced periodontal disease. The oral biome is normally in balance, providing a harmonious relationship with the host. When the biologic environment becomes skewed in the direction of these red complex pathogens that include *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* a greater inflammatory response in the local environment is likely.[3]

The cytokines induced by this inflammatory response draw destructive cells into the local environment (periodontium) hastening bone loss.[4] Furthermore, salivary and plasma enzymes also play a role in tissue destruction.[5] A responsibility of periodontists is to attempt to counteract the biologic, biochemical, and bacteriologic instigators of this inflammation and bone loss around teeth. This is crucial because periodontitis is well known to be associated with other illnesses and conditions such as cardiovascular disease, diabetes, rheumatoid arthritis, peripheral artery disease, respiratory diseases, osteoporosis, and pregnancy complications.[6] When examining patients, periodontists should know the various risk factors for periodontitis, including alcohol consumption, smoking, and obesity.[7]

OSA is a clinical condition in which a person has multiple incidents of partial or complete blockage of the upper airway while sleeping.[8] Partial obstructions are referred to as "hypopneas." Complete obstructions are called "apneas."[8] Gastaut et al first identified OSA in 1965.[9] This occurred while they were observing obese patients with hypoventilation problems when sleeping.[10] Epidemiological studies have shown that OSA is the most prevalent type of sleep-disordered breathing.[11] The severity of OSA is measured using the apnea hypopnea index (AHI). This index measures the total number of apneas and hypopneas per hour of sleep. An AHI score of 5 to 15 indicates mild OSA, 16 to 30 is considered moderate, and a score above 30 indicates severe OSA.

OSA has been shown to affect 24% of men and 9% of women.[8] Management of this condition is thought to be required when the AHI score is greater than 5 if there are also symptoms, which generally are nonspecific but may include excessive daytime sleepiness, chronic fatigue, and habitual snoring, or when the AHI score is above 30 whether there are symptoms or not.[12] The severity of OSA can also be determined by judging the degree of blood oxygen desaturation measured by oximetry.[8] It has been shown that numerous comorbid diseases, such as hypertension, stroke, angina, and cardiac dysrhythmias, could arise as a result of sleep apnea.[13] The most notable risk factors for OSA include advanced age, male sex, smoking, alcohol consumption, and obesity.[11]

Various mechanisms as to how periodontitis and OSA affect one another have been suggested. According to Lattore et al, these mechanisms are "(1) the dryness of the mucous membranes produced by oral respiration frequently observed in individuals with OSA (due to oral breathing or the pharmacological effects of hypotensive drugs), which enables the greater colonization of the periodontal microbiota; (2) the systemic inflammation that occurs in both OSA and periodontitis; (3) the oxidative stress that occurs in both diseases; and (4) the risk factors and comorbidities common to OSA and periodontitis."[14]

Periodontitis and OSA Association Studies

In efforts to elucidate what exactly links periodontal disease and OSA, various studies have examined the association between these two disorders (Table 1). Researchers Gunaratnam et al conducted the first of these studies in 2009. Conducted in Australia, this cross-sectional study of 66 subjects (54 males and 12 females) with an average age of 54.9 years old revealed that there was an association between OSA and periodontitis and that a higher occurrence of periodontitis was found in subjects that were diagnosed with OSA than in subjects that were not diagnosed with OSA. Specifically, the authors found that 77% to 79% of people with OSA also had periodontitis, and they also saw a substantial relationship between clinical attachment loss and total sleep time.[15]

In 2013, Seo et al conducted a cross-sectional study in Korea where 687 subjects (460 males and 227 females) with an average age of 55.85 years old were observed. The authors found that there was a significant association between periodontitis and OSA. The prevalence of periodontitis was noted to be 17.5% and the prevalence of OSA was 46.6%, and, most importantly, 60% of the subjects who were diagnosed with periodontitis also had OSA. The authors noticed specifically that OSA was associated with probing depths of more than or equal to 4 mm and with clinical attachment loss of more than or equal to 6 mm. A final observation by Seo et al was that periodontitis was associated with OSA in subjects 55 years of age or older but was not associated in subjects less than 55 years of age.[16]

Also in 2013, Ahmad et al performed a study in the United States that looked at the association between periodontitis and OSA. In this case-control study, the authors examined 154 subjects (61 males and 93 females) with an average age of 61 years old. Fifty of the subjects had moderate to severe periodontitis, while the other 104 subjects had gingivitis or mild periodontitis. The gingivitis and mild periodontitis groups acted as the controls in this study. As with the previously two mentioned studies, this analysis also found a significant association between OSA and periodontitis. Specifically, Ahmad et al found that the groups with moderate to severe periodontitis had a much higher chance of having OSA. In total, the prevalence of periodontitis was seen to be 32.5%. Sixty percent of the moderate to severe periodontitis group was seen to have an increased risk for OSA compared to just 28% of the gingivitis and mild periodontitis patients.[17]

Keller et al conducted yet another study in 2013 in Taiwan. This case-control study examined 7,321 subjects with OSA and 21,963 control subjects without OSA. The ratio of males to females was 18,232 to 11,052, and the average age of all subjects was 47.6 years old. This study again showed a noteworthy association between periodontitis and OSA, with 33.8% of subjects with OSA shown to have periodontitis while only 22.6% of patients without OSA had periodontitis.[18]

In 2015, Loke et al executed a cross-sectional study in the United States with 100 subjects (91 males and 9 females) whose average age was 52.6 years old. Of the 100 subjects, 73% were found to have moderate to severe periodontitis, and in terms of OSA, 26 subjects were normal, 21 had mild OSA, 19 had moderate OSA, and 34 had severe OSA. Unlike in the previously cited studies, the authors did not find any meaningful association between moderate to severe periodontitis and OSA. There was, however, a substantial association seen between AHI score and the percentage of plaque along with an association between age and moderate to severe periodontitis.[19]

Sanders et al performed a cross-sectional study in 2015 within a Hispanic population that included 12,469 adults between the ages of 18 and 74 years. The authors ultimately found a strong association between periodontitis and OSA.[20] The most significant association was seen in subjects that were less than 55 years of age; also, if subjects had an AHI score above zero, they had an increased chance of having periodontitis. It was even shown that the number of subjects with periodontitis was 11 times higher in the group that had an AHI score above 15 compared to those who had an AHI score of zero.[21]

In contrast, in 2016 Sales-Peres et al conducted a cross-sectional study in Brazil with 108 subjects (23 males and 85 females) with an average age of 40.1 years old and concluded that there was no meaningful association between periodontitis and OSA. In their study they specifically analyzed patients who were classified as class III obese. What they did find was an association between OSA and neck circumference.[22]

Another study performed in 2016 by Al Habashneh et al looked at 296 male subjects from a primary healthcare facility in Jordan whose average age was 40 years old. The authors concluded that people are twice as likely to have periodontitis if they are high risk for sleep apnea compared to those who are low risk for sleep apnea.[23]

In searching for an association between periodontitis and OSA, Latorre et al in 2018 studied 199 subjects (92 males and 107 females) with an average age of 49.9 years old. They ultimately concluded that there was a substantial association between periodontitis and mild OSA (AHI score 5 to 15). Furthermore, this specific association

TABLE 1

Studies Examining Association Between Periodontal Disease and Obstructive Sleep Apnea (OSA)

Study (Author, Year)	No. of Subjects	Average Age (Years)	Key Findings
Gunaratnam et al,[15] 2009	66 (54 males, 12 females)	54.9	77%–79% of people with OSA also had periodontitis substantial relationship between clinical attachment loss and total sleep time
Seo et al,[16] 2013	687 (460 males, 227 females)	55.85	60% of subjects diagnosed with periodontitis also had OSA periodontitis associated with OSA in subjects ≥55 but not in subjects <55
Ahmad et al,[17] 2013	154 (61 males, 93 females)	61	subjects with moderate to severe periodontitis had much higher chance of having OSA 60% of moderate to severe periodontitis group had increased risk for OSA compared to 28% of gingivitis and mild periodontitis group
Keller et al,[18] 2013	7,321 with OSA, 21,963 without OSA (18,232 males, 11,052 females)	47.6	noteworthy association between periodontitis and OSA 33.8% of subjects with OSA had periodontitis; 22.6% without OSA had periodontitis
Loke et al,[19] 2015	100 (91 males, 9 females)	52.6	no meaningful association between moderate to severe periodontitis and OSA strong association between AHI score and percentage of plaque
Sanders et al,[20] 2015	12,469	18–74	strong association between periodontitis and OSA, especially in subjects <55 subjects with periodontitis much higher in group with AHI score >15
Sales-Peres et al,[22] 2016	108 (23 males, 85 females)	40.1	no meaningful association between periodontitis and OSA association between OSA and neck circumference
Al Habashneh et al,[23] 2016	296 males	40	people at high risk for OSA twice as likely to have periodontitis compared to those at low risk for OSA
Latorre et al,[14] 2018	199 (92 males, 107 females)	49.9	association between periodontitis and OSA more frequent in patients diagnosed with hypertension or hypertensive cardiomyopathy
Nizam et al,[4] 2014	52	-	moderate or severe OSA associated with increased levels of IL-6 and IL-33
Nizam et al,[24] 2015	50	-	statistically significant association of salivary ProMMP-2 enzyme, plasma ProMMP-9 enzyme, salivary MMP-9 enzyme, and salivary NE with OSA
Nizam et al,[25] 2016	52	-	OSA not associated with TNF-α, OPG, or RANKL moderate or severe OSA associated with IL-6 levels; apelin associated with severe OSA

AHI = apnea hypopnea index, IL = interleukin, MMP = matrix metalloproteinases, NE = neutrophil elastase, OPG = osteoprotegrin, RANKL = soluble receptor activator of nuclear factor kappa B ligand, TNF-α = tumor necrosis factor

was shown to occur more often in women who were diagnosed with hypertension or hypertensive cardiomyopathy. Regarding the men, it was seen that periodontitis was associated with severe OSA (AHI score higher than 30) when these same men were diagnosed with either hypertension or hypertensive cardiomyopathy.[14]

In 2014, Nizam et al specifically examined various salivary cytokines to see if there was any association between OSA and periodontitis. They looked at various salivary cytokines known to be associated with periodontal disease, including interleukin (IL)-1β, IL-6, IL-21, and IL-33 and pentraxin-3 (PTX3). They observed the various concentrations of these salivary cytokines in patients with OSA and compared them to patients without OSA. Of the 52 subjects in the study, 13 were control subjects without OSA, 17 were in the mild to moderate OSA group, and 22 had severe OSA. It was concluded that OSA was associated with increased levels of IL-6 and IL-33 in moderate or severe cases; however, no association was seen between IL-1β, IL-21, or PTX3 and OSA.[4]

A year later, in 2015, Nizam et al conducted another study exploring whether salivary and serum collagenases play any role in a possible association between OSA and periodontal disease. The study included various matrix metalloproteinases (MMPs) known to play a role in periodontal disease. The various salivary and serum collagenases that were examined included ProMMP-2, MMP-2, ProMMP-9, MMP-9, neutrophil elastase (NE), and myeloperoxidase (MPO). Of the 50 subjects in the study, 13 were without OSA, 17 had mild to moderate OSA, and 20 had severe OSA. The study ultimately failed to support any association between OSA severity and periodontitis in regard to MMPs or neutrophil enzymes. However, it was shown that there was an inversely proportional and statistically significant association of salivary ProMMP-2 enzyme, plasma ProMMP-9 enzyme, salivary MMP-9 enzyme, and salivary NE with OSA. No meaningful association was found between OSA and plasma ProMMP-2 enzyme, salivary ProMMP-9 enzyme, plasma NE, and both salivary and plasma MPO.[24]

A final study by Nizam et al was conducted in 2016 that again examined various salivary and serum cytokines to determine if there was any association between OSA and periodontitis. They looked at various cytokines known to either be associated or not associated with periodontal disease. This study was similar to their 2014 study, but this time they included tumor necrosis factor (TNF-α), osteoprotegrin (OPG), and soluble receptor activator of nuclear factor kappa B ligand (RANKL). Similar to the 2014 study this analysis also measured IL-6. However, this study also measured the hormone apelin. In total, there were 52 subjects in the study, 13 of which were control subjects without OSA, 17 were in the mild to moderate OSA group, and 22 were in the severe OSA group. The authors ultimately concluded that OSA was not associated with TNF-α, OPG, or RANKL, and once again an association was shown between IL-6 levels and moderate or severe OSA. Apelin was shown to be associated with severe OSA.[25]

Discussion

Based on the various studies conducted over the past 10 years, there are conflicting views on whether there is an association between periodontitis and OSA. On one hand, a number of studies showed a strong relationship between the two conditions, which could indicate that periodontitis and OSA may share some type of biologic mechanism. Conversely, some studies concluded there was no significant association between the two. Thus, further, more detailed exploration is needed to obtain a more definitive answer regarding this potential association.

Studies that showed an association between periodontitis and OSA within populations included the works by Gunaratnam et al,[15] Seo et al,[16] Ahmad et al,[17] Keller et al,[18] Sanders et al,[20] Al Habashneh et al,[23] and, finally, Lattore et al.[14] In all seven of these studies, an association was shown between periodontal disease and OSA. All of these studies showed there was higher incidence of periodontitis in OSA patients, or higher incidence of OSA in patients with periodontitis. These studies, however, could not prove causality. These studies may provide an opening to a better understanding of the type of patient that might be at risk for both diseases.

The studies outlined various explanations for the association between these two diseases. One hypothesis included the fact that both OSA and periodontitis patients seem to suffer from chronic systemic inflammation. Nizam et al studied the various salivary and serum cytokines and salivary and serum collagenases known to be associated with periodontal disease to see if these same biological markers were increased in patients with OSA. One could then conclude that if OSA and periodontitis share similar biologic markers, then these specific markers may be the mechanism linking the two.

Ultimately, the only biologic marker that was associated with both OSA and periodontal disease was IL-6.[4,25] IL-6 is known to be an inflammatory cytokine that plays a role in recruiting T cells during chronic inflammation. It is also known to play a role in the eventual breakdown of bone that is seen in periodontal disease.[4] However, it was interesting that various MMPs and NE, known to be increased in periodontal disease and ultimately play a role in breaking down the extracellular matrix component of the periodontium, were actually associated with OSA in an inversely proportional way. Instead of these MMPs and NE being higher, as they are in periodontitis patients, these biomarkers were actually shown to be less prevalent in OSA patients.[24] An exception to this was shown in a study by Ye et al who demonstrated an increase in MMP-9 in patients with OSA and this association with OSA was statistically significant.[26] This data suggests a possible mechanism via IL-6 and MMP-9 that may play a role in the interplay between OSA and periodontal disease. Further research, however, is needed to gain more understanding of these various mechanisms.

In terms of biologic markers, it is interesting that IL-33, which is known to be anti-inflammatory, was seen to be increased in OSA and have a statistically significant association.[4] This contradicts a study by Buduneli et al, which shows that IL-33 is seen in lower numbers of patients with periodontitis.[27]

Contrasting the numerous studies that showed a connection between OSA and periodontitis were the studies by Loke et al[19] and Sales-Peres et al,[22] which indicated that there was no significant connection between the two. However, these studies demonstrated, respectively, an association between AHI score and the amount of plaque and an association between OSA and neck circumference. This lends credence to the idea that there are likely confounding variables involved in regard to these two illnesses. This is corroborated by the fact that OSA and periodontitis share similar risk factors,

such as obesity, alcohol consumption, and smoking.[7,11] These shared risk factors likely play a role in the purported association. This also could explain how both OSA and periodontitis are associated with similar illnesses, such as hypertension or hypertensive cardiomyopathy.[14] In other words, certain patient types may be at greater risk.

Seo et al described a final hypothesis for the association between OSA and periodontitis that had to do with the act of mouth breathing. It is known that patients with OSA have an increased incidence of mouth breathing, and that in people who are mouth breathers, there is an increase in observed periodontitis. This is because mouth breathing produces dry mouth, which, in turn, hinders the oral cavity and saliva from adequately destroying the bacteria that causes periodontal disease. This ultimately leads to a dysbiosis, or microbial imbalance in the oral cavity, which leads to chronic inflammation and periodontal breakdown.[16] Ahmad et al challenged this hypothesis, finding that there was no significant relationship between dry mouth and periodontitis.[17] They stated this could be because saliva does not ultimately flow into the periodontal pockets.[28]

Conclusion

Based on this information, periodontists should play a fairly significant role in the diagnosis and treatment of OSA. Although the specific mechanisms and interplay between periodontal disease and OSA is unknown and more research is needed, periodontists should be able to recognize patients who are at risk for OSA or who already have OSA, because it will help them more effectively maintain these patients' oral health and manage their periodontal disease. Because periodontists often see patients two or more times per year, they should be able to assess the situation involving OSA and be aware of the symptoms and refer patients accordingly, whether to an appropriate medical colleague or a dentist with advanced training in sleep medicine. By being vigilant, periodontists can have an immense impact on their patients' overall well-being by diagnosing and assisting in the treatment of this widespread health problem.

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