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Systematic Review

Relationship between periodontal disease and obstructive sleep apnea in adults: A systematic review

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ABSTRACT

The purpose of this systematic review was to evaluate whether there are scientific evidence regarding the association between periodontitis and obstructive sleep apnea (OSA) in adults. An electronic search was performed on MEDLINE/PubMed for prospective and retrospective longitudinal studies, cohort studies, and case–control studies conducted in human adults affected by both OSA and periodontitis. Two reviewers extracted the data using a custom Excel spreadsheet. A methodological assessment of the quality of the studies was performed using the Newcastle–Ottawa Scale. Fourteen studies were included. All studies evaluated the association between periodontitis and OSA. None of the studies evaluated the cause–effect relationship. Eleven studies found a significant positive relationship between periodontitis and OSA, whereas three found no statistically significant association. Several study limitations were observed, such as lack of standardization of study groups, diagnosis of periodontitis and OSA, and differences in study design. Evidence of a plausible association between periodontitis and OSA was found. The possible relationship could be explained by systemic inflammation, oral breathing, and the comorbid relationship attributable to common risk factors. Observational and randomized controlled studies are needed to clarify the mechanism of interaction between the two conditions.

Key Words: Obstructive sleep apnea, periodontitis, review, sleep medicine

INTRODUCTION

Obstructive sleep apnea (OSA) is a respiratory disorder characterized by recurrent episodes of an obstruction of the upper airways during sleep called apneas (if the airways are completely obstructed) or hypopneas (if the obstruction is only partial).[1] Recent epidemiological studies show a high prevalence of this disease, with significant health, social, and economic consequences.[2] It is estimated that it affects from 10% to 50% of the general population, with some subgroups at a higher risk.[3] However, the data may be underestimated due to the difficulty of diagnosing this condition.[4] These pathological respiratory occurrences may be followed by transient arousals leading to the restoration of patency of the upper airways. In most cases, the awakenings are not complete, and the patient remains unaware of it. These alterations induce oxidative stress, sympathetic activation, and metabolic dysregulation.[5] Periodontitis is a chronic infection and an inflammatory disease caused by bacterial pathogens that initiate an inflammatory response by the host.[6] The synergetic

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effect of bacterial toxins and host immune response results in the destruction of periodontal tissues, manifested clinically as loss of alveolar bone, progressive loss of periodontal attachment, pocket formation, and, ultimately, tooth loss.[7] Periodontitis can affect subjects of any age: from children still in primary dentition to the elderly. The prevalence of periodontitis in the population varies with age: It is <1% in pediatric age but can reach 43% in the adult or geriatric population.[8] There is convincing evidence in literature about an association between periodontitis and other systemic diseases such as ischemic cardiovascular disease, type 2 diabetes mellitus, and obstetric complications (birth of premature and/or underweight babies). Similarly, for OSA, there is scientific evidence supporting an association with cardiovascular diseases, cerebrovascular diseases, gastroesophageal reflux, and type 2 diabetes mellitus.[9] In recent years, there has also been increasing interest in the potential association between periodontitis and OSA as they are frequent disorders, which have common risk factors, and they are both associated with systemic inflammation and cardiovascular morbidity.[10]

This correlation could imply coexisting periodontitis as an important mediator of inflammation in OSA or vice versa. The possibility that coexisting periodontitis may still be an unknown confounder in the relationship between OSA and cardiovascular morbidity needs consideration. The purpose of this systematic review is to evaluate whether there is scientific evidence regarding the association between periodontitis and OSA by analyzing the available literature.

MATERIALS AND METHODS

The protocol for this systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11] The proposed focus question was: "Is there a relationship between OSA and periodontitis, considering the existing scientific literature?"

Inclusion/exclusion criteria

In this systematic review, Participant, Intervention, Comparison, and Outcome (PICO) criteria were used. The PICO system was designed to answer the following question: "Is there a relationship between OSA and periodontitis, considering the existing scientific literature?" (P) Population: human male and female adults; (I) Intervention: comorbidity of OSA syndrome and periodontal disease; (C) Control: human adults not affected by both OSA and periodontal disease; (O) Outcome: any relationship between OSA and periodontitis.

Epidemiological studies concerning the relationship between OSA and periodontitis were included. Male and female subjects over the age of 18 affected by both OSA and periodontitis were considered. It was chosen to consider only the studies in which diagnosis of periodontitis was formulated following the classification systems of periodontal and peri-implant diseases and conditions resulting from the 2017 World Workshop organized jointly by the American Academy of Periodontology and the European Federation of Periodontology[12] or the classification system of periodontal diseases of 1999.[13] In these articles, the authors used parameters such as probing depth (PPD), clinical attachment level (CAL), plaque index (PI), and bleeding on probing (POB) to diagnose periodontal disease. The diagnosis of OSA, on the other hand, had to be done by polysomnography (PSG) conducted in a sleep laboratory or at home with portable devices (HST). Studies that determined the risk of OSA through the evaluation of the Mallampati index,[14] tonsillar hypertrophy, and the use of validated questionnaires such as Epworth Sleepiness Scale (ESS),[15] Berlin questionnaire,[16] and STOP-BANG questionnaire[17] were also taken into consideration.

This review included prospective and retrospective longitudinal studies, cohort studies, case–control studies, in human adults, with no restrictions on sample size and geographical location, published between 2000 and December 2021. The comparison group was represented by samples with non-OSA and nonperiodontitis subjects. Clinical cases, systematic reviews, review articles, abstracts, animal studies, and publications not in English were excluded from this review. Studies that did not directly assess the relationship between OSA and periodontitis were also excluded.

Search strategy and selection process

To ensure a complete and exhaustive evaluation of the scientific evidence, a bibliographic search was performed, with the contribution of a clinician (EM), using electronic databases. Search was conducted on MEDLINE/PubMed to identify articles published from 2000 to December 2021. Two limitations were

applied to the literature search: human studies and year of publication. The following databases were searched using a combination of keyword terms and subject headings to represent sleep apnea and periodontal disease. The search strings for identifying the studies are shown in Table 1. The first search strategy (# 1 search MEDLINE), relating to the terms MeSH and Free Terms descriptors of OSA, found 55,954 publications, and the second search (# 2 search MEDLINE), relating to the MeSH terms descriptors of periodontitis, identified 91,449 citations. The joint use of the two searches with the Boolean operator "AND" produced 70 articles.

The literature search enabled the identification of studies potentially eligible for inclusion in the systematic review. The selection of articles to be included in the review was carried out in several stages. The first phase made it possible to identify the works of possible interest by reading the title and abstract of each individual contribution; in the second phase, the reviewers examined the full text of the selected articles and identified the pertinent ones. To ensure an objective, transparent, and reproducible evaluation of the literature, the identified studies were independently analyzed and evaluated by two reviewers (GR and EM). Any discrepancy on the work evaluation outcome was discussed and resolved by consensus.

Data extraction

A customized Excel spreadsheet was prepared to organize and collect the main information of the studies included in the systematic review. While one reviewer extracted the data, another verified the extracted data. Any disagreements were resolved through discussion between the two.

From each included publication, information was extracted relating to surname of the first author, country in which the study was carried out, article's year of publication, study design, reference population (sample size, females, males, and mean age), diagnostic criteria of OSA and periodontitis, study objective, study results, and authors' conclusions.

Table 1: Search strategy

Step	Keywords	Citations
#1	sleep apnea syndromes [MeSH Terms] or obstructive sleep apnea [MeSH Terms] or obstructive sleep or obstructive sleep apnea syndrome or obstructive sleep apnea hypopnea syndrome or OSAHS or OSA or sleep disordered breathing	55.954
#2	periodontitis [MeSH Terms] or periodontal disease [MeSH Terms] or gingival disease [MeSH Terms] or periodontal attachment loss [MeSH Terms] or alveolar bone loss [MeSH Terms] or gingival recession [MeSH Terms] or periodontal pocket [MeSH Terms] or tooth loss [MeSH Terms]	91.449
#3	1 AND 2	70

Quality assessment

Before conducting the analysis, in order to explore the study result variability (heterogeneity), it has been hypothesized that the effect size may differ in relation to the methodological quality of the studies. To define the validity of the studies selected during the full-text phase, an independent evaluation has been carried out for each article.

The quality of the studies that met the inclusion criteria was independently assessed by two authors using the Newcastle–Ottawa Scale (NOS) based on study type. The NOS was then used for the evaluation of nonrandomized studies to assess the risk of bias in case–control studies,[18] while cross-sectional observational studies were evaluated using an adapted form of NOS, developed by Herzog *et al*.[19] These tools allow the evaluator to assign a quality score at three levels ("good", "fair," or "poor") based on the consideration of different elements. The tool for case–control studies evaluates 8 elements divided into 3 groups: selection of study groups, comparability of groups, and exposure assessment. The tool for cross-sectional studies evaluates 7 elements divided into 3 groups: selection of study groups, comparability of groups, and results.

A Star system was used, which provides up to a maximum of 9 for case–control studies and 10 for cross-sectional ones. Studies are therefore classified into 3 groups of bias: low (score >8), medium (score 6–8), and high risk (score <6). The high risk of bias results in a poor-quality evaluation, while the low risk of bias implies a good-quality assessment. Therefore, the greater the risk of bias, the lower the study quality. If the ratings differed, the authors discussed the findings to reach an agreement.

RESULTS

The flowchart proposed by Moher *et al*. was used to outline the phases of the inclusion of the articles in the PRISMA document [Figure 1].[11]

Through the bibliographic search on PubMed, 70 articles were identified, published between 2000 to

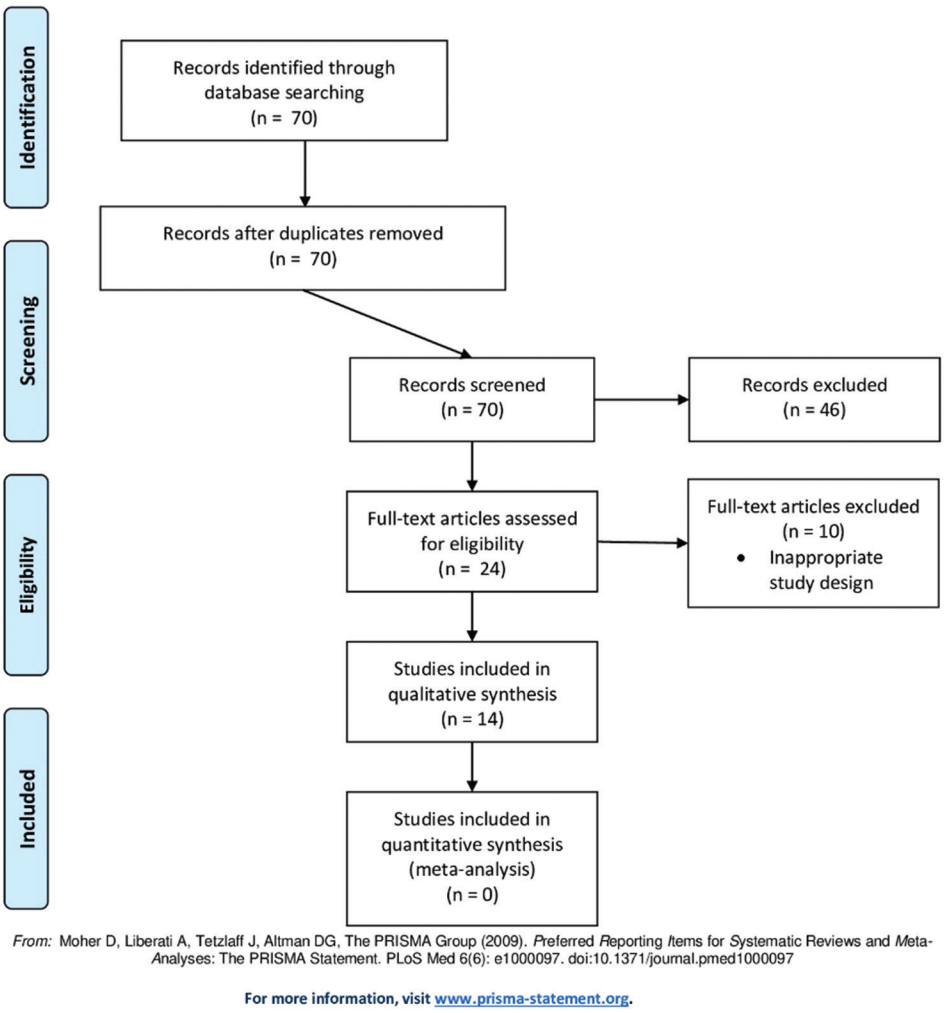

Figure 1: Preferred reporting items for systematic reviews and meta-analyses 2009 flow diagram.[11]

December 2021, while only one article was identified through the search in scientific journals. In the first screening phase, 46 articles were excluded because they did not meet the inclusion criteria. In the full-text screening phase, 10 studies were excluded because their full text was not available or it did not meet the eligibility criteria, while 14 studies were included. No relevant unpublished studies were identified.

Risk of bias in studies

The mean NOS score for the case–control studies was 5.2 [range = 4–7; Table 2]. The risk of bias was found mainly in the representativeness of cases, in the definition of controls, in the design and analysis of the study, and in the nonresponse rate. The mean NOS score for the cross-sectional studies was 7.8 [range = 7–10; Table 3]. The greatest risk of bias was found in nonresponders, sample size, study design, and control of confounding factors. Among the case–control studies, four were found to have a high risk of bias as they scored <6 stars, while two studies had a medium risk of bias with a score between 6 and 8. Low risk of bias was found in three cross-sectional studies with scores >8 stars, while the remaining five studies scored between 6 and 8, indicative of medium risk of bias. Based on the risk of bias assessment tools, three[20-22] studies achieved "good" quality, seven[23-29] "fair" quality and four[28,30,31] "poor" quality.

Results of syntheses

Table 4 summarizes the main findings of the articles included in this systematic review. A statistical synthesis of the results was not possible as study designs, participants, interventions, and outcomes were variable between the included studies; therefore, the author of the present paper focused on the description of the studies, their results, their applicability, and their limitations, preferring qualitative synthesis to meta-analysis. Of the 14 studies that were selected, six were case–control[23,24,30-33] and eight were

Table 2: Newcastle–Ottawa Scale for case–control studies

Is the case definition adequate?	Representativeness of the case	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	Risk of bias
★		★	-	★★	★	★	-	Medium
★	-	★	-	-	★	★	-	High
★	-	★	-	-	★	★	-	High
★	-	★	-	-	★	★	-	High
★	★	★	-	★★	★	★	-	Medium
-	★	★	-	★★	-	★	-	High

Table 3: Newcastle–Ottawa Scale for cross-sectional studies

Representativeness of the sample	Sample size	Ascertainment of exposure (risk factor)	Nonrespondents	Comparability of subjects in different groups	Assessment of outcome	Statistical test	Risk of bias
-	★	★	-	★★	★★	★	Medium
★	-	★★	-	-	★★	★	Medium
★	★	★★	-	-	★★	★	Medium
★	-	★★	★	★★	★★	★	Low
★	★	★★	★	★★	★★	★	Low
★	★	★★	-	-	★★	★	Medium
★	-	★★	★	★★	★★	★	Low
★	★	★	-	★★	★★	-	Medium

cross-sectional.[20-22,25-29] The studies included in the review were representative of a total sample of 43,773 individuals. The sample size in the studies ranged from 52 to 29,284 adult subjects. The age ranged from 21 to 85 years and 56% were male subjects. Three of the studies came from the United States,[21,24,28] four from Turkey,[21,30-31] while the rest came from Australia,[29] Taiwan,[33] Brazil,[27] Colombia,[26] Jordan,[20] Korea,[22] and China.[25] All studies evaluated the association between periodontitis and OSA. Seven studies[20-25,28] also evaluated the dose–response relationship and one[33] evaluated the evidence of the efficacy of periodontal interventions on the onset and severity of OSA. Eleven studies diagnosed OSA using PSG in a sleep clinic or using the home sleep test,[21-23,25,26,28,29,30-33] using AHI as the primary outcome, while three studies[20,24,27] used self-administered validated questionnaires. The types of questionnaires used in the studies were STOP,[24] Berlin questionnaire,[20,27] and the ESS.[27] Only two studies[25,29] reported more than one outcome (AHI, mean SaO2, minimal SaO2, 4% ODI, rapid eye movement, and total sleep time). Periodontitis was assessed using clinical (CAL, PPD, REC, PI, and BOP) and radiographic measures in all studies. Furthermore, four studies[23,30-32] evaluated inflammatory biomarkers in gingival crevicular fluid (GCF) and saliva.

Association between periodontitis and obstructive sleep apnea

All 14 studies evaluated the association between periodontitis and OSA. The prevalence of periodontitis ranged from 32.5% to 96.4% in case–control studies and from 15% to 85.2% in cross-sectional studies. The prevalence of OSA diagnosed by PSG or HST ranged from 20.4% to 75%, while the prevalence of OSA risk determined by validated questionnaires was 15%–81.5% in three studies. Eleven studies found a significant positive relationship between periodontitis and OSA. In four of these,[24,25,33] the adjusted odds ratio (AOR) for periodontitis in patients with diagnosed OSA or at high-risk OSA was 3.69 (95% confidence interval [CI], 1.22–11.2), 1.75 (95% CI, 1.68–1.88; $P < 0.001$), 1.84 (95% CI, 1.18–2.87), and 4.1 (95% CI, 1.9–11.4) times greater than checks. Sanders *et al.*[21] found that the odds of periodontitis were 1.6 (95% CI, 1.1–2.2) in mild OSA and 1.5 (95% CI, 1.0–2.3) in moderate/severe OSA. Latorre *et al.*[26] reported higher odds (odds ratio = 1.37; 95% CI, 1.11, 2.68; $P = 0.041$) for periodontitis in mild OSA compared to non-OSA patients. This association was more frequent in women with hypertension or hypertensive cardiomyopathy, while periodontitis was associated

Table 4: Data extraction

Study design	Population	Diagnosis or risk for OSA	Periodontitis assessment	Objective	Results	Authors' conclusion	Quality of the studies
Cross-sectional	*n*=93 subjects All males age range: 24–35 years 19 - OSA 74 - non-OSA	PSG at home according to AASM criteria	CAL, PPD, BOP	OSA-periodontitis association; dose–response relationship	Prevalence of OSA: 32.5%. BOP and CAL significantly higher in the OSA group. No significant difference for PPD in the two groups. Weak but positive correlation between OSA severity and that of periodontitis	Significant association between OSA and periodontitis. Low SaO_2 could be a predictive index of periodontal disease	Fair
Cross-sectional	*n*=199 subjects 107 males; 92 females Age range: 30–85 years (mean age 49 years)	PSG at sleep clinic according to AASM criteria	CAL, PPD, REC	OSA-periodontitis association	Prevalence of periodontitis: 62.3%. Significant association between periodontitis and mild OSA (P=0.041)	Significant association between periodontitis and mild OSA, more frequent in women with hypertension and hypertensive cardiomyopathy. Significant association between periodontitis and OSA (moderate or severe) in men with hypertension or hypertensive cardiomyopathy	Fair
Case–control	*n*=163 subjects 41 females; 122 males Age range: 30–68 years (mean age 45±9 years) 83 - OSA 80 - non-OSA	PSG according to AASM criteria	PI, BOP, PPD, CAL, GI, GCF, IL-1β, TNF-α, hs-CRP, serum hs-CRP	OSA-periodontitis association; dose–response relationship	Prevalence of periodontitis in the OSA group significantly higher than in the control (P<0.001). Periodontal clinical parameters and GCF IL-B concentrations higher than in the controls. Prevalence of severe periodontitis higher in the severe OSA group than in mild OSA, but no significant difference	Higher prevalence of periodontitis and higher levels of GCF IL-B and serum hs-CRP	Fair
Case–control	*n*=52 subjects 20 females; 32 males Age range: 21–64 years 17 - mild/moderate OSA 22 - severe OSA 13 - non-OSA	PSG according to AASM criteria	PI, BOP, PPD, CAL, salivary and serum IL-6, TNF-α, OPG, sRANKL, APELINA	OSA-periodontitis association	Change in bacterial plaque composition in cases. Correlation between OSA and severity of periodontal indices significantly higher salivary levels of IL-6 and apelin in cases than in control (P<0.05). No significant difference in both groups for other biomarkers serum significant association between salivary IL-6 levels and OSA severity indices	The increase in salivary concentrations of IL-6 and apelin may have an impact or be due to periodontitis in OSA patients	Poor
Cross-sectional	*n*=108 obese subjects with class III malocclusion 85 females; 23 males Age range: 30–60 years	Berlin questionnaire and ESS	PPD, CAL, BOP	OSA-periodontitis association	No association between *P* and OSA risk	There is no association between periodontitis and OSA risk in class III obese patients	Fair

Contd...

Table 4: Contd...

Study design	Population	Diagnosis or risk for OSA	Periodontitis assessment	Objective	Results	Authors' conclusion	Quality of the studies
Cross-sectional	*n*=296 subjects All males Age range: 30–60 years (mean age 40 years)	Berlin questionnaire	PPD, CAL, BOP, GI, PI	OSA-periodontitis association; dose–response relationship	Patients with high risk for OSA showed higher PPD and CAL than patients with low risk for OSA	Positive association between periodontitis and high risk of OSA. Periodontitis in patients with high risk for OSA was more generalized and severe	Good
Case–control	*n*=50 subjects 20 females; 30 males Age range: 21–64 years 17 - mild/moderate OSA 20 - severe OSA 13 - non-OSA	PSG at sleep clinic according to AASM criteria	PPD, CAL, BOP, PI, salivary and serum MMP-8, proMMP-2, MMP9, TIMP-1, MPO, NE	OSA-periodontitis association	Periodontal parameters were higher in the severe OSA group but without statistically significant differences (P>0.05). Serum MMP-9 was significantly lower in severe OSA than in control (P=0.046). Salivary levels of NE and proMMP-2 were significantly lower in the OSAS groups compared to the control group (P<0.05)	There is no pathophysiological link between the severity of OSAS and clinical periodontal status via neutrophil products and MMPs	Fair
Cross-sectional	*n*=12.469 subjects 7473 females; 4996 males Age range: 18–74 years 1783 - AHI 0 7039 - AHI 0.1–4.9 2298 - AHI 5–14.9 1349: AHI ≥15	PSG at home according to AASM criteria	PPD, BOP, REC, CAL	OSA-periodontitis association; dose–response correlation	Dose–response relationship between prevalence of severe periodontitis and severity of AHI. This correlation was stronger in the subgroup 18–34 years	Significant association between OSA e periodontal disease	Good
Cross-sectional	*n*=100 subjects 9 females; 91 males Age range 28–79 years (mean age 52.6 years) 21 - OSA mild 19 - OSA moderate 34 - OSA severe 26 - non-OSA	PSG according to AASM criteria	CAL, PPD, REC, % sites with plaque, % sites with PD≥5 mm, % sites with CAL≥3 mm	OSA-periodontitis association; dose–response relationship	Prevalence of periodontal disease: 73%. No significant difference in the prevalence of periodontitis between the different grades of AHI and with the periodontal indices	OSA was not significantly associated with the presence of moderate or severe periodontitis except for % of sites with plaque	Fair
Case–control	*n*=52 subjects 20 females; 32 males Age range: 21–64 years 17 - mild/moderate OSA 22 - severe OSA 13 - non-OSA	PSG at sleep clinic according to AASM criteria	CAL, PPD, BOP, PI, number of teeth present, salivary concentration of IL-Iβ, IL-6, IL-21, IL-33, PTX3	OSA-periodontitis association	IL-6 and IL-33 were significantly higher in OSA group than controls (P<0.05). No significant difference between all groups in IL-Iβ, IL-21, and PTX3 concentrations. Significant correlation between CAL and IL-21. Significant correlation between CAL, PD, and OSA severity indices	OSA does not have a prominent effect on IL-Iβ, IL-21, and PTX3 levels. OSA, independently of its severity, could increase IL-6 and IL-33 levels. No pathophysiological link between OSA severity and periodontal status via salivary cytokines	Poor

Contd...

Table 4: Contd...

Study design	Population	Diagnosis or risk for OSA	Periodontitis assessment	Objective	Results	Authors' conclusion	Quality of the studies
Case–control	*n*=154 subjects 93 females; 61 males Mean age 61 years 50 - severe or moderate periodontitis 104 - gingivitis or mild periodontitis	STOP-Bang questionnaire	PI, GI, CAL, BOP, PPD, REC, mobility, furcation involvement, radiographic bone loss	OSA-periodontitis association; dose–response relationship	HR-OSA: 60% of severe or moderate periodontitis patients and 28% of controls. Patients with severe or moderate periodontal disease had 4, 1 times greater odds of risk for OSA	Significant association between moderate or severe periodontitis and risk for OSA	Fair
Case–control	*n*=29.284 subjects 11.052 females; 18.232 males Mean age 47±15 years 7321 - OSA 21963 - controls	PSG	PPD ≥3 mm, BOP, tooth mobility, color and shape of gingiva tissue, radiographic bone loss	OSA-periodontitis association; periodontal treatment efficacy	Prevalence of periodontal disease in OSA cases: 33.8%. Prevalence of periodontitis in control group: 22.6%. Significant difference in the prevalence of OSA in subjects undergoing periodontal surgery compared to those not treated	Significant association between OSA and periodontitis	Poor
Cross-sectional	*n*=687 subjects 227 females; 460 males Age range: 47–77 years (mean age 55±6 years)	PSG at sleep clinic or at home	CAL, PPD, BOP, REC, PI, GI	OSA-periodontitis association; dose-respond relationship	Prevalence of periodontitis: 17.5%. Prevalence of OSA: 46.6%. Prevalence of OSA in subjects with periodontitis: 60%	Significant association between OSA and periodontitis in subjects ≥55 years old. Dose–response association between periodontal disease, CAL, PPD, and increasing severity of OSA	Good
Cross-sectional	*n*=66 subjects 12 females; 54 males Mean age 54±12 years	PSG	CAL, PPD, BOP, REC, PI	OSA-periodontitis association	Prevalence of periodontitis: 77%–79%, depending on periodontal definition. Significant association between CAL and total sleep time	The prevalence of periodontitis in OSA patients was higher than in non-OSA	Fair

PSG: Polysomnography; ASAM: American Academy of Sleep Medicine; ESS: Epworth Sleepiness Scale; CAL: Clinical attachment level; PPD: Periodontal probing depth; BOP: Bleeding on probing; PI: Plaque index; GCF: Gingival crevicular fluid; IL: Interleukin; TNF-α: Tumor necrosis factor alpha; hs CRP: High-sensitivity C-reactive protein; PD: Pocket depth; OSA: Obstructive sleep apnea; AHI: Apnea-hypopnea index; PTX3: Pentraxin 3 protein; OSAS: Obstructive Sleep Apnea Syndrome; OPG: Osteoprotegerin; MMP: Matrix metalloproteinase protein; TIMP-1: TIMP metallopeptidase inhibitor 1 ; MPO: Myeloperoxidase protein; NE: Neutrophil elastase; REC: Recession

with severe OSA in men with hypertension or hypertensive cardiomyopathy. Two case–control studies[30,31] compared inflammatory biomarkers between cases with mild/moderate OSA and severe OSA and non-OSA controls. They found significant changes in plaque microbe composition ($P < 0.01$) and significantly higher levels ($P < 0.05$) of salivary interleukin (IL)-6 and salivary IL-33 in cases compared to controls. Salivary apelin was significantly higher in the severe OSA group than in controls. Clinical attachment loss (CAL) and pocket depth (PD) were significantly correlated with the incidence and duration of apnea ($P < 0.05$) and with OSA severity indicators. Gunaratnam *et al*.[29] found that CAL was significantly correlated with one of the OSA indicators (total sleep time; $P < 0.05$). Gamsiz-Isik *et al*.[23] concluded that all periodontal clinical parameters, serum concentrations of hs-CRP, and GCF IL-1β were significantly ($P < 0.05$) higher in patients with OSA than in controls. Al-Habashneh *et al*.[20] found the association between periodontitis and high risk of OSA (HR-OSA) among patients who scored positive in two or more categories of the Berlin questionnaire. In contrast, three studies found no significant association between periodontitis and OSA. Nizam *et al*.[32] compared serum and salivary levels of collagenase (proMMP-2, MMP-9, and NE) in OSA and non-OSA patients, finding no pathophysiological link between OSA severity and periodontal status. Loke *et al*.[28] reported that OSA was not significantly associated with the presence of moderate or severe periodontitis. Multivariate logistic regression analysis predicting the association of moderate/severe periodontitis with AHI score, age, and smoking habit indicated a significant association with age but no significant association with OSA. Sales-Peres *et al*.[27] also found no statistically significant differences between periodontitis and the risk of OSA in obese patients as determined by the Berlin and ESS questionnaires.

Dose–response relationship in terms of severity and/or prevalence

The dose–response relationship was examined in seven studies. Sanders *et al*.[21] initially reported a correlation of severe periodontitis with AHI ≥15/h (OR = 6.9, 95% CI, 4.8, 10.0). After adjusting for confounding factors, the relationship remained significant but was attenuated in strength and no longer dose–response. Loke *et al*.[28] examined a possible dose–response relationship by stratifying the sample into four groups using the AHI as a variable. Although the percentage of subjects with moderate/severe periodontitis progressively increased with increasing severity of OSA, the finding was not statistically significant (Chi-square test, $P = 0.111$). AHI categories were significantly associated with the percentage of sites with plaque ($P = 0.037$), but not with bleeding on probing or CAL. The study concluded that there was no dose–response relationship between the prevalence and/or severity of periodontal disease and the severity of AHI. Gamsiz-Isik *et al*.[23] reported a higher prevalence of severe periodontitis in patients with severe-to-moderate OSA (52.2%) compared to mild OSA (31.2%), but there was no significant difference. Seo *et al*.[22] studied the dose–response relationship between OSA severity (AHI categories <5/h, 5–10/h, ≥10/h) and periodontitis. An increase in AHI was associated with a higher probability of CAL and PPD (AOR = 1.97; 95% CI, 1.07, 3.65) in subjects 55 years of age and older. Chen *et al*.[25] found a positive, but weak, correlation between the severity of OSA and that of periodontitis. Ahmad *et al*.[24] reported an increase in the percentage of moderate/severe periodontitis cases with the increase in the number of affirmative responses on the OSA STOP screening questionnaire. On the previously validated questionnaire, two or more affirmative responses indicated an HR-OSA. Twenty percent of moderate/severe periodontitis cases in their study reported an affirmative response to the OSA questionnaire, so the percentage increased to 47.6, and 100% as the number of responses increased to four. Finally, Al Habashneh *et al*.[20] identified HR-OSA cases among patients who scored positive in two or more categories of the Berlin questionnaire. A positive association was observed between periodontitis and HR-OSA, which showed greater PD and CAL compared to patients with LR-OSA.

Evidence of treatment efficacy (reversibility)

In addition to evaluating the association, Keller *et al*.[33] analyzed the prevalence of OSA among periodontal patients and compared it with the prevalence of OSA among periodontal patients undergoing gingivectomy or periodontal flap surgery. They stated that the prevalence of OSA eased after periodontal therapy and the results were statistically significant (AOR = 1.36, 95% CI, 1.18, 1.56; $P = 0.002$), justifying it with a possible reduction in inflammatory contribution, sustained by chronic periodontitis.

DISCUSSION

The main purpose of this systematic review was to investigate the association between OSA and periodontitis, through a qualitative evaluation of the available literature. These diseases share multiple risk factors, and it has been suggested that both are associated with systemic inflammation and have an impact on the development of hypertension, cardiovascular disease, cerebrovascular disease, and type 2 diabetes.[34]

To date, very few studies have been conducted that have assessed the relationship between OSA and periodontitis.

Lembo *et al*.[35] also performed a systematic review to investigate a possible correlation between the two conditions: they concluded that although there is evidence of a plausible association between OSAS and periodontitis, it should be considered as low evidence and it is still unclear the pathophysiological mechanism that could link these two conditions, if there is a cause–effect relationship nor whether there is a dose–response relationship.

Among the articles included in the present review, those that demonstrated an association between the two pathologies justified it by formulating different hypotheses: systemic inflammation, oral respiration, and comorbid relationship.

Systemic inflammation

Some studies suggest an inflammatory link between OSA and periodontitis, considering that both diseases present an increase in some inflammation mediator molecules. Hypoxia in patients with OSA would promote an increase in adhesion molecules, C-reactive protein, transcription factor (nuclear factor-κB), some inflammatory cytokines (interleukin IL-1B, IL-6, and tumor necrosis factor-alpha), and an activation of circulating neutrophils.[29,32] The resulting inflammatory response could then potentiate the disease in those who already suffer from inflammatory diseases (such as cardiovascular, cerebrovascular, pulmonary, and neurocognitive diseases, as well as type 2 diabetes and arthritis), or trigger inflammatory diseases in people with a genetic, behavioral, and environmental predispositions.[30,31] Increased levels of pro-inflammatory mediators and C-reactive protein have also been observed in patients with periodontitis.[28]

In periodontitis, the host's response to periodontal pathogenic microorganisms causes an increase in systemic inflammatory factors and the destruction of the integrity of periodontal tissues.[36,37]

Mouth breathing

Another factor that may explain the association between the two conditions could be dry mouth due to oral breathing during sleep. In OSA, oral breathing is a classic feature that leads to dry mouth and therefore could be indirectly associated with periodontitis through the changes it can cause to the oral environment. In a healthy patient without nasal involvement, mouth breathing accounts for approximately 4% of total ventilation; this percentage tends to increase with aging. In their study, Seo *et al*.[22] affirm that the prevalence of oral respiration appears to be higher in patients with OSA. By generating dry mouth, this type of breathing tends to decrease the self-cleaning and antibacterial effect of saliva. It is therefore possible to notice an increase in bacterial colonization and consequent gingival inflammation. These two factors can increase the risk of developing periodontal disease or trigger its progression.

Comorbidity

Finally, a possible comorbid relationship between the two conditions has emerged from the literature. OSA and periodontitis have several common risk factors such as tobacco use, male sex, aging, alcohol consumption, obesity, and diabetes, which increase the vulnerability of the development of the two diseases. The simultaneous presence of periodontitis and OSA in an individual would therefore be attributable to common risk factors that would act as a link to comorbidities, in contrast to the first two hypotheses in which there is a causal link. It should also be noted that periodontitis is a common disease which affects up to 43% of the general population.[8] According to a study by Heinzer,[3] OSA would reach 10%–50% of the general population. It is therefore presumable that these two conditions can coexist in the same individual without causing a link between them.

Limitations

It is necessary to consider that the findings summarized in this systematic review present some limitations. Although most studies indicated a statistically significant association between periodontitis and OSA, the results need to be interpreted with caution because of the low quality of evidence in many studies.

First, most of the included studies had a cross-sectional design and therefore it is not possible to identify

a causality or directionality between OSA and periodontal disease. The diversity and limited number of studies did not allow a convincing level of evidence or perform quantitative analyses.

One-third of the studies were found to be of poor quality, mainly due to the lack of calibration of the periodontal examiners, the lack of sample size estimation, and the absence of control for potential confounders. The remaining studies were classified as having a moderate-to-low risk of bias. Three[30,31] of the four high risk of bias studies were conducted by the same authors and were based on the same sample. They had some limitations such as the small number of subjects (n = 52) and the absence of subgroups based on periodontal disease status (healthy, gingivitis, or periodontitis). Their results should be therefore interpreted with caution.

The assessment of periodontal disease and the definitions used differed between studies; this may have led to an over- or underestimation of the disease prevalence. Despite the calibrated classification of periodontal disease, the case–control division is performed using several measures that can be influenced by the operator. Measuring the level of plaque, bleeding, mobility, furcation defect, and attachment loss by different operators using different techniques can create some variability and a margin of error. In addition, some studies are limited to a partial periodontal assessment of the mouth compared to others with six measurement points for each tooth.

By being aware of the initial assumptions, the examiner's objectivity can be subject to bias during periodontal data collection, hence the need for a blinded approach.

Similarly, the AHI cutoffs for OSA assessment varied between studies.

The use of concurrent control subjects was not done in two studies. Instead, their results were compared to historical controls from data published in the Australian National Survey of Adult Oral Health[29] and the Longitudinal Health Insurance Database 2000.[33] CAL is a measure of past disease and not necessarily current disease; therefore, the time between exposure and illness cannot be confirmed. Case selection in studies can be done either by using databases of patients who responded positively to questionnaires or by clinical examination. It is desirable that an individualized and standardized approach is more accurate for the diagnosis of periodontitis and OSA.

Since the included studies came from different regions, and periodontal prevalence and severity are influenced by demographic and social factors, the results may have been influenced. Another probable limitation is found in studies that have not distinguished smokers from nonsmokers. In fact, smoking affects not only the increased levels of salivary cytokines but also the risk of OSA and periodontitis. Likewise, the possibility of having control group members with undiagnosed asymptomatic OSA or other sleep disorders (e.g., snoring) can lead to a lack of uniformity in control groups.

In general, OSA is also more likely to be diagnosed in a patient being treated for periodontitis than in a person unaware of having the condition. This could increase the correlation rate again. None of the studies were completely corrected for known confounders.

The standardization of study groups according to each of these categories is therefore necessary to improve the internal validity of the studies.

CONCLUSION

This review highlights some evidence of a plausible association between periodontitis and OSA. Several theories have been hypothesized to explain a link between the two conditions: (1) periodontitis causes chronic inflammatory responses in sensitive hosts and acts as a mediator of inflammation for OSA or vice versa; (2) oral breathing associated with OSA increases the expression of periodontitis; and (3) the relationship between the two conditions is comorbid rather than causal as they both share common risk factors.

No conclusions can be drawn about the efficacy of periodontal disease treatment modalities due to insufficient evidence. Future research should therefore provide evidence from observational prospective studies trying to overcome the limitations currently found in the literature. Furthermore, as most of the papers had a cross-sectional design, it was not possible to clearly define the cause–effect relationship. Therefore, better structured observational studies are needed to confirm this association and randomized controlled studies are needed to clarify the interaction mechanism between the two conditions.

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