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Abstract: Purpose Since both obstructive sleep apnoea (OSA) andperiodontitis are associated with systemic inflammation andcardiovascular morbidity, we questioned whether there maybe an association between these two disorders.Materials and methods A standard periodontal examinationwas undertaken in a group of 66 (54 men and 12 women)treatment-naÃ¨ve patients diagnosed with OSA [apnoea-€“hypopnoea index (AHI) >5/h] to derive a number ofquantitative variables which could then be used to determinethe prevalence of periodontitis in a group of patients.Results The prevalence of periodontitis in our study groupwas 77-€“79%, depending on the definition used. This wasalmost four times that of historical controls derived from arecent national survey. When sleep-related variables werecompared against periodontal variables, significant correlationswere found between periodontal clinical attachmentlevel and total sleep time.Conclusion Our pilot study suggests that OSA is associatedwith periodontitis. Further research is needed to elucidatethe nature of this association.

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Obstructive Sleep Apnoea and Periodontitis: A Novel Association?

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ABSTRACT

Purpose: Since both obstructive sleep apnoea (OSA) and periodontitis are associated with systemic inflammation and cardiovascular morbidity, we questioned whether there may be an association between these two disorders.

Method: A standard periodontal examination was undertaken in a group of sixty six (54 males and 12 females) treatment naïve patients diagnosed with OSA (Apnea-Hypopnea Index (AHI) > 5/hr), to derive a number of quantitative variables which could then be used to determine the prevalence of periodontitis in a group of patients.

Results: The prevalence of periodontitis in our study group was 77-79%, depending on the definition used. This was almost four times that of historical controls derived from a recent national survey. When sleep related variables were compared against periodontal variables, significant correlations were found between periodontal clinical attachment level and total sleep time.

Conclusion: Our pilot study suggests that OSA is associated with periodontitis. Further research is needed to elucidate the nature of this association.

Keywords: Obstructive sleep apnoea; periodontitis; prevalence; inflammation

INTRODUCTION

Obstructive Sleep Apnoea (OSA) is a common disorder in which recurrent collapse of the upper airway during sleep results in intermittent hypoxemia and sleep fragmentation. It has been shown to be a risk factor for hypertension [1-3], and is implicated in the development of transient ischemic attacks [4] and stroke [5]. Further association has been demonstrated with coronary heart disease [6, 7], heart failure [7], cardiac arrhythmias [8], and impaired glucose tolerance and type 2 diabetes mellitis [9].

There is evidence of local upper airway [10, 11] and systemic inflammation [12] in patients with OSA. It has been proposed that systemic inflammation resulting from OSA could be one of the major mechanisms, independent of hypertension, which leads to the development of vascular morbidities [12]. Several studies have demonstrated that patients with OSA have increased plasma markers of systemic inflammation, notably increased levels of inflammatory cytokines [13-15], adhesion molecules [16-18], and activation of circulating neutrophils [17]. These studies suggest that activation of various inflammatory processes may directly contribute to atherogenesis and lead to the development of cardiovascular disease. The exact mechanism is not certain, but the underlying systemic inflammation from OSA may be due to the hypoxia/reperfusion injury from intermittent hypoxia that occurs with OSA [19]. Intermittent hypoxia occurring in OSA may stimulate transcription factors such as nuclear factor-κβ and increase production of cytokines [20]. The episodic hypoxia in OSA also leads to increased production of reactive oxidative species and, via various pathways, to the formation of other systemic inflammatory mediators [19]. The resultant inflammatory response could then potentiate disease in those that already have inflammatory disease,

for example cardiovascular disease, or trigger inflammatory diseases in people with existing genetic, behavioural and environmental exposure.

Periodontitis is a common chronic disease caused by pathogenic bacteria that trigger an inflammatory response in the supporting tissues of teeth [21]. This can result in destruction of the supporting tissues of the teeth in susceptible individuals that is clinically evident as the progressive loss of periodontal attachment, pocket formation, loss of alveolar bone and, ultimately, tooth loss [21]. Established risk factors for periodontitis include smoking [22, 23] and diabetes [22-24]. The prevalence of periodontitis depends on the definition used. That of moderate and severe periodontitis in Australia [25] is estimated to be between 19 to 23% of the population which is similar to that reported in other developed countries [23, 26, 27]. The prevalence and severity of periodontitis increases with age and is greater in males compared to females [25, 26]. Associations have also been shown between periodontitis and plaque levels [22, 23, 27], obesity [28, 29], socioeconomic status (SES) [30-32], education [25] and ethnicity [30-32].

The relationship between periodontitis and systemic diseases has been investigated with conflicting results as demonstrated by the evidence for [33, 34] and against [35, 36] a greater prevalence of periodontitis in those with rheumatoid arthritis [33, 35] and osteoporosis [34, 36]. While diabetes is a risk factor for periodontitis [22-24], the relationship between the two conditions may be bi-directional [37, 38]. Periodontitis may have a mild effect on the outcome and markers of cardiovascular disease [39, 40]. Periodontitis may be linked to cardiovascular diseases via various putative mechanisms. Firstly, periodontal pathogens and their products may directly cause injury to the endothelium and contribute to initiation of atherogenesis [41].

Secondly, periodontitis and cardiovascular disease share common risk factors. Thirdly, periodontitis may contribute to a general systemic inflammatory burden by increasing the production of many inflammatory mediators [42].

Given that OSA and periodontal disease are common disorders, and both are associated with systemic inflammation and cardiovascular morbidity, we questioned whether they may be associated. Such an association could implicate co-existent periodontitis as an important mediator of inflammation in OSA, or vice versa. At the very least, the possibility that co-existent periodontitis could be an as yet unknown confounder in the relationship between OSA and cardiovascular morbidity merits consideration. Hence, the aim of this exploratory study was to examine the possible association between OSA and periodontitis. Specifically, we hypothesised that the prevalence of periodontitis is higher amongst patients with OSA than in the general population.

MATERIALS AND METHODS

Patients

Potential subjects were identified from newly diagnosed patients with OSA at a Sleep Disorders Clinic in a university teaching hospital, where the majority of referrals are from primary care physicians. Patients with an AHI > 5/hour were diagnosed as having OSA. A total of 174 eligible patients were identified. Eligible subjects willing to participate in the study were then recruited by phone polling. All subjects were informed of the purpose and objectives of this study, and written consent was obtained. The research protocol was approved by the institutional ethics committee. The inclusion criteria required subjects to:

- be diagnosed with OSA (have a polysomnography derived AHI >5/hour)

- be aged 18 years and over
- have had no previous treatment for OSA.

Those subjects with a medical condition requiring antibiotic prophylaxis (against endocarditis) prior to periodontal examination were excluded from the study. Patients who had periodontal treatment within the previous three months were excluded since clinical periodontal variables could be altered by recent periodontal treatment [43].

Data Collection

Of the 174 eligible patients, 121 could be contacted by phone. Thirteen patients were not suitable because of the presence of exclusion criteria. Sixty six patients agreed to participate in the study. The most common reason for declining participation among the other 42 patients was work commitments precluding attendance for the dental examination. Once consent was obtained, subjects were required to undergo a formal periodontal examination. At this visit, the personal and clinical characteristics of the subjects were recorded. Baseline demographic characteristics included: age, gender, body mass index (BMI), level of education, time since last dental visit, number of dental visits within last 5 years, history of diabetes and smoking.

The dental examiner (KG) was blinded to the OSA variables of each patient until after the completion of the periodontal examination. The severity of periodontitis was determined by measuring the probing pocket depth (PPD) and clinical attachment level (CAL). Gingival recession (REC) occurs in periodontitis when the gingival margin may migrate toward the apex of the tooth. Baseline periodontal assessments in this study included the following standard measures: PPD, CAL, REC and bleeding on probing (BOP). The Lobene Modfied Gingival Index (GI) [44], a non-invasive gingival index, was measured to indicate the level of gingival inflammation present. The Silness and

Loe plaque index (PI) was measured to indicate the amount of plaque present [45]. PPD was defined as the distance between the gingival margin and the periodontal probe tip. The tip of the probe was taken to be at the apical extent of the gingival sulcus. REC was defined as the distance between the cemento-enamel junction and the gingival margin. CAL was defined as the distance between the cemento-enamel junction and the bottom of the sulcus if REC was present. If there was no REC then CAL was defined as being equal to (PPD – 3). BOP was defined as bleeding from the sulcus or periodontal pocket. All measurements were taken at six sites at all existing teeth. All measurements were rounded to the nearest millimetre.

OSA variables for each patient were obtained by standard polysomnography prior to the periodontal examination [46]. Polysomnography scoring was performed by experienced accredited sleep technologists. Sleep variables included: total sleep time (TST), rapid eye movement sleep, AHI, oxygen saturation level (SaO_2), and oxygen desaturation index (ODI). AHI was calculated as the total number of apnoeas and hypopnoeas per hour of sleep. Apnoea was defined as complete airflow cessation for at least 10 seconds. Hypopnoea was defined as a great than 50% reduction in amplitude of airflow or thoraco-abdominal wall movement for greater than or equal to 10 seconds with an accompanying oxygen desaturation of at least 3% and/or associated with arousals. The ODI was defined as the frequency oxyhaemoglobin desaturation ($\geq$4%) per hour.

Calibration and Reliability

An important potential source of error in this study concerns the reproducibility of periodontal probing measurements. In order to minimize the possible effects of this error, the periodontal examination was performed by a single examiner (KG). Prior to the commencement of the study the examiner was calibrated against the periodontal variables

to be measured, and intra-examiner reliability tested by re-scoring a sample of sites at the same appointment. These sites were randomly selected by the dental assistant. Intra (r=0.78) and inter (r=0.75) examiner reliability results were assessed and found to be similar to the reported reproducibility in the literature [47].

Data Handling

The prevalence of periodontitis in the current study was defined according to the two definitions used in the recently published Australian National Survey of Adult Oral Health (NSAOH) [25]. NSAOH used the Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) and National Center for Health Statistics (NCHS) definitions [25]. According to the CDC/AAP definition, periodontitis is defined as the presence of two or more interproximal sites with $\geq$ 4mm CAL, not on the same tooth, or two or more interproximal sites with PPD $\geq$ 5mm, not on the same tooth. According to the NCHS definition, periodontitis is defined as the presence of at least one periodontal pocket with a probing depth of 4 mm or more and CAL $\geq$ 3 mm at the same site on a tooth. In the NSAOH, the prevalence of periodontitis was then calculated according to these definitions based on measurement of the relevant clinical parameters at three sites per tooth.

Statistical Analysis

A priori, it was considered that a greater than two fold increase in prevalence of periodontitis from the general population (21%) to the OSA patients would be clinically important. Based on these proportions, a sample size of 65 subjects would allow for a study power of >90% with a two-sided significance test α=0.01. Sample size calculations made allowance for the cross-sectional nature of the study and were calculated utilising PS Version 2.1.30 statistical software [48, 49]. Correlations between clinical indicators of

OSA and periodontal disease were examined using both parametric (Pearson) and non parametric methods (Spearman) in order to search for associations between the two conditions, taking into account the relatively small sample size as well as the expected high variance in the data. A step-wise regression and generalized linear modelling procedure using SAS Version 8.2 (Statistical Application Software, SAS Institute. Cary. NC) was used to adjust for significant covariates such as age, smoking and diabetes, in addition to compensating for the cluster effects of periodontal analysis.

RESULTS

Table 1 lists the demographic details of the sample group. Males comprised the majority of subjects examined. The mean age was 54.9 yrs (±12.8). The median age was 57 years. Patients diagnosed and treated for diabetes comprised 9% of the sample group. Forty-five percent of the subjects indicated a previous history of smoking (now ceased), while 9% identified themselves as current smokers. The majority of the patients had completed a tertiary qualification. The patients in this sample group demonstrated a history of regular dental attendance. The mean BMI for the group was 30.5 kg/m² (range 18.3kg/m² to 51.2kg/m²). The majority of this sample group could be considered overweight (82% had BMI > 25kg/m^2) or obese (47% had BMI > 30kg/m^2).

Table 2 shows results for the measured sleep variables. A wide range in OSA severity from mild to very severe was noted within the sample. However, the majority of patients could be considered to have at least moderate OSA (AHI >15/hr).

Table 3 shows the periodontal variables measured. The average PPD and CAL were based on measurements taken at six sites at all teeth for each patient. The mean PPD

for the sample group was 2.8mm. The mean CAL for the sample group was 2.15mm. The average CAL ranged from 0.13mm to 5.33mm per person.

Prevalence data for periodontitis are presented in Table 4 according to the two definitions of periodontitis used in this study, as well as by age groups. There is a notable difference in the prevalence to that of the Australian national survey (NSAOH) regardless of the definition used or the age group studied. Overall, the prevalence of periodontitis in our study group was 77-79%, depending on the definition used. There was almost a four-fold increase in the prevalence of periodontitis in our study group compared to the national survey.

When sleep variables were compared to periodontal variables, significant associations were found between CAL and TST ($r = -0.287$); $p < 0.05$. Multiple linear regression analysis was performed with CAL as the dependent (continuous) variable. Independent variables entered in the model included age, gender, smoking status, diabetes, BMI and sleep variables. Age and TST ($p < 0.05$) were found to be the only independent predictors of CAL values. The adjusted R^2 for the model was 0.29.

DISCUSSION

The results of this study support our hypothesis that the prevalence of periodontitis in a group of patients with OSA is greater than the national average [25]. There was about a four-fold increase in the overall prevalence in the recruited group in comparison to the national average [25]. The prevalence of periodontitis depends on the definition used. Although other definitions are available [50, 51], those used in this study were chosen in order to be consistent with the two definitions used in NSAOH to enable

direct comparison. The prevalence of OSA in the recruited group was higher than that reported in NSAOH regardless of the age group and the disease definitions applied.

The increased prevalence of periodontitis in our group in comparison to the national average could be due to either the existence of a true association between periodontitis and OSA or due to OSA and periodontitis sharing several overlapping aetiological factors. Exploring the latter, smoking [22, 23] and diabetes [22-24] are established risk factors for periodontitis. However, the effect of diabetes and smoking on the increased prevalence of those with periodontitis in our group appears to be minimal. For example, the prevalence of patients with diabetes in our sample group was higher than the national average [52]. However, the absolute number of patients with diabetes was small (6 subjects) and consistent with the reported association between OSA and diabetes [53]. In contrast, the level of cigarette smoking in our sample group was similar to the national level if never smokers are considered [52]. The prevalence of current smokers was lower than the national average (9% vs. 21%) [52].

The subjects recruited to this study could be assumed to have belonged to a higher SES [54] group due to the geographic location from which they were recruited, in addition to their education level, the latter being substantially higher than the national average [55]. The rate of dental attendance and maintenance in our group was much higher than the general population, as reported by NSAOH [25]. In general, the level of oral hygiene as indicated by the relatively low value of PI, could also be considered to be good in our group of patients [22, 23, 27]. Past association studies have shown that factors such as higher SES, better education and regular dental maintenance should reduce the prevalence of periodontitis [22, 23, 27]. However, the prevalence of

periodontitis was greater in our sample group despite these factors, thus further supporting a true association between OSA and periodontitis.

While the proportion of males was greater in the recruited subjects, the sample was similar to the proportion of males diagnosed with OSA in a sleep clinic context. The prevalence of periodontitis in males has been shown to be higher in some cross sectional studies [25, 26]. However as seen in the Australian survey [25], the magnitude of difference in prevalence between the two gender groups is small and is unlikely to explain the increased prevalence in our sample [25].

Cross sectional studies investigating the association between periodontitis and obesity have shown conflicting results with positive association [28, 29] as well as no association [56] between different measures of obesity and periodontitis. However, obesity is an established risk factor for OSA [57]. Not surprisingly, the level of obesity in this group of OSA patients is higher in comparison to the level of obesity in the Australian population [52]. In comparison, 53% of adults in the Australian population can be considered overweight or obese [52]. It should be noted that the sample group in the current study were older than the general population. Considering that the prevalence of obesity increases with age, peaking at about 50-65 yrs, the level of obesity in this sample group may be in close agreement with the national average.

Thus it appears that these overlapping risk factors alone may not be sufficient to explain the observed high prevalence of periodontitis in our study. Hence the possibility of a causal association between OSA and periodontitis merits consideration. However, we did not find any significant correlations between OSA indices and periodontal

measures, perhaps reducing the likelihood of a causal association. The only significant correlation was between CAL and TST, the biological significance of which is unclear.

Subjects with OSA may also have a mouth breathing tendency [58, 59] and we question whether mouth breathing could be an explanation for a higher prevalence of peridontitis in OSA. Past cross-sectional studies have shown an association between mouth breathing and gingivitis in prepuberscent and teenage children [60, 61]. However, there are no studies exploring the association between mouth breathing and periodontal disease in adults. Hence, the effect of mouth breathing in the pathogenesis of periodontitis is unclear, and seems worthy of further study.

Regardless of whether there is a causal association between periodontitis and OSA, there are potentially important implications of our findings. Firstly, periodontitis could be a previously unknown confounder in the relationships between OSA and cardiovascular disease, and OSA and inflammation. Hence future studies will need to account for this potential confounder. Secondly, OSA may increase the presence and severity of periodontitis by contributing to increased systemic inflammation

Our exploratory study has a number of important limitations. Firstly, there is the potential for selection bias that may have resulted in a sample biased toward the presence of dental conditions. However, this is unlikely as we deliberately excluded patients with a history of a known diagnosis of periodontitis or its treatment within the last 3 months. Furthermore, the main reason for declining participation in the study was work commitments precluding attendance at the required dental visit. It is uncertain whether this may have introduced selection bias related to socioeconomic status. Secondly, we used a historical (NSAOH) [25] rather than concurrent control group. This historical control group consisting of 5505 subjects was large and contemporary. Whether control

subjects had known or occult OSA is unknown, but this would tend to have reduced the observed difference in periodontitis prevalence between our patients and the control group, making our estimated difference in prevalence conservative. Thirdly, the periodontal examiner was not blinded to the study hypothesis. Hence the potential for over-diagnosis of periodontitis cannot be ruled out, despite being considered very unlikely.

In conclusion, our pilot study suggests that the prevalence of periodontitis may be higher in patients with OSA. Given the potential importance of such an association in furthering our understanding of the pathophysiology of inflammation and its consequences in both periodontitis and OSA, it is important to conduct further studies to verify our prevalence findings and to elucidate the nature of the relationship.

ABBREVIATIONS

AHI, apnoea-hypopnoea index

BMI, body mass index

BOP, bleeding on probing

CAL, clinical attachment level

CDC/AAP, Centers for Disease Control and Prevention and the American Academy of Periodontology

GI, gingival index

NSAOH, National Survey of Adult Oral Health

NCHS, National Center for Health Statistics

ODI, oxygen desaturation index

OSA, obstructive sleep apnoea

PI, plaque index

PPD, probing pocket depth

REC, gingival recession

SaO_2, oxygen saturation level

SES, socioeconomic status

TST, total sleep time

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Table 1 - Demographic data of recruited subjects

		Number of subjects (%)
Age		
	18-34 yrs	5 (8)
	35-54 yrs	24 (36)
	55-74 yrs	31 (45)
	> 75 yrs	7 (11)
Gender		
	Male	54 (82)
	Female	12 (18)
Education		
	Tertiary	34 (52)
	Trade	8 (12)
	year 12	16 (24)
	< year 12	8 (12)
Last dental visit		
	< 12 months	54 (82)
	> 12 months	12 (18)
Dental visits within last five years		
	< 5 visits	31 (47)
	5 to 10 visits	28 (42)
	> 10 visits	7 (11)
Smoking		
	Never	30 (45.5)
	Former	30 (45.5)
	Current	6 (9)
Diabetes		
	Yes	6 (9)
	No	60 (91)

Data from 66 patients recruited presented as number of subjects and percentage of sample.

Table 2 - Summary of polysomnographic variables for study group

	Mean (SD) for group	**Median (minimum, maximum) for group**
TST (min)	345.4 (68.5)	354.5 (160.5 - 512.5)
Rapid eye movement sleep(min)	53.75 (24.3)	51.75 (3.5 - 103)
AHI (per hour)	36.55 (25.77)	29.05 (5.7 - 137.2)
Mean SaO_2 (%)	91.3 (5.1)	93 (70 - 98)
ODI 4% (per hour)	23.7 (25.4)	15.6 (0.5 - 130.6)

Table 3 - Summary of patient characteristics: periodontal variables for study group

	Mean, SD for group	**Median (minimum, maximum) for group**
Overall PPD (mm)	2.80, 0.33	2.79 (2.21, 3.79)
Overall CAL (mm)	2.15, 1.20	2.27 (0.13, 5.33)
Overall GI (units)	0.54, 0.42	0.51 (0.06, 2.50)
Overall PI (units)	0.45, 0.31	0.37 (0.10, 1.87)
Overall BOP (%)	9, 8	7 (0, 47)

Table 4 - Prevalence of periodontitis according to definition and age group (%)

Age group (yrs)	CDC/AAP		NCHS	
	Current study	NSAOH	Current study	NSAOH
15-34	40	7	40	12
35-54	71	25	75	23
55-74	87	44	80	24
> 75	100	61	100	26
All ages average	79	23	77	19

Periodontitis prevalence from current study compared to prevalence from NSAOH according to different age groups and the two disease definitions

CDC/AAP: Centers for Disease Control and Prevention and the American Academy of Periodontology
NCHS: National Center for Health Statistics

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