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OBSTRUCTIVE SLEEP APNOEA AND PERIODONTITIS

by

Kogulan Gunaratnam BDS (Syd) BSc (Monash)

A treatise submitted in partial fulfilment of the requirements for the degree of

Master of Dental Science

Discipline of Periodontics
Faculty of Dentistry
University of Sydney

2008

CANDIDATE'S CERTIFICATE

This is to certify that the work presented in this thesis was carried out by the candidate in the Faculty of Dentistry, University of Sydney, at the Department of Respiratory Medicine, Royal North Shore Hospital and at Sydney Dental Hospital. Any contribution made to the research by others with whom I have worked is explicitly acknowledged in the treatise. The work presented in this treatise has been submitted only to the University of Sydney for a higher degree.

Kogulan Gunaratnam

ACKNOWLEDGEMENTS

I would like to thank my supervisors Dr. Barbara Taylor and Prof. Peter Cistulli for their encouragement to commence this original project. Their constant help and support during the formulation of this project, recruitment of patients, and preparation of this manuscript has been invaluable. Their critical review of my work has helped me improve the quality of this manuscript. Through their direction, I have managed to learn a great deal about scientific methodology and writing. I would also like to thank Dr. Brad Curtis for his help with the statistical analysis of the data as well as his input on the preparation of this manuscript.

Finally, I would like to thank my family and especially my wife, Chithroobi, for their encouragement during the long process of my course and preparation of this manuscript. In particular, Chithroobi's help in formatting my manuscript and her support during the rigorous demands of my course has been much appreciated.

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PART A: REVIEW OF THE LITERATURE

ABBREVIATIONS

AASMT: American Academy of Sleep Medicine Taskforce

AAP: American Academy of Periodontology

AHI: apnoea hypopnoea index

BMI: body mass index

BOP: bleeding on probing

CAD: coronary artery disease

CAL: clinical attachment level

CDC: Centers for Disease Control

CI: confidence interval

CPAP: continuous positive airway pressure

CRP: C-reactive protein

CVD: cardiovascular disease

EDS: excessive daytime sleepiness

ESR: Erythrocyte sedimentation rate

ICAM: intercellular adhesion molecule

IL: interleukin

MI: myocardial infarct

NHANES: National Health and Nutritional Examination Survey

NO: Nitric Oxide

NSAOH: National Survey of Adult Oral Health

NCHS: National Center for Health Statistics

NFκβ: nuclear factor kappa beta

OSA: obstructive sleep apnoea

OSAHS: obstructive sleep apnoea/hypopnoea syndrome

OSAS: obstructive sleep apnoea syndrome

PD: probing depth

PSG: polysomnography

RDI: respiratory disturbance index

ROS: reactive oxygen species

SDB: sleep disordered breathing

SES: socioeconomic status

TNF-α: tumour necrosis factor alpha

VCAM: vascular cellular adhesion molecule

1. INTRODUCTION

Obstructive sleep apnoea (OSA) and its associated daytime symptoms form a syndrome, obstructive sleep apnoea-hypopnoea syndrome (OSAHS) that affects about 5% of the population worldwide (Young et al 2002a, Pack 2006). OSA is characterized by repeated episodes of upper airway obstruction during sleep, resulting in recurrent hypoxemia and sleep fragmentation (Hensley & Ray 2005). These in turn are associated with neurocognitive disorders, hypertension and cardiovascular complications (Pack 2006). Current therapies for this condition include surgical interventions, oral appliances and continuous positive airways pressure (CPAP). Systemic and local airway inflammation has recently been linked to OSA and is hypothesized to increase the risk of cardiovascular complications (Lavie 2005). While the exact mechanism is not certain, it is believed that the underlying systemic inflammation from OSA is due to the hypoxia/reperfusion injury from intermittent hypoxia that occurs with OSA (Lavie 2005). Specifically, the episodic hypoxia in OSA leads to increased production of reactive oxidative species (ROS) and, via various pathways, in the formation of systemic inflammatory mediators. The resultant inflammatory response is then responsible for the increased cardiovascular morbidity and mortality by potentiating disease in those that already have inflammatory disease or triggering inflammatory diseases in people with existing genetic, behavioural and environmental exposure.

Periodontitis involves the supporting structures of the tooth and is a disease caused by specific bacteria that triggers an inflammatory response (Kinane 2001). Tissue damage and destruction, including loss of the connective tissue attachment between the tooth and the jaw, together with resorption of supporting bone, is initiated by the micro-organisms

and mediated by the host response. Periodontitis, which is a severe form of periodontal disease, is one of the most common chronic infections in the world. The prevalence of moderate to severe periodontitis across the globe is in the range of 5 to 20 % (Burt 2005).

Recent studies have speculated on an association between periodontitis and systemic inflammation in, for example, diabetes (Soskolne & Klinger 2001), rheumatoid arthritis (Mercado et al. 2000) and cardiovascular disease (CVD) (Beck & Offenbacher 2005), but no research has been undertaken on the link between OSA and periodontitis. This review will focus on features of OSA, inflammation and periodontitis to examine if there is a possible link between OSA and periodontitis by means of systemic inflammation.

2. OBSTRUCTIVE SLEEP APNOEA

2.1 Description

2.1.1 Historical considerations

Physicians in the 19th century first described sleep related breathing disorders after clinical observation of patients. They reported a pattern of breathing that was characterized by cyclical fluctuation with periods of central apnoeas or hypopnoeas alternating with periods of hyperpnoea in a gradual waxing and waning fashion that is now called Cheyne-Stokes respiration, named after the physicians who first described it. Then in the late 19th century, descriptions of cases of obesity with extreme excessive sleepiness surfaced. Some physicians remarked on the similarity of these cases to that of Joe, the fat boy in Charles Dickens' book 'The Pickwick Papers', enabling them to use

the term ‘Pickwickian syndrome’ to describe the combination of obesity and marked excessive sleepiness (Pack 2006). However this term has now become restricted to a specific condition (Burwell et al. 1956). Much of the research in sleep disordered breathing (SDB) has occurred since the 1950s, particularly in the last 20 years. Work done in the 1960s on subjects displaying ‘classical’ Pickwickian features showed that periodic cessation of respiration associated with marked fluctuations in heart rate occurred in these subjects during sleep. However, OSA was not fully recognised until assessments of airflow at the nose, throat, as well as thoracic movements, were performed. These showed that the cessation of respiration was due to obstruction of the upper airway (AASMT 1999).

2.1.2 Definitions of syndromes in sleep related breathing disorders

Many types of abnormal breathing events during sleep have been described. Together with signs and symptoms, these can be used to describe several different syndromes that commonly fall under the broad category of Sleep Related Breathing Disorders.

Some examples of these are:

- ‘Pickwickian syndrome’ described patients with obesity, hypercapnia, cor pulmonale, erythrocytosis and daytime hypersomnolence (Burwell et al. 1956).
- Obstructive sleep apnoea syndrome (OSAS), first used for subjects with daytime hypersomnolence and polysomnographically proven obstructive apnoeas (Guilleminault et al. 1976).
- Upper airways resistance syndrome described patients who had typical symptoms of OSA but who did not have symptoms of obstructive apnoeas or hypopnoeas.

An increase in negative oesophageal pressure during inspiration, commonly terminating with an arousal was seen in these cases (Guilleminault et al. 1993).

- A central sleep apnoea syndrome as described in the literature (AASMT 1999).

Varying definitions were being used in the literature so in 1999 the American Academy of Sleep Medicine Task Force proposed standard criteria that can used to define the various syndromes (AASMT 1999). The key features of four separate syndromes associated with abnormal breathing events or SDB were defined. They were:

a. OSAHS
b. central sleep apnoea syndrome
c. upper airways resistance syndrome
d. sleep hypoventilation syndrome.

The key features, diagnostic criteria, severity criteria and predisposing factors for each of these syndromes were described. It should be noted that the definition of OSAHS describes OSA together with its health impact (AASMT 1999, Hensley & Ray 2005), i.e. symptoms of daytime sleepiness, and associated features such as hypertension. The terms, features and definitions of OSA, OSAHS and SDB are often used interchangeably and described similarly in the literature (Hensley & Ray 2005). This review will mainly focus, where possible, on literature that discusses OSA and/or uses the definition and features of OSA.

2.1.3 Features of OSA

OSA is characterised by recurrent episodes of partial or complete upper airway obstruction during sleep. This results in repetitive events of reduction, hypopnoea, or complete cessation, apnoea, of airflow despite efforts to breath. These events are terminated by a brief awakening which restores the normal breathing. However, this only lasts until the next event, thus setting up a repetitive cycle which results in sleep becoming fragmented. In addition, oxygen desaturation and a gradual increase in partial pressure in carbon dioxide also occur. The consequences of these events are excessive daytime sleepiness (EDS) and diminished neurocognitive function as part of OSAHS.

2.2 Assessment

2.2.1 Diagnostic criteria

The criteria for the diagnosis of OSA are currently based on the apnoea/hypopnoea index (AHI) (AASMT 1999, Hensley & Ray 2005). Overnight monitoring indicating five or more obstructed breathing events per hour during sleep is considered abnormal. These events may include any combination of obstructive apnoea/hypopnoea or respiratory effort related arousals as defined below.

As part of the OSAHS, an individual may also show other symptoms like:

- daytime sleepiness
- choking or gasping during sleep
- recurrent awakenings from sleep
- unrefreshing sleep

- daytime fatigue
- impaired concentration

2.2.2 Obstructive apnoea/hypopnoea and respiratory effort–related arousal event

An event that is characterised by a transient reduction in breathing or its complete cessation is an obstructive apnoea/hypopnoea event as defined by American Academy of Sleep Medicine. In this definition it is not necessary to distinguish an apnoea from a hypopnoea for the purpose of routine clinical practice (AASMT 1999). An obstructive apnoea/hypopnoea event must fulfil criteria 1 or 2 plus criteria 3 of the following (AASMT 1999):

1. A clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern).
2. A clear amplitude reduction of a validated measure of breathing during sleep that does not reach the above criterion but is associated with either an oxygen desaturation of >4% or an arousal.
3. The event lasts 10 seconds or longer.

However, the definition of apnoea and hypopnoea is in flux (Iber et al. 2007). For example, hypopnoea was recently defined to be either a nasal pressure signal drop of ≥30% with ≥4% desaturation (for ≥10 seconds), or a nasal pressure signal drop of ≥50% with ≥3% desaturation/arousal (for ≥10 seconds) while apnoea was defined as a drop in

the peak thermal sensor excursion ≥90% from baseline (for ≥10 seconds) (Iber et al 2007). A respiratory effort–related arousal event describes something that does not meet the criteria for an apnoea or hypopnoea but rather the respiratory effort that leads to awakening from sleep. Such events must last 10 seconds or longer and have a pattern of progressively more negative oesophageal pressure, terminated by a sudden change in pressure to a less negative level and an arousal (AASMT 1999). While the use of oesophageal pressure is the preferred method of assessing change in respiratory effort, nasal pressure can also be used under recent definitions (Iber et al. 2007).

2.2.3 Severity criteria

The common grading of severity for OSA is based on the AHI and is shown in Table 1.

Table 1. Grading of OSA.	
Normal	less than 5 events per hour
Mild	5-15 events per hour
Moderate	15 to 30 events per hour
Severe	greater than 30 events per hour

The severity of OSAHS is described by taking into account the grade of OSA, based on the AHI as above, plus the severity of daytime sleepiness. The grading for severity of sleepiness is defined as (AASMT 1999):

1. Mild: Unwanted sleepiness or involuntary sleep episodes occur during activities that require little attention. Examples include sleepiness that is likely to occur while watching television, reading, or travelling as a passenger. Symptoms produce only minor impairment of social or occupational function.

2. Moderate: Unwanted sleepiness or involuntary sleep episodes occur during activities that require some attention. Examples include uncontrollable sleepiness that is likely to occur while attending activities such as concerts, meetings, or presentations. Symptoms produce moderate impairment of social or occupational function.
3. Severe: Unwanted sleepiness or involuntary sleep episodes occur during activities that require more active attention. Examples include uncontrollable sleepiness while eating, during conversation, walking, or driving. Symptoms produce marked impairment in social or occupational function.

2.2.4 Diagnostic methods

The gold standard for the diagnosis of OSA is the full overnight polysomnography (PSG) (Hensley & Ray 2005). This method requires trained personnel in a sleep laboratory to operate. PSG is a comprehensive recording of the biophysical changes that occurs during sleep. It consists of various measurements including electroencephalogram, muscle activity including submental electromyogram, channels of electrooculogram, respiratory airflow, respiratory effort (thoracic and abdominal breathing movements), oxygen saturation and electrocardiography (Ross et al. 2000). Body position and snoring are also frequently monitored in formal sleep studies.

Other diagnostic methods that can be used as alternatives to PSG that are less invasive or cheaper can be partial channel PSGs, partial night or daytime PSGs, portable sleep monitoring devices for use at home, radiologic imaging of the head and neck for anatomic abnormalities predictive of OSA (including cephalometry, magnetic resonance imaging and CT scans), anthropomorphic measurements (such as neck circumference, nasopharyngeal and laryngeal endoscopic measurements of upper airway structure and

function) and focused questionnaires (e.g. The Berlin questionnaire (Netzer et al. 1999)). These methods in general show limited sensitivity and specificity and some can be considered as 'controversial' at best (Ross et al. 2000).

Even though there are now portable sleep recording systems that can perform unattended PSG in the patient's home, in-laboratory testing with a technician present remains the standard and is required by many insurers, (e.g. Medicare of the United States) before they will pay for treatment of the condition. In fact, recent research on the cost-effectiveness and economic implications of diagnostics for sleep apnoea showed that full PSG was the most cost-effective of PSG, home systems, and empirical therapy (Chervin et al. 1999).

2.3 Prevalence

2.3.1 General trends

Epidemiological studies have demonstrated a varying degree in prevalence of OSA (Table 2). Recent studies have estimated a higher prevalence than older studies. The range of prevalence depends on the age group selected as well as the criteria used to diagnose OSA. In a review (Young et al. 2002a), prevalence estimates from studies for OSA of at least mild severity, ranged from 3 to 28%. For OSA of at least moderate severity, estimates range from 1 to 14% (Ancoli-Israel et al. 1995, Bearpark et al. 1995, Bixler et al. 2001, Bixler et al. 1998, Gislason et al. 1988, Kripke et al. 1997, Young et al. 1993). When comparisons are made of studies with in-laboratory PSG conducted on large samples, the prevalence estimates are in closer agreement. Results from large scale studies in Wisconsin (Young et al. 1993), Pennsylvania (Bixler et al. 2001, Bixler et al.

1998), and Spain (Duran et al. 2001) are given in Table 2 and Table 3. On the basis of the average of prevalence estimates from these studies, predominantly of white men and women with mean body mass index (BMI) of 25 to 28, the review estimated that roughly 1 of every 5 adults has at least mild OSA and 1 of every 15 has at least moderate OSA (Young et al. 2002a).

Table 2. Summary of epidemiological studies on the prevalence of OSA

Location	N	Age (years)	Men	Women	Diagnosis of OSA
Busselton, Australia (Bearpark et al. 1995)	294	40-85	10%	N/A	RDI ≥ 10
Wisconsin, USA (Young et al. 1993)	602	30-60	9%	4%	AHI ≥ 15
Pennsylvania, USA (Bixler et al. 1998, 2001)	1741	≥ 20	7.2%	2.2%	AHI ≥ 15
Newcastle, Australia (Olson et al. 1995a)	2202	35-69	5.7%	1.2%	RDI ≥ 15
Vitoria-Gasteiz, Spain (Duran et al. 2001)	555	30-70	14.2%	7%	AHI ≥ 15

Table 3. Summary of epidemiological studies on the prevalence of OSAHS

Location	N	Age (years)	Men	Women	Diagnosis of OSAHS
Wisconsin, USA (Young et al. 1993)	602	36-60	4%	2%	AHI > 5, EDS
San Diego, USA (Kripke et al. 1997)	355	40-64	11%	5.3%	O_2 sat 4%
Pennsylvania, USA (Bixler et al. 1998, 2001)	1741	≥ 20	3.9%	1.2%	AHI ≥ 10, EDS

2.3.2 Australian studies

The prevalence of OSA in Australia seems to be similar to that of other developed countries. In an Australian study conducted in Busselton, Western Australia, 294 men aged 40 to 65 yrs were recruited for home monitoring of their snoring and sleep apnoea. Using the Respiratory Disturbance Index (RDI) which is similar to the AHI, 26% of the subjects had a RDI of at least 5, and 10% had an RDI of at least 10 (Bearpark et al. 1995). If symptoms of daytime sleepiness were included, then 3% of the sample qualified for the minimum criteria for OSAHS. The preliminary results from the Wisconsin Cohort study showed a prevalence of 4% for men and 2% for women for OSAHS when daytime symptoms were included (Young et al. 1993). A cross-sectional study on a random sample of 2202 subjects aged 35 to 69 yrs was undertaken in Newcastle, Australia (Olson et al. 1995a). Of the 441 respondents to the questionnaire, 79 people had a RDI of >15. This gives a minimum prevalence of OSA in this sample of 3.6%, being 5.2% and 1.2% in men and women respectively.

2.3.3 Race

Almost all of the epidemiological data has been from developed countries on mainly Caucasian subjects. Thus the prevalence of OSA among different races in developing nations is unknown. There is contradictory evidence as to whether OSA prevalence is as high or higher in African-Americans as in Caucasians. One study (Ancoli-Israel et al. 1995) found that the odds of having an AHI of 30 or higher was 2.5 times greater in African-Americans relative to Caucasians after controlling for BMI and other confounding factors (Ancoli-Israel et al. 1995). Similarly in participants less than 25 years of age, the prevalence of OSA (adjusted for BMI and other potentially confounding

factors) was higher in African-Americans than in Caucasians in the Cleveland Family Study (Redline 1998). In contrast, the prevalence of OSA was not higher in African-Americans compared with Caucasians, on the basis of in-home PSG of more than 6,000 participants in the multicenter Sleep Heart Health Study. This study also adjusted for age, gender and BMI (Young et al. 2002b).

Using a two-stage sampling methodology and in-laboratory PSG, a study similar to the Busselton study, was carried out on a sample of 784 Hong Kong men of 30 to 60 years of age (Ip et al. 2001). Of the 153 who completed PSG studies, 25% had AHI of 15 or more events per hour. The self-selection of men more likely to have OSA may have biased the results in this study. In order to adjust for this, the authors made a conservative assumption that there were no cases of OSA among the non-participants of the sample of 784 men, and estimated the prevalence of OSA (defined as an AHI of 15 or more) to be 5%, and of OSAHS (defined as an AHI of 5 or more plus EDS) to be 4%.

The remarkable similarity in prevalence of OSA in the Hong Kong sample to that in the Australian and American samples poses some questions. Obesity is a strong risk factor for OSA and is prevalent in white populations, but is relatively uncommon in Asian countries. There was only a weak association between BMI and OSA in the Hong Kong study. This led the authors to hypothesise that other strong OSA risk factors may exist that are more prevalent in Chinese relative to Western populations, such as craniofacial features that compromise the upper airway.

2.3.4 Age

OSA prevalence appears to increase steadily with age in midlife, but age-related trends in older age are unclear. Several studies have found OSA to be highly prevalent in people

older than age 65 years (Ancoli-Israel et al. 1991, Bixler et al. 2001, Bixler et al. 1998, Young et al. 2002b). This relationship of prevalence to age appears to be independent of gender. In cohort studies, samples with wide age ranges have been present, thus allowing internal comparisons of prevalence in broad categories of older age and middle age without the problem of inter-study methodological differences, such as definition of OSA (see Table 2, Table 3). For example, the study based in Pennsylvania, showed those aged greater than 65 years had twice the prevalence of OSA (Bixler et al. 2001, Bixler et al. 1998). The Spanish study showed that the prevalence of OSA in those aged greater than 70 years old was three and four times as that of those under the age of 70 years old for and AHI >5 and an AHI >15 respectively (Duran et al. 2001). The data from the Sleep Heart Health study showed that the prevalence increased steadily with age (Young et al. 2002b).

The data from these studies suggest that prevalence tends to level off after age 65 years rather than there being a continual rise in prevalence with age due to accumulating cases. This trend, if correct, implies either a relative increase in the mortality rate in association with OSA (unless it is independently fatal) or a remission of OSA with aging. Conversely, it is also possible that biases, including poor measurement of OSA in older people may explain some or all of the age-related prevalence trends seen in cross-sectional studies. Furthermore, it is not known at present if OSA in older age differs, if at all, from the typical OSA of younger or middle age with respect to pathophysiology.

2.3.5 Gender

A 2- to 3-fold greater risk for men compared with women has been reported in most epidemiological studies that have estimated gender-specific prevalence (Young et al.

2002a) (See also Table 2, Table 3). The reason for this discrepancy is still not understood. Some of the reasons proposed include differences in sex hormones, environmental exposures (e.g. smoking), health or behavioural habits and anatomical differences (Young et al. 2002a). On the other hand, the administration of oestrogen and progesterone to men (or postmenopausal women) has not been shown to reduce AHI (Shaver & Zenk 2000). Furthermore, no conclusive findings have emerged from the few studies that have investigated differences in upper airway dimensions and upper airway fat deposits when comparing men and women, albeit, in some small samples (Leech et al. 1988, Popovic & White 1998, Schwab 1999, Ware et al. 2000, Whittle et al. 1999).

2.4 Morbidity and mortality

2.4.1 Overview

OSA is also associated with some leading medical conditions of mortality in the developed countries such as hypertension, CVD and cerebrovascular diseases. OSA may also lead to neurobehavioural morbidities such as daytime sleepiness and impaired cognitive function that may, in turn, contribute to motor vehicle crashes and job-related accidents (Desai 2002).

The National Commission on Sleep Disorders Research (Ross et al. 2000) estimated that OSA may be responsible for 38,000 cardiovascular deaths per year and annual costs of $42 million for related hospitalizations. The cumulative eight-year mortality of untreated OSA has been estimated to be as high as 37% for patients with an apnoea index ≥20, where apnoea index is defined as the number of apnoeic episodes/hour sleep. This is in

comparison to a mortality of 4% for patients with apnoea index lower than 20 (He et al. 1988).

2.4.2 Daytime sleepiness, diminished neurocognitive function and motor vehicle crashes

There is evidence that OSA is an important cause of daytime sleepiness. In the Wisconsin sleep study, approximately 23% of women and 16% of men with an AHI of 5 or more were reported to have experienced sleepiness when compared to 2-3% of non snoring men and women with an AHI of less than 5 (Young et al. 1993). When the Epworth Sleepiness Scale was used, as in the Sleep Heart Health Study, there was significant increase in 'sleepiness' with increasing AHI (Gottlieb et al. 1999). The association of AHI with sleepiness was similar in subjects older and younger than age 65 years and was independent of gender, BMI, or evidence of insufficient sleep time (Gottlieb et al.1999). Treatment studies have also shown that EDS, which is a feature of OSA, can be improved after treating OSA with CPAP. These studies have used oral placebo or sham CPAP as controls in patients clinically identified with OSA (Ballester et al. 1999, Engleman et al. 1999). However, patients presenting for evaluation and treatment of OSA might not be representative of subjects with elevated AHI in the general population because asymptomatic individuals are less likely to be evaluated for the presence of OSA than are those who complain of sleepiness.

With respect to cognitive function, population-based studies exploring the effect of OSA on diminished neurocognitive function show weaker associations than results from clinic-based studies (Young et al. 2002a). It has been proposed that selective referral of the most impaired patients for sleep laboratory evaluation is likely to cause a bias towards

finding stronger associations. In the Wisconsin Sleep Cohort Study, psychomotor function and memory factors derived from a neuropsychological test battery were investigated as OSA outcomes (Kim et al. 1997). OSA severity, indicated by the AHI, was significantly related to diminished psychomotor efficiency. The association of OSA and psychomotor efficiency, adjusted for age and education, was not explained by measures of fatigue or daytime sleepiness. Similar findings were reported from a study of 848 participants in the Danish MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) cohort: an AHI of 5 or greater was significantly associated with self-assessed concentration problems but not with memory (Jennum & Sjol 1993).

Several studies have shown that patients with OSA have a poor performance on driving simulators and higher rate of motor vehicle crashes based on self-reporting as well as crash records (Aldrich 1989, Barbe et al. 1998, Findley et al. 1989, George 2001, Horne & Reyner 1995). There is a possibility of overestimation in these studies due to selection bias (Young et al. 2002a). The population studies in Wisconsin and Spain suggest strong association between undiagnosed OSA and objectively measured motor vehicle crashes. Men and women with an AHI of 15 or greater had an odds ratio of 7.3 for multiple crashes in a 5-year period (adjusted for age and miles driven per year) in comparison with those with an AHI less than 5 and no habitual snoring (Young et al. 1997). Similarly severity was compared between motor vehicle crash victims from two hospitals and control subjects from primary care health centres (Teran-Santos et al. 1999). The odds ratio of having a motor vehicle crash by those with OSA (defined by AHI $\geq$10) compared with control subjects was 6.3 (Teran-Santos et al. 1999). In both studies, self assessed sleepiness did not explain the associations of OSA and motor vehicle crash history. In a treatment study, the use of CPAP in compliant patients with OSA decreased the accident rate to virtually zero (Findley et al.2000). The accident rate of this group of

patients in Colorado, USA, with OSA prior to CPAP treatment was 0.07 crashes per driver per year as opposed to 0.01 crashes per driver per year for all Colorado drivers (Findley et al. 2000).

2.4.3 Hypertension

OSA is independently associated with hypertension. Early cross-sectional studies reported mixed findings. Several of these studies found a positive association between hypertension and various types of SDB including snoring, OSAHS and OSA (Gislason et al. 1987, Gislason et al. 1993, Hla et al. 1994, Young et al. 1997), whereas others did not (Bearpark et al. 1993, Jennum and Sjol 1993, Olson et al. 1995b, Enright et al. 1996). However, not all the studies adjusted for confounding factors such as age, race, gender, and BMI (Hla et al. 1994, Olson et al. 1995b, Young et al. 1997).

Stronger evidence for a link between hypertension and OSA is from four recent large cross-sectional population based studies and one prospective study. All of these studies controlled for common confounding factors such as obesity, age and gender and BMI (Young et al. 2002a). An association between OSA and hypertension appears to be present even at the mild end of the OSA severity spectrum. Despite the modest magnitude of the association, the high prevalence of OSA implies that it may be responsible for a substantial portion of the population burden of hypertension. In spite of this, the potential for resolving hypertension by treating OSA remains unclear.

The four large cross-sectional population-based studies have estimated associations between polysomnographically assessed AHI and daytime hypertension where the latter

is defined as use of antihypertensive agents or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. A Spanish study of 555 men and women in Spain reported that even those with an AHI greater than zero had increased odds of hypertension relative to those with an AHI of zero (Duran et al. 2001). A significant association was found between AHI and hypertension in a cross-sectional sample of 6,132 men and women participating in the Sleep Heart Health Study. Relative to an AHI less than 1.5, the odds ratios were , respectively, 1.1, 1.2, 1.3, and 1.4 for AHI categories of 1.5 to 5, 5 to 15, 15 to 30, and 30 or greater (Nieto et al. 2000).

A significant cross-sectional association between OSA and hypertension was found in study involving a sample of 1,741 men and women in Pennsylvania, USA. The associations were complex and generally indicated a stronger relationship between OSA and hypertension in younger and less obese participants than in older, heavier participants (Bixler et al. 2000).

None of these studies were able to demonstrate that OSA predated hypertension because of their cross-sectional design. However, the prospective analysis from the Wisconsin Sleep Cohort provides stronger evidence (Peppard et al. 2000a, Peppard et al. 2000b). Even a minimally elevated AHI at baseline (AHI ≤5 events per hour) was associated with 42% (95% CI, 13 to 78%) increased odds of developing hypertension over a 4-year follow-up period. A dose–response relationship was observed for more severe categories of AHI, with an odds ratio of 2.9 (95% CI, 1.5 to 5.6) for an AHI of 15 or greater versus an AHI of zero events per hour. There appeared to be a plateau in the hypertension response at high levels of OSA severity. Such a plateau was also noted in the cross-

sectional study from Spain (Duran et al. 2001) and the Sleep Heart Health Study (Nieto et al. 2000).

Finally, the effectiveness of blood pressure reduction by treating OSA with CPAP has been addressed in numerous intervention studies (Davies et al. 1994, Guilleminault et al. 1996, Pankow et al. 2000, Rauscher et al. 1992, Akashiba et al. 1995, Akashiba et al. 1993, Ali et al. 1992, Barbe et al. 1996, Dimsdale et al. 1995, Engleman et al. 1996, Faccenda et al. 2001, Jennum et al. 1989, Mayer et al. 1991, Suzuki et al. 1993, Wilcox et al. 1993). These studies showed mixed results. This may have been due to inadequate study power since OSA may have but a modest effect on the magnitude of blood pressure. Furthermore, if OSA leads to vascular damage, it is also possible that elevated blood pressure due to OSA in patients could persist even when OSA is treated (Young et al. 2002a).

2.4.4 Cardiovascular morbidity and mortality

2.4.4.1 Mechanisms

Several mechanisms have been put forward by authors to be important in the pathogenesis of CVD by OSA (Young et al. 2002a, Lavie 2005, Shamsuzzaman et al. 2003, Gozal et al. 2008, Benjamin et al. 2008). In general, these mechanisms are proposed to contribute to the cardiovascular risk independently of smoking and other common risk factors such as hypertension, diabetes and hyperlipidaemia. However, the extent to which each of these mechanisms may contribute to the pathogenesis of CVD is unknown. Cardiovascular outcomes could be related to OSA via mechanisms other than hypertension that might include (Young et al. 2002a):

- chronic sympathetic hyperactivity (Carlson et al. 1993, Dimsdale et al. 1995, Fletcher et al. 1987, Narkiewicz et al. 1998)
- vascular injury and acceleration of atherosclerosis due to episodic hypoxemia (Gainer 1987),
- elevated pulmonary blood pressure and consequent risk of right heart hypertrophy (Guidry et al. 2001) and heart failure (Bradley 1992); and
- increased risk of plaque ruptures and subsequent cardiovascular or cerebrovascular events (Lavie 2005).

In a review of the literature, sympathetic activation, vascular endothelial dysfunction, oxidative stress, inflammation, coagulation and metabolic dysregulation were put forward as mechanisms that could contribute to the risk of CVD (Shamsuzzaman et al. 2003).

Exploring these mechanisms further, increased levels of endothelin have been shown to cause sustained vasoconstriction and other vascular changes. Evidence of endothelial dysfunction is observed in patients with OSA (Schulz et al. 2000, Kato et al. 2000). While it should be noted that endothelial dysfunction is also associated with other co-morbidities of CVD such as hypertension, smoking, hyperlipidaemia and diabetes, the authors suggest that endothelial dysfunction may be an independent risk factor for CVD.

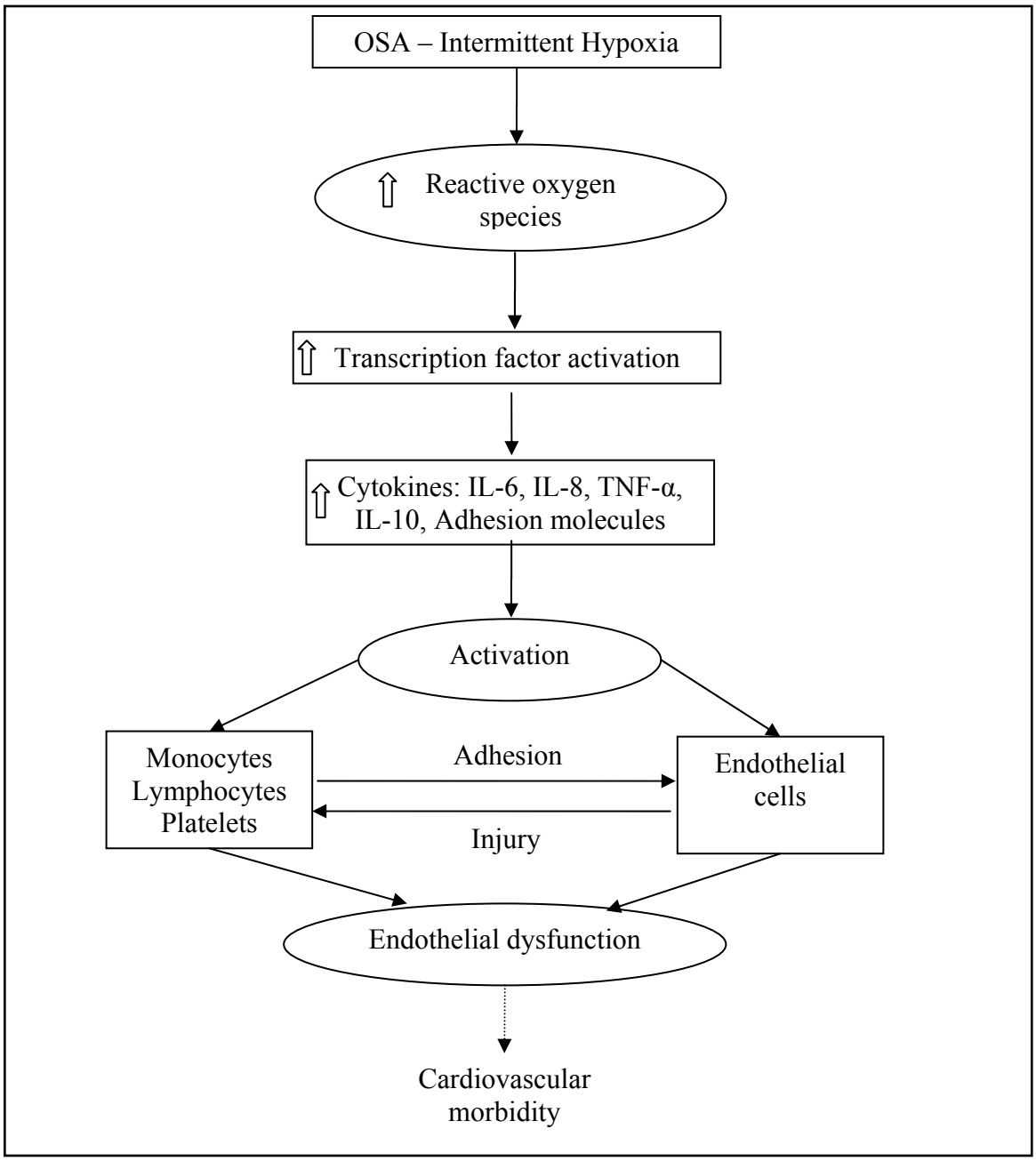
Recently it has been shown that inflammation may be a component in the progression of CVD (Lisman et al. 2002, Ridker et al. 2003). Furthermore adhesion of circulating leukocytes to endothelial cells is involved in initiation of atherosclerosis. The combination of hypoxia (Hartmann et al. 2000) and sleep deprivation (Vgontzas et al. 1999, Vgontzas et al. 1997) which is characteristic of OSA may lead to increased levels

of inflammatory markers. Hypoxia could also lead to the production of adhesion molecules. Since levels of adhesion molecules have be shown to be greater in patients with OSA (Chin et al. 2000, Ohga et al. 1999, Ohga et al. 2003, El-Solh et al. 2002), it is possible that OSA could increase cardiovascular morbidity through increased systemic inflammation.

OSA could cause an increase in coagulability. For example, an increase in platelet aggregability is evident in patients with OSA (Sanner et al. 2000) and treatment of OSA by CPAP therapy reduces platelet aggregability (Bokinsky et al. 1995, Eisensehr et al. 1998, Sanner et al. 2000). Increases in nocturnal and daytime levels of fibrinogen (Wessendorf et al. 2000, Chin et al. 1996) and blood viscosity (Nobili et al. 2000) are also likely to increase the likelihood of clot formation and atherosclerosis in patients with OSA.

In another, more integrated model, all of the above mechanisms could act in synergy with the production of ROS as the central step that could lead to endothelial dysfunction and, ultimately, adverse cardiovascular consequences (Refer Figure 1 – modified from (Lavie 2005)).

Figure 1. Proposed mechanisms for endothelial dysfunction (Lavie 2005)



Key: **TNF-α**: tumour necrosis factor alpha; **IL**: interleukin; ↑: leads to an increase in

Theoretically, repeated apnoea-related hypoxic events in OSA, cause hypoxia/reperfusion injury, which initiates oxidative stress (Lavie 2005). Specifically, the episodic hypoxia in OSA leads to increased production of superoxide ion and other ROS through various enzymatic pathways. Indirect proof of this is seen through studies which show increased production of ROS in patients with OSA (Dyugovskaya et al. 2002, Findley et al. 1988,

McKeon et al. 1990, Schulz et al. 2000). An increase in ROS production is likely to activate redox-sensitive transcription factors such as nuclear factor kappa beta (NFκβ), hypoxia inducible factor-1 and 'AP-1' (Piacentini & Karliner 1999). For example, in vitro studies have shown that hypoxic conditions activate NFκβ in cardiomyocytes (Kacimi et al. 1997). Other stimuli associated with oxidative stress such as cytokines, UV radiation and H_2O_2, have also been shown to induce NFκβ (Toledano & Leonard 1991, Peng et al. 1995, Helenius et al. 1996). These transcription factors could up-regulate the production of some common inflammatory mediators including tumour necrosis factor alpha (TNF-α) and Interleukin (IL) -6 (Chin et al. 2000, Entzian et al. 1996, Ohga et al. 1999, Vgontzas et al. 1997, Ryan et al. 2006) which can then in turn activate leukocytes, lymphocytes, granulocytes, monocytes and endothelial cells, as well as adhesion molecules (Dyugovskaya et al. 2002). The activation of endothelial cells, circulating leukocytes, and platelets facilitates interactions between circulating cells and endothelial cells lining the vasculature, further amplifying the inflammatory response. Increased adhesion between activated leukocytes, platelets and endothelial cells could result in endothelial cell injury. This injury to endothelial cells then leads to endothelial dysfunction, which is proposed to be the 'first step in atherosclerosis' (Lavie 2005).

2.4.4.2 Results of studies

Manifestations of CVD morbidity and mortality such as myocardial infarction (MI), angina, heart failure, stroke and cardiac arrhythmias have been presented in several cross-sectional and case control studies. Thus, for the most part, only indirect evidence is available to implicate OSA in the aetiology and progression of CVD. Until recently, no large scale epidemiologic longitudinal studies have included measures of OSA. This may be due to the considerable expense involved in establishing the diagnosis of OSA in large

population samples. Patients with OSA also often have co-morbidities such as obesity, hypertension, and impaired glucose tolerance. Thus, the independent effect of OSA on cardiovascular risk in these patients may be obscured. Association studies of OSA with CVD have assessed the impact of OSA on particular manifestations of CVD as well as the broad disease category by itself. The following section will review some of these studies in detail.

Case control studies of patients assessed for OSA after MI support an association between the two conditions. One case control study showed relative risk in the order of 23.3 for MI when patients with the higher AHI were compared to those with lower AHI after adjusting for age, BMI, hypertension and smoking habits (Hung et al. 1990). Another hospital based study compared recently diagnosed victims of MI and healthy controls (Saito et al. 1991). There was an association between AHI and MI and cardiac arrhythmias were also observed in many of the apnoeic patients. Nonetheless, this study did not adjust for age, BMI or other co-morbidities (Saito et al. 1991). In contrast, a prospective clinical trial of patients with a history of MI failed to show an association between RDI and MI (Koehler & Schafer 1996). Several studies have also reported on associations between coronary artery disease (CAD) and OSA. Two case control studies carried out by the same group in men (Mooe et al. 1996a) and women (Mooe et al. 1996b) on angiographically verified CAD reported significant associations between OSA and CAD after adjusting for age, hypertension, BMI, diabetes and smoking.

An association with an Odds Ratio of 3.0 was found between OSA and CAD in a Swedish study of 62 patients that adjusted for various disease co-morbidities. In a multiple logistic regression model, OSA still remained independently associated with CAD (Peker et al. 1999). The finding of an association after adjustment for hypertension

implies that hypertension is not the only mechanism by which the risk of cardiovascular morbidity is increased.

Association between OSA and stroke have been shown in case control studies of 59 patients and 19 age and gender matched controls (Bassetti et al. 1996) and a study of 128 patients with transient ischaemic attacks or stroke and 25 controls matched for age, gender and BMI (Bassetti & Aldrich 1999). A longitudinal study over four years of 1189 patients found an association between OSA and stroke. On the other hand, the increased odds ratio in this study was no longer significant after adjusting for age, gender and BMI (Arzt et al. 2005). An association of stroke with OSA has also been found in a large scale study of 6424 patients. Of the 1023 participants who self-reported at least one CVD symptoms, an odds ratio of 1.58 was found for having stroke in those with OSA compared to those without OSA. This study also found associations with other CVD disease manifestations and mild to moderate OSA (Shahar et al. 2001). Similarly, there are three cohort studies using a broader disease classification of CVD and its manifestations (Peker et al. 2002, Doherty et al. 2005, Marin et al. 2005).

A well controlled seven year Swedish Cohort study of 60 male OSA patients and 122 non-OSA male controls (defined by AHI <5), found that the incidence of at least one CVD event or symptom was 36.6% in the OSA group compared to 6.6 % in the non-OSA controls (Peker et al. 2002). All of the patients involved in this cohort were free from CVD and hypertension at baseline. In addition, BMI, age, baseline blood pressure, and smoking habits were matched between the two groups. Hypertension, angina pectoris, stroke, MI, cardiac arrhythmias, congestive heart failure, and cardiovascular death were all considered as a CVD event. Another cohort study with an average of 7.5 yrs follow up investigated the effects of CPAP on compliant and non-compliant OSAS patients who

were matched for BMI (Doherty et al. 2005). All of the included patients had an AHI >15 as well as daytime sleep symptoms. Total CVD events (defined as deaths and CVD symptoms) were more common in the group of patients who were intolerant of CPAP compared to the CPAP treated group (31% versus 18%). Interestingly, while there was a trend, no significant differences between the groups were found in the development of new CVD symptoms. Thus the difference in total CVD events is probably due to the greater incidence of death in the non-compliant group. Patients non-compliant with CPAP therapy may have been non-compliant with other treatment as well.

The third cohort study consisted of five groups of patients. The study investigated fatal and non-fatal CVD events over an average follow up period of 10.1 years (Marin et al. 2005). The five groups were those with untreated severe OSA, untreated patients with mild-moderate OSA, simple snorers, patients treated with CPAP, and healthy participants. The incidence of fatal cardiovascular events and non-fatal cardiovascular events were 1·06 (per 100 person-years) and 2·13 (per 100 person-years); 0·55, and 0·89; 0·34 and 0·58; 0·35 and 0·64; and 0·3 and 0·45 respectively. These groups were matched for BMI and age but not for hypertension or diabetes. A large scale Israeli study that adjusted for BMI, presented mortality rate for different age groups comprising of 14,589 male patients aged over 20 yrs of age (Lavie et al. 2005). The group of patients presented for an OSA diagnosis and were then followed up for an average of 4.7 yrs. At the end of the follow up period, any deaths of patients in this group, as recorded in the National Registry of Deaths, were noted but the causes of death were not presented. Altogether, 372 deaths were recorded with a mortality rate was 5.55/1,000 patient yrs, increasing with OSA severity. Cox proportional analysis revealed that RDI and BMI significantly influenced mortality. Another finding was that males aged over 50 years of age having an increased mortality. The lack of information about possible confounders and treatment

effects should be taken into consideration in the interpretation of these results. Despite these limitations, taken together, the above studies suggest that OSA is associated with CVD morbidity and mortality.

2.5 Risk factors and predictors

2.5.1 Overview

A risk factor is defined as an environmental exposure, an aspect of behaviour, or an inherent characteristic which is associated with a disease (Burt 2005). The association may or may not be causal although, increasingly, the use of the term implies causality. There are a number of risk factors for OSA (see Table 4). These include craniofacial and upper airway abnormalities by themselves and syndromes that may result in these abnormalities, and increased body weight or obesity. Genetics and family aggregation may also be predictive for OSA (AASMT 1999). Other factors that have an association with increased probability of OSA include smoking, menopause, age, gender and race. Other factors that increase the probability of OSA include alcohol ingestion before bedtime and nasal congestion and rhinitis.

Table 4. Risk factors that enhance the probability of OSA
Obesity
Alcohol ingestion before bedtime
Respiratory allergies and nasal congestion
Male gender
Family aggregation
Syndromes
Marfan disease
Pierre-Robin syndrome
Treacher Collins syndrome
Hypothyroidism
Acromegaly
Down syndrome
Anatomical factors
Obesity, large neck circumference, or both
Retrognathia
Dental overbite
Dental malocclusion
Dislocation of temporomandibular joint during mouth opening
Macroglossia
Oedema, erythema, or both of the uvula
Elongated and low-hanging soft palate
Narrow mandible
Narrow maxilla
Narrow retroglossal area
Tonsillar hypertrophy
Adenoid hypertrophy
Nasal septal deviation
Nasal obstruction from any cause

2.5.2 Obesity

Many cross-sectional clinic-based (Davies et al. 1992, Davies & Stradling 1990, Grunstein et al. 1993, Hoffstein & Mateika 1992, Katz et al. 1990) and population-based studies (Bearpark et al. 1993, Jennum et al. 1992, Jennum & Sjol 1993, Stradling & Crosby 1991, Young et al. 1993) using various indices of OSA have found significant associations between OSA and measures of excess body weight. Almost all of these associations have been positive and there is wide agreement that obesity is a risk factor for OSA (AASMT 1999).

The ways by which excess body weight may affect breathing are as follows. Firstly, it may result in alterations in upper airway structure and function such as a change in geometry and increased collapsibility. In this situation the location of the excess fat deposits in obesity may be important. For example, cross-sectional studies have shown that neck morphology (Bearpark et al. 1993, Davies et al. 1992, Hoffstein & Mateika 1992, Olson et al. 1995a, Stradling & Crosby 1991) is associated with OSA. Secondly, it may disturb the relationship between respiratory drive and load compensation. Thirdly, in patients with OSA, obesity-related reductions in functional residual capacity have known to occur. This characteristic and the increased whole-body oxygen demand may also affect breathing (Strobel & Rosen 1996).

There is evidence that excess weight can be causal for OSA. For example, longitudinal monitoring of a subset of the subjects from the Wisconsin Sleep Study showed that a 10% increase in weight lead to a six fold increase in development of OSA in patients who were initially free of OSA. Loss of weight may reduce OSA severity and symptoms. Small scale intervention studies have assessed OSA before and after either surgical

(Charuzi et al. 1985, Harman et al. 1982, Peiser et al. 1984, Rajala et al. 1991) or dietary (Kansanen et al. 1998, Kiselak et al. 1993, Nahmias et al. 1993, Noseda et al. 1996, Rajala et al. 1991, Rubinstein et al. 1988) weight loss. Nevertheless, most of these were of short duration. In a review it was concluded that there was greater relative weight loss, in terms of mean percent reduction from baseline weight, in the studies of surgical weight loss than in those of dietary loss (Young et al. 2002a). Accordingly, the surgical studies tended to show a greater mean reduction in AHI. The only randomized study reported in the literature monitored a group of 15 obese men and women who received dietary weight loss instruction against a control group of 8 obese men and women who did not receive weight loss instruction (Smith et al. 1985). In this study of less than 9 months duration, the treatment group experienced a mean weight loss of 9% and a significant mean reduction of 47% in the frequency of apnoeas (from 55 to 29 events per hour). There was a slight increase in mean weight in the control group with a non-significant increase in apnoea frequency.

2.5.3 Smoking

Some cross-sectional studies have found an association between smoking and OSA (Jennum et al. 1992, Jennum & Sjol 1993, Schmidt-Nowara et al. 1990, Stradling & Crosby 1991). Although a causal role for smoking in OSA is biologically plausible, it is not yet firmly established as a risk factor. The only epidemiologic study to focus on smoking (Wetter et al. 1994), showed that current smokers were three times (95% CI, 1.4 to 6.4) more likely to have OSA than never-smokers. In the same study, former smokers were not more likely to have OSA than never-smokers. Hence, if smoking does contribute to increased prevalence of OSA it is likely that the effect of smoking is reversible with smoking cessation. Conflicting results from the Sleep Heart Health Study

(Newman et al. 2001) found an inverse association between current smoking and OSA after adjusting for several factors, including age and BMI. Current smokers had significantly fewer respiratory disturbance events as assessed by in-home PSG compared to non smokers. The explanation put forward by the authors in this case was that the inverse association might indicate that persons with severe OSA may have been more prone to quit smoking.

3. INFLAMMATION

3.1 Process

3.1.1 Overview

Inflammation is generally a protective response that occurs as a response to an insult. The ultimate outcome of inflammation should be to rid the body of the cause of an injury and then to repair the consequences (Mitchell & Cotran 2003). The protective and healing processes are interwoven to dilute, destroy or otherwise neutralize or 'wall off' the cause of the insult. Then the process of healing of the damaged tissue is initiated, either by regeneration of native parenchymal cells or by filling the defect with scar tissue or, in some cases, both (Mitchell & Cotran 2003). While inflammation along with repair is a protective response, it may also be potentially harmful and may contribute to the pathogenesis of many acute and chronic diseases such as tuberculosis, rheumatoid arthritis, inflammatory bowel disease (ulcerative colitis and Crohn's disease) and periodontitis.

The inflammatory response is made up of a complex set of highly orchestrated events involving many different cells and molecules. Essentially, an initial inflammatory stimulus triggers the release of chemical mediators from plasma or cells local to the site of the injury. The stimulus can be (Mitchell & Cotran 2003):

- infective agents
- hypoxia
- chemical and drugs (environmental, self administered, therapeutic)
- physical (mechanical, thermal and electrical injury)
- nutritional abnormalities
- abnormal immunological responses

The chemical mediators act alone, together or in sequence to amplify the initial inflammatory response (Roitt 2001). They also then modulate the initial inflammatory response as well as the subsequent vascular and cellular responses. The inflammatory response is terminated when the injurious stimulus is removed and the chemical/inflammatory mediators have been dissipated or inhibited.

Inflammation is divided into two phases: acute and chronic (Mitchell & Cotran 2003). Acute inflammation is of short duration typically lasting from a few minutes to a few days. The main characteristics of acute inflammation are the exudation of fluid and plasma proteins (oedema) and the emigration of leukocytes, predominantly neutrophils. Chronic inflammation is of longer duration and is associated histologically with the presence of lymphocytes and macrophages, the proliferation of blood vessels, fibrosis and tissue necrosis. Overlap of these phases can occur (Mitchell & Cotran 2003).

3.1.2 Acute inflammation

A critical function of acute inflammation is the delivery of leukocytes to the site of injury. This is achieved by increased local blood flow, structural changes in the microvasculature to permit leukocyte emigration, and their accumulation in the focus of the injury (Cotran & Mayadas-Norton 1998). Leukocytes ingest offending agents, kill bacteria and other microbes, degrade necrotic tissue and foreign antigens. Leukocytes may also prolong inflammation and induce tissue damage by releasing enzymes, chemical mediators and toxic oxygen radicals. Acute inflammation has the classical cardinal features of heat (calor), redness (rubor), swelling (tumor), pain (dolor) and loss of function (functiolaesa) which occurs much later. These classical features are the result of vascular and cellular changes in acute inflammation (Mitchell & Cotran 2003).

The vascular changes involve vasodilation and increased vascular permeability with structural changes that allow plasma proteins to leave the circulation (Cotran & Mayadas-Norton 1998). Cellular events involve the migration of leukocytes from the circulation and their accumulation in the area of the injury (Imhof & Dunon 1995). The type of leukocyte recruited to the area depends on the nature of the injury as well as the age of the inflammatory process. Neutrophils dominate for the first day in acute inflammation and are replaced by monocytes. The events that are involved in the recruitment of leukocytes at an inflammatory site involve:

- endothelial activation,
- increased expression of selectins and selectin ligands

- leukocyte rolling, facilitated by relatively loose selectin binding to carbohydrate ligands
- firm adhesion, facilitated by increase in integrin affinity for endothelial ligands
- transmigration between endothelial cells using platelet endothelial cell adhesion molecule-1

After leaving the blood vessels, the leukocytes migrate toward the site of the injury along a chemical gradient in a process called chemotaxis (Imhof & Dunon 1995). Substances that can be chemotactic include soluble bacterial products, components of the complement system, products of the lipoxygenase pathway and cytokines. Once the leukocytes have been recruited to the site of injury, phagocytosis and degranulation enable the recognition, engulfment, degradation and killing of noxious stimuli such as bacteria and their products (Roitt 2001).

3.1.3 Chemical mediators of inflammation

Many chemical mediators direct the events in inflammation (Roitt 2001, Mitchell & Cotran 2003). These can circulate in the plasma after being produced by the liver or can be produced locally by a variety of sources including mast cells, platelets, lymphocytes and leukocytes. They can be divided into exogenous and endogenous mediators. Bacterial products and toxins can act as exogenous mediators of inflammation. Notable among these is endotoxin, or lipopolysaccharide of Gram-negative bacteria. For example, endotoxin can trigger complement activation, resulting in the formation of anaphylatoxins C3a and C5a which cause vasodilation and increase vascular permeability. Endotoxin also activates Hageman factor, which in turn leads to activation of both the coagulation and fibrinolytic pathways. Endogenous mediators of inflammation are produced from within the (innate and adaptive) immune system itself, as well as other systems. There is considerable functional overlap and redundancy of inflammatory mediators. The mediators are (Roitt 2001):

- vasoactive amines (histamine, serotonin)
- neuropeptides (Substance P)
- plasma proteases (belonging to the kinin, clotting, fibrinolytic and complement systems)
- arachidonic acid metabolites (prostaglandins, leukotrienes and lipoxins)
- cytokines (TNF- α, IL-1, IL-2, IL-4, IL-6 and interferons)
- Platelet Activating Factor
- nitric acid and oxygen derived free radicals

3.1.4 Chronic inflammation

Chronic inflammation is of prolonged duration with the processes of active inflammation, tissue destruction and attempts at repair proceeding simultaneously. Chronic inflammation may follow acute inflammation, especially when acute inflammation cannot be resolved due to persistence of the stimulus/injury or due to interference in the normal process of healing. Some forms of injury may produce a chronic inflammatory response from the outset without acute inflammation. Although chronic inflammation begins as a low-grade, slow, asymptomatic response, the overall damage arising from the inability to resolve inflammation may result in substantial injury (Mitchell & Cotran 2003). Chronic inflammation is often associated with irreversible destruction of normal parenchyma. Fibrous connective tissue then fills the resultant defects. Chronic inflammation can arise from viral infections. Persistent microbial infections from mycobacteria, Treponema Pallidum and fungi could also evoke an immune response called delayed hypersensitivity which could lead to chronic infection. Prolonged exposure to toxic agents can also set up a chronic inflammation. Autoimmune diseases result from an immune response to self-antigens. This constant renewal of self antigens ensures the chronicity of the process.

The characteristics of chronic inflammation are different to those of acute inflammation. Acute inflammation is distinguished by vascular changes, oedema and a largely neutrophilic infiltrate. Chronic inflammation is characterized by infiltration with a higher proportion of mononuclear cells, including macrophages, lymphocytes and plasma cells than in acute inflammation; tissue destruction, largely directed by the inflammatory cells; and repair, involving new vessel proliferation (angiogenesis) and fibrosis (Majno 1998).

The increased proportion of macrophages and lymphocytes is thought to be the mainstay of chronic inflammation. These macrophages in chronic inflammation are believed to be 'activated' in a process that results in increased cell size, increased content of lysosomal enzymes, and a greater ability to kill ingested organisms (Adams 1989). Activation of macrophages is thought to be due to cytokines secreted by T lymphocytes, bacterial products, various mediators produced during acute inflammation, and extracellular matrix proteins such as fibronectin. After activation the macrophages themselves secrete more biologically active products including acid and neutral proteases, complement components and coagulation factors, ROS and Nitric Oxide (NO), arachidonic acid metabolites, and cytokines (Adams 1989).

Similarly lymphocytes are also 'activated'. This happens initially when an activated macrophage presents an antigen to a lymphocyte (Gulbins et al. 1995). Once activated, the lymphocytes can then produce a variety of inflammatory mediators including interferon-gamma, to further stimulate macrophages (Gulbins et al. 1995). Cytokines produced by activated macrophages then further activate the lymphocytes. This sets up a cycle with macrophages and lymphocytes stimulating one another until the antigen or injury is removed or, as in some chronic diseases, persistent.

3.2 Markers

The systemic effect of inflammation has been termed an acute-phase reaction. Its most obvious effect is fever and systemic shock is its most severe consequence (Mitchell & Cotran 2003). Symptoms such as malaise, anorexia and increased somnolence are common. There are also other effects such as accelerated degradation of skeletal muscle proteins and hypotension noticed infrequently. Cellular changes are also known to occur

including: hepatic synthesis of a variety of proteins (e.g. complement and coagulation proteins); alterations in the number and/or proportions of white blood cells; and changes in the proportion and production of cytokines (Feghali & Wright 1997). The cytokines IL-1, IL-6 and TNF-α are key mediators of the acute phase reaction released by leukocytes and other inflammatory cells. Once these cytokines reach the brain via systemic circulation, they affect the thermoregulatory receptors of the hypothalamus. By binding with endothelial receptors on vessel walls or interacting with local microglial cells, cytokines activate the arachidonic acid pathway. Fever is then induced by Prostaglandin E2, one of the products of this pathway (Funk 2001).

Leukocytosis, which is an increase in the white blood cell count, is a feature common to inflammatory reactions, especially in response to bacterial infection. This increase is also thought to be due to the effect of IL-1 and TNF-α on the bone marrow. Inflammation leads to systemic changes in the serum level of other molecules and cells. For example the cytokine IL-6 stimulates the hepatic synthesis of several plasma proteins including fibrinogen (Fenghali & Wright 1997). Elevated fibrinogen levels cause erythrocytes to agglutinate more readily explaining why inflammation is associated with a higher erythrocyte sedimentation rate (ESR). Similarly, other cellular and molecular markers can be used to diagnose, predict and treat the inflammatory process and diseases that occur. Some examples of diseases with a chronic inflammatory basis are listed in Table 5. Some of these diseases have been classified as chronic inflammatory disease for a long time (Kasasbeh et al. 2006). On the other hand, the inflammatory basis to disease such as atherosclerosis (and the CVD that arise from it), has only been identified in the last 10 to 20 years (Kasasbeh et al. 2006, Lavie 2005). The association between these diseases and systemic markers has been shown through cross-sectional studies, prospective and intervention studies. The cellular and molecular markers identified in some common

chronic diseases are listed below (Table 5). These markers have been identified in cross-sectional, case-control and interventional studies. They have been measured using a variety of body fluids including peripheral blood, sputum, expired air condensate and gases, urine and faeces.

Table 5. Some common markers identified in inflammatory diseases	
DISEASE	**MARKERS IDENTIFIED**
Rheumatoid arthritis	IL-1 (Braddock & Quinn 2004); TNF-α (O'Hara et al. 2006); VEGF (O'Hara et al. 2006); IL-6 (Cronstein 2007); CRP (Hilliquin 1995)
Inflammatory bowel disease	CRP, fibronectin, fibrinogen, prothrombin, TPA, MMPs, complement proteins (Vermeire et al. 2006); IL-1 (Braddock & Quinn 2004); MMP (Meijer et al. 2007)
Giant cell arteritis	CRP (Azhar et al. 2005); ESR (Schwedt et al. 2006)
Systemic lupus erythematosus	ESR (Almehed et al. 2007); B-lymphocytes (O'Hara et al. 2006); VCAM and ICAM (Zaccagni et al. 2004); monocytes (Steinbach et al. 2000)
Chronic obstructive pulmonary disease	NO, IL-8, IL-6, CRP, TNF-α, LTB4, MMPs, neutrophils, macrophages, lymphocytes (Jones & Agusti 2006); IL-1 (Braddock & Quinn 2004)
Asthma	Substance P (O'Connor et al. 2004); NO (Ehrs et al. 2006); IL-6, TNF-α (Carpagnano et al. 2005); IL-8 (Hollander et al. 2007); eosinophils (Deykin 2006); leukotrienes (Sampson et al. 2003)
Atherosclerosis or cardiovascular disease	CRP, leukocyte count, fibrinogen, IL-1, IL-2, IL-6, ICAM-1, VCAM-1, ELAM, E-selectin, complement factors C3 and C4, IgE, IgG, IgA, IgM, MMP-2, MMP-9 (Lind 2003)

Key:
TNF-α: tumour necrosis factor alpha; **IL**: interleukin; **NO**: Nitric Oxide; **LTB4**: leukotriene B4; **CRP**: C-reactive protein; **MMPs**: matrix metalloproteinases; **VCAM-1**: vascular cellular adhesion molecule; **ELAM**: endothelial leukocyte adhesion molecule; **Ig**: immunoglobulin; **ESR**: erythrocyte sedimentation rate; **ICAM**: Intercellular adhesion molecule

3.3 Links between OSA and inflammation

3.3.1 Overview

Table 6. Inflammatory markers identified in obstructive sleep apnoea syndrome*	
Systemic inflammation	**Local inflammation**
↑ C-reactive protein	↑ IL-6
↑ IL-6	↑ 8-isopentane
↑ TNF-α	↑ neutrophils
↑ VEGF	↑ $CD4^+$ T cells
↑ EPO	↑ $CD4^+$ T cells
↑↓ Adiponectin	
↑ Reactive oxygen species	
↓ Nitric oxide	
VEGF, Vascular endothelial growth factor; EPO, erythropoietin; ↓, decrease in; ↑, increase in.	

*Modified from Bergeron et al. (2005)

Systemic and airway inflammation may be the cause of neurocognitive sequelae, cardiovascular complications and metabolic syndrome (Phillips & Somers 2002, Vgontzas et al. 2005) associated with OSA. This underlying inflammation has been attributed to upper airway mechanical tissue injury and systemic hypoxemia. Intermittent hypoxia occurring in OSA could stimulate transcription factors such as NFκβ and hypoxia inducible factor-1, and increase production of cytokines (Semenza 2001). Another adaptive response by the body to hypoxia in OSA is to increase the plasma levels of vascular endothelial growth factor and erythropoietin by stimulating erythrocyte production and neovascularization. The intermittent nature of nocturnal hypoxia in OSA may also predispose patients to produce ROS. These ROS are the cause of ischemia-reperfusion injury and are associated with activation of inflammatory cells in OSA. For

example, increased monocyte adhesion molecule expression and oxidative metabolism has been shown in patients with OSA (Dyugovskaya et al. 2002).

Systemic inflammation in OSAS is characterized by increased plasma levels of inflammatory markers such as TNF-α , IL-6, C-reactive protein (CRP), IL-1b, ROS and adhesion molecules (Hatipoglu & Rubinstein 2003, Lavie 2005) (Table 6). The systemic inflammatory state seen in patients with OSA may be independent of obesity (Hatipoglu & Rubinstein 2003, Shamsuzzaman et al. 2002, Yokoe et al. 2003). Interestingly the activation of NFκβ seems to occur during severe rather than moderate hypoxia (Kacimi et al. 1997). Thus it is possible that the extent to which ROS activated transcription factors contribute to the increased inflammatory burden may not be uniform in all patients. This may partly explain the variation in the results of studies exploring the plasma levels of inflammatory markers. Many inflammatory molecules, especially cytokines, act in a flexible and complex network with significant overlap and redundancy between the functions of these molecules. Conclusions drawn from these studies about the effect of OSA on levels of inflammatory markers should be made with consideration of the complex regulation of these markers.

The confounding effects of obesity must be considered when examining the relationship of OSA to systemic inflammation as increased levels of inflammatory markers may simply reflect the effects of obesity rather than OSA. Adipose tissue produces pro-inflammatory cytokines such as TNF-α (Hotamisligil et al. 1995) and IL-6 (Mohamed-Ali et al. 1997) that upregulate the hepatic synthesis of acute-phase proteins (Castell et al. 1990). It is estimated that approximately 30% of circulating IL-6 is produced by adipose tissue (Mohamed-Ali et al. 1997). There is also evidence to indicate that visceral adipose tissue secretes more TNF-α and IL-6 than subcutaneous adipose tissue (Fried et al. 1998,

Tsigos et al. 1999). The serum levels of certain inflammatory markers such as IL-6 show diurnal variation (Vgontzas et al. 1999, Entzian et al. 1996) and age- related changes (Daynes et al. 1993). Furthermore, review of numerous studies has concluded that weight loss can lead to a reduction in CRP levels (Selvin et al. 2007). It is also pertinent that other medical conditions such as hypertension, diabetes mellitus and CVD which are independently associated with higher inflammatory markers, are also taken into account and adjustments made for them in the analysis of data. Conversely the effect of these conditions can be controlled by excluding subjects with these conditions in studies during recruitment.

The literature exploring the link between OSA and inflammation consists of case-control, cross-sectional and treatment studies. The aims of these studies have been to show either an association between increased inflammatory markers in OSA patients compared to a control group; to show an increase in OSA variables such as AHI and oxygen saturation levels matching a concomitant increase in inflammatory markers; or a decrease in inflammatory markers after treatment of OSA. There is inconsistency in the association found between the study markers and OSA in these case control and cross-sectional studies. This is likely to be due to differences in inclusion criteria, size of study groups, disease classification, time taken for treatment and adjustment for confounding factors. Recognizing these potential limitations, the following section is a detailed analysis of the available literature on OSA and markers of systemic inflammation.

3.3.2 Local inflammation

Local airway inflammation in OSAS has been assessed mainly in surgical specimens obtained from uvulopalatopharyngoplasty and tonsillectomy (see Table 6). A study

comparing the uvulas obtained by uvulopalatopharyngoplasty of 21 OSA patients and 5 healthy patients found extensive leukocyte infiltration in the samples of OSA patients (Sekosan et al. 1996). Interstitial oedema and the number of plasma cells in the lamina propria of the uvula were higher in patients with OSA than in the controls.

Another study showed similar results (Paulsen et al. 2002). In this study, biopsies from three patients with habitual snoring, nine patients with mild to severe OSA, and 43 cadavers were analysed. Scanning electron microscopy and immunohistochemical staining revealed significant diffuse infiltration of leukocytes, mainly T cells, inside the lamina propria of the patient group, which was not observed in the control group. A significant reduction in surface area of connective tissue papillae was also seen. The authors hypothesised that progressive structural changes in the mucosa caused by the trauma of snoring is a possible contributory factor to upper airway collapsibility.

The presence of nasal inflammation was confirmed in a study that analysed nasal lavage (Rubinstein 1995). The number of polymorphonuclear leukocytes (PMNs) and the concentrations of bradykinin and vasoactive intestinal peptide were quantified in nasal lavage fluid of eight non-smoking patients with OSA and six matched controls before and after sleep. The total number of cells, the percentage of PMNs, and bradykinin and vasoactive intestinal peptide concentrations were significantly higher in patients with OSA in comparison to the controls both before and after sleep. Morphometric analysis was done on tissue from seven non-snoring control subjects and eleven patients with OSA following palatal surgery (Boyd et al. 2004). Inflammatory cells, predominantly $CD4^+$ and activated $CD25^+$ T cells, were increased in the muscular layer of patients with OSA. Inflammation was also present in mucosa, but with a different pattern consisting

predominantly of $CD8^+$ (2.8 fold increase) and activated $CD25^+$ T cells (3.2 fold increase).

Another study investigated the influence of weight and OSA status on inflammatory and histologic features of the uvula (Series et al. 2004). The investigators proposed that the level of inflammatory markers is linked to obesity rather than to sleep-related breathing disorders. Tissue samples were resected during uvulopalatopharyngoplasty in 11 snorers without OSA, 11 subjects with OSA and of similar BMI and age, and 8 additional obese subjects with OSA and subsequently examined by immunohistochemistry and histologic staining techniques. T cell ($CD4^+$, $CD8^+$) and macrophage counts were higher in the more obese apnoeic subjects than in the other two groups. Interestingly in all patients, T cell counts correlated with BMI, but there was no relationship with the AHI. Local airway inflammation has also been assessed using inflammatory markers in exhaled breath (Depalo et al. 2008) and sputum samples (Depalo et al. 2008, Salerno et al. 2004). Exhaled NO and NO synthase were analysed using chemiluminescence and immunochemistry respectively within three groups of patients consisting of 18 obese patient with OSA, 15 obese patients without OSA and 10 healthy patients of average weight (Depalo et al. 2008). There was significantly increased NO in OSA and in obese patients than in healthy subjects. OSA and obese patients also showed a higher percentage of neutrophils and a lower percentage of macrophages in the induced sputum compared to healthy subjects. In addition, OSA and obese patients showed higher inducible NO synthase expression in neutrophils and in macrophages with respect to healthy subjects.

3.3.3 Inflammatory markers and systemic inflammation

Case control and intervention studies have shown a relationship between inflammation and OSA. Morning plasma levels of TNF-α, IL-1β, and IL-6 were measured in 12 sleep apnoeics, 11 narcoleptics, 8 idiopathic hypersomniacs, and 10 normal controls. Levels of TNF-α and IL-6 were significantly elevated in sleep apnoeics compared to those in normal controls while IL-1beta concentrations were not different between sleep disorder patients and controls (Vgontzas et al. 1997). The primary factor influencing TNF-α value was the degree of nocturnal sleep disturbance, whereas the primary determinant for IL-6 levels was the BMI. In a follow up study, obese middle-aged men with sleep apnoea were first compared with obese non-apnoeic age and BMI matched men and age-matched lean men (Vgontzas et al. 2000). All subjects were monitored using PSG. The plasma concentration of IL-6 and TNF-α were higher in obese men with OSA compared to obese men without OSA. They concluded that OSA is associated with elevated plasma concentrations of IL-6 and TNF-α independently of obesity. In another case control study higher concentrations of IL-6 were found in OSA patients than obese patients, who in turn had a higher level than healthy patients (Carpagnano et al. 2002). Levels of 8-isoprostane levels were found to be higher in OSA patients than in obese subjects and healthy subjects. A positive correlation between these two markers and neck circumference and AHI was also found. These findings suggest that inflammation and oxidative stress are characteristic in the airways of OSA patients but not always in obese subjects, and that their levels depend on the severity of the OSA.

A case control study was conducted with 22 newly diagnosed patients (18 males and 4 females) who were otherwise healthy (Shamsuzzaman et al. 2002). The CRP levels in these patients were compared to that obtained from 20 control subjects without OSA (15

males and 5 females) who were matched for age and BMI. Plasma CRP levels were significantly higher in patients with OSA than in controls. Using a multivariate analysis, CRP levels were independently associated with OSA severity and severity of OSA was proportional to the CRP level. Similarly, in a university based cross-sectional sample, CRP was associated with OSA even after adjusting for obesity (Punjabi & Beamer 2007). This sample was also free of hypertension, diabetes and CVD.

While CRP, IL-6 and TNF-α represent the common serum markers of inflammation, there has also been studies of other inflammatory markers. Association has been shown between OSA and adhesion molecules such as intercellular adhesion molecule (ICAM) -1 and vascular cellular adhesion molecule (VCAM) -1 (El-Solh et al. 2002, Ohga et al. 1999). Exhaled pentane, an indicator of oxidative stress, and NO were measured as markers of inflammation in 20 patients with OSA and 8 healthy control subjects (Olopade et al. 1997). It was found that exhaled nasal pentane and NO were increased after sleep only in patients with OSA. By contrast, there were no significant differences in exhaled nasal and oral pentane, and nasal NO levels before and after sleep in control subjects. An association was also shown between OSA and serum levels of neoptrin, a marker of macrophage activity, in a study of 55 men free of medical co-morbities, after adjusting for BMI and body fat measures (Punjabi et al. 2007a).

While there is some evidence that the severity of OSA will theoretically result in a greater inflammatory burden, it is uncertain if there is any difference in resultant systemic inflammation between OSA and its related syndrome OSAHS that manifest as EDS. A study of 50 consecutive OSA patients without or with EDS (hence OSAHS), as well as 20 controls showed that although patients with OSAS have elevated levels of ICAM-1, IL-6, and TNF-α, there was no statistically significant difference in any of the

inflammatory mediators between patients with EDS and without EDS (Bravo Mde et al. 2007). In contrast, plasma levels of IL-6 appeared to correlate with daytime sleepiness in OSAS patients and in healthy individuals after sleep loss (Vgontzas et al. 1999).

These studies suggest a relationship between OSA and some common inflammatory markers. While obesity and other co-morbidities may contribute to the general inflammatory burden, OSA also seems to independently contribute to systemic inflammation. It is difficult to predict the contribution of apnoea, obesity and other co-morbidities to increased inflammation and whether their relative contribution is the same in extreme conditions, for example, very high BMI or very high AHI. In addition, it is unknown as to whether there is indeed a linear relationship, a plateau effect or a threshold in the initiation of inflammation. Controlled studies are needed to elucidate if the increased inflammatory burden in OSA patients is due to hypoxia or excessive sleep disturbance.

3.3.4 Intervention studies

Most intervention studies have involved treating OSA patients, either with CPAP or surgery, and analysis of the pre and post-treatment levels of inflammatory markers. It has been proposed that the decrease in inflammatory markers after the intervention illustrates a link between OSA and systemic inflammation (Hatipoglu & Rubinstein 2003, Lavie 2005). For example, the effect of one month of CPAP on inflammatory markers was compared between 30 patients with moderate and severe OSAHS and 14 obese control subjects (Yokoe et al. 2003). The initial levels of CRP and IL-6 were significantly higher in patients with OSAHS than in obese control subjects. IL-6 production by monocytes was higher in patients with OSAHS than in obese control

subjects. CPAP significantly decreased levels of CRP and IL-6, plus spontaneous IL-6 production by monocytes. In patients with OSAHS, multiple regression analysis revealed that factors influencing levels of CRP were severity of OSAHS and BMI and those influencing levels of IL-6 were BMI and nocturnal hypoxia. The effects on various markers of Etanercept®, a medication that neutralizes TNF-α and is approved by the Food and Drug Administration for the treatment of rheumatoid arthritis, was tested in eight obese males with OSA (Vongtzas et al.2004). These patients participated in a pilot, placebo-controlled, double-blind study during which PSG, fasting blood glucose and plasma levels of IL-6, CRP, insulin, and adiponectin were obtained. The medication decreased sleepiness compared with placebo. A decrease in AHI relative to placebo was also observed. IL-6 levels were significantly decreased after Etanercept® administration compared with placebo. However, no differences were observed in the levels of fasting blood glucose and plasma CRP, insulin, and adiponectin when Etanercept® was compared to the placebo. The authors suggested that this may indicate the significant role of inflammatory cytokines to the pathogenesis of OSA or sleepiness. In a study of OSAHS patients treated with CPAP, non treated OSAHS patients and controls, CPAP decreased apnoea, oxygen desaturation, and circulating ICAM-1 and IL-8 levels in OSAHS patients (Ohga et al. 2003). The circulating levels of ICAM-1, IL-8, and monocytes chemotactic protein-1 in untreated OSAHS patients were significantly higher than those in the controls.

The effect of CPAP on visceral fat accumulation and the level of leptin, a hormone involved in the control of body weight has been studied (Chin et al.1999). CPAP reduced Leptin levels in a few days and the amount of visceral fat after six months of therapy. The reduction of visceral fat during CPAP therapy occurred with and without weight loss. In a study analysing the effect of surgical treatment (Kataoka et al. 2004), 27

patients diagnosed with OSAHS, seven non-apnoeic patients with chronic tonsillitis (non-OSAHS patients), and four healthy subjects were recruited. Using high-sensitivity Enzyme-Linked ImmunoSorbent Assay, the plasma TNF-α level in patients with OSAHS were significantly elevated in comparison to normal healthy subjects. In contrast, there was no difference between the patients with non-OSAHS and healthy subjects. Surgical treatment to enlarge the upper airway in patients with OSAHS significantly decreased TNF-α levels. This study also suggests a possible role for surgical treatment of patients with OSAHS in reducing systemic inflammation.

4. PERIODONTITIS

4.1 Description

4.1.1 Definition

Periodontal disease encompasses both gingivitis and periodontitis. Periodontitis is one of the most common chronic diseases in the world. Periodontitis is a disease of microbial aetiology that triggers an inflammatory response in the supporting tissues of the teeth. This can result in destruction of the supporting tissues in susceptible persons that is clinically evident as the progressive loss of periodontal attachment, pocket formation, loss of alveolar bone and, ultimately, tooth loss. Thus the aim of periodontal therapy is to prevent the destruction of the supporting periodontal tissues, thereby preserving the natural dentition. Periodontitis is the result of complex interrelationships between infectious agents and host factors. Current evidence indicates that most destruction of the periodontium is host mediated, driven by a bacterial challenge from the plaque biofilm

(Sanz et al. 2005). Moreover environmental, acquired and genetic risk factors can modify the expression of disease and may affect the onset or progression of periodontitis.

While periodontal disease encompasses both gingivitis and periodontitis as tangible clinical forms, the two entities may in fact be stages in a continuum of the same inflammatory disease (Kinane et al. 2005). The progression of gingivitis to periodontitis has been shown in animal models (Lindhe et al. 1975). Nevertheless, not all patients with gingivitis go on to develop periodontitis. The weight of evidence indicates that prevention of gingival inflammation prevents periodontitis (Kinane 2001). Since the primary aetiology of both gingivitis and periodontitis is the microbial biofilm, the most effective way to prevent both conditions is personal and professional disruption of the plaque biofilm.

4.1.2 Clinical and histological features

The features of healthy gingiva are stated as: pink colour and firm consistency; gingival tissues that do not bleed on gentle probing; interdental gingival tissues that fill the space below the contact areas between the teeth (Kinane 2001). Healthy gingiva often exhibits a stippled appearance and a knife-edge margin between the soft tissue and the tooth (Kinane 2001). The features mentioned above are generally not present in gingivitis and periodontitis where the gingivae appear red and inflamed with a soft consistency (Kinane 2001). Due to the inflammation present, the gingival tissues bleed on probing or in response to touch. Formation of pathological pockets between the tooth and the gingival tissues can occur without loss of connective tissue attachment anchoring the tooth in gingivitis, or with loss of connective tissue attachment in periodontitis. In the case of periodontitis, other clinical features include loss of alveolar bone supporting the tooth,

mobility and drifting of teeth, loss of interdental papilla and gingival recession (Kinane 2001).

In theory, the normal gingiva is free from histological evidence of inflammation (Page & Schroeder 1976), but this ideal condition is very rarely seen histologically. This is because most human gingival tissues are slightly inflamed due to the constant presence of microbial plaque, no matter how clinically healthy their appearance. Even in the very 'healthy' state, the gingiva has a leukocyte infiltrate that is predominantly comprised of neutrophils or polymorphonuclear leukocytes (Payne et al. 1975, Seymour et al. 1983). This neutrophil defence usually operates well. Oral hygiene and the host response is usually enough to reduce the bacterial load and is important in preventing the gingivitis lesion from becoming established. If, however, there is an overload of microbial plaque, then the neutrophils and the epithelial barrier will not be sufficient to control the infection. The result is that the gingival tissue becomes very inflamed and this is clinically seen as gingivitis (Loe at al. 1965, Seymour et al. 1983). Most individuals develop clinical signs of gingivitis after 10–20 days of plaque accumulation (Van der Weijden et al. 1994). Gingivitis is reversible if the plaque is removed by effective plaque control measures (Loe et al. 1965).

While the clinical changes in this early stage can be subtle, histologically there are distinct changes including the classical signs of inflammation. These changes include opening of the capillary beds that would otherwise be closed. Tissue swelling can be seen due to the influx of serum transudate and proteins from the blood, as well as inflammatory cells such as neutrophils, macrophages and lymphocytes into the tissue. Histologically, not only does the early gingivitis lesion appear to have a heavy inflammatory cell infiltration, but plasma cells are also present in low numbers (Seymour

et al. 1983, Brecx et al. 1987, Brecx et al. 1988). The clinically established gingivitis lesion has no bone loss or apical migration of epithelium along the root. In histological sections plasma cell density, that is, the density of cells that produce antibodies, is only 10–30% of the total leukocyte infiltration (Kinane 2001).

Periodontitis is histopathologically similar to chronic (established) gingivitis and there is a greater than 50% density of plasma cells (Berglundh & Donati 2005). Whether or not there is progression from gingivitis to periodontitis depends on the individual, and if it does, requires varying amounts of time. At least 6 months may be needed for the lesion of gingivitis to change to periodontitis (Brecx et al. 1988). A landmark paper defined four histopathological stages of periodontal inflammatory changes: *the initial, early gingivitis, established gingiviti and advanced periodontitis lesion* (Page & Schroeder 1976). It is important to note that the evidence available at that time largely consisted of animal biopsies and some human adolescent biopsies.

Their description, based on this material, is now considered not to be fully applicable in the normal adult situation (Kinane & Lindhe 1997) because it is very difficult to find healthy gingival tissues that are completely free of histological signs of inflammation. As mentioned before, some plaque accumulation occurs in even the most clean and healthy dentitions of people with clinically healthy gingiva. Hence, modifications of the initial, early, established gingivitis and periodontitis have been described (Kinane & Lindhe 1997) based on the earlier model (Page & Schroeder 1976) (Summarized in Table 7).

Table 7. Clinical and histological features of periodontal disease		
Condition	**Clinical features**	**Histological features**
Pristine gingiva	Clinically perfect	- histologically perfect
Normal healthy gingiva	Clinically normal	- lesion is localized to the region of the gingival sulcus - tissues affected include a portion of the junctional epithelium (JE) and the most coronal part of the connective tissue - dilation of the arterioles, capillaries and venules of the dentogingival plexus - increase in permeability of the microvascular bed - migration of neutrophils from the vascular plexus below the junctional and sulcular epithelium into the JE and gingival sulcus - the inflammatory infiltrate occupies 5% to 10% of the gingival connective tissue below the epithelium; loss of collagen is localized to the inflammatory infiltrate area
Early gingivitis	Tissues look inflamed: there is oedema and erythema	- inflammatory infiltrate of mononuclear leukocytes develops at the site of the initial lesion - the vessels below the junctional epithelium remain dilated, but the number increases due to the opening up of previously inactive capillary beds - lymphocytes and macrophages predominate at the periphery of the lesion with the presence of only a sparse number of plasma cells - at this stage, the infiltrate occupies about 15% of the gingival connective tissue, with collagen destruction in the infiltrated area reaching 60–70% - the infiltrating cells take up the space created by the collagen destruction
Established gingivitis	Lesion exhibits more oedematous swelling. The pocket epithelium is not attached to the tooth surface.	- further increase in the size of the affected area and a predominance of plasma cells and lymphocytes at the periphery of the lesion - macrophages and lymphocytes are detectable in the lamina propria of the gingival pocket - prominent neutrophil infiltration of the junctional and sulcular epithelial is present - the junctional and sulcular epithelium may proliferate and migrate deeper into the connective tissue - the gingival sulcus deepens and the coronal portion of the junctional epithelium is converted into pocket epithelium

Table 7 (Continued). Clinical and histological features of periodontal disease		
Condition	**Clinical features**	**Histological features**
Periodontitis	Periodontal pocket formation, surface ulceration and suppuration, destruction of the alveolar bone and periodontal ligament, tooth mobility and drifting, and eventually tooth loss	- same features are present as in the established gingival lesion, but accompanied - by destruction of the connective tissue attachment to the root surface and the apical migration of the epithelial attachment - progression of gingivitis to periodontitis is marked by the change from T-cell to B-cell predominance - bone destruction begins along the crest of the interdental septum around the communicating blood vessels - the epithelium proliferates apically along the root surfaces - this leads to extension of finger-like projections of pocket epithelium into the deep connective tissues

Seymour et al. hypothesized that a change from T-cell to B-cell dominance causes periodontitis to develop from gingivitis (Seymour et al. 1979). Since plasma cells and B cells constitute the major part of the leukocytes in the periodontitis lesion, it was assumed that T helper (Th) -2 functions may dominate over the dependant Th1. However there are few studies using comparative designs and unbiased quantitative methods regarding Th-1 and Th-2 cells in periodontitis. The consensus is that the relative dominance of B cells and plasma cells in periodontitis lesions cannot entirely be explained by enhanced Th-2 functions but may be because of an imbalance between Th-1 and Th-2 (Berglundh & Donati 2005).

4.2 Assessment

4.2.1 Diagnostic method

Periodontal probing assesses:

- pocket depth (PD) which is defined as the distance between the gingival margin and the bottom of the sulcus.
- gingival recession which is defined as the distance between the cemento-enamel junction and the gingival margin.
- clinical attachment level (CAL) which is defined as the distance between the cemento-enamel junction and the bottom of the sulcus.

Measurement of all three of these parameters is redundant, since measurement of any two of these parameters establishes that of the third. Periodontal probing also generates information regarding bleeding on probing (BOP) and suppuration from the periodontal pocket.

Plaque and gingival indices can be used as an indicator of the amount of plaque and a measure of gingival inflammation. Various indices have been proposed. In general these indices are used in epidemiological studies rather than in day to day clinical practice.

4.2.2 Diagnostic criteria

The basic clinical measures of periodontal disease are CAL, PD, gingival bleeding or BOP, and radiographic assessment of bone loss. CAL and PD are respectively determined, indirectly and directly, using a periodontal probe. CAL remains the 'gold standard' for the diagnosis of periodontitis although it is a measure of accumulated past disease rather than current activity. Despite this, the case definition of periodontitis has varied remarkably in many clinical and epidemiological studies. Some epidemiological and clinical studies have incorporated PD and BOP into a case definition of periodontitis because they are considered more indicative of current disease activity (Tonetti et al. 2005). To further complicate the issue, there is wide variation in the threshold values used in the definition of a case, regardless of the indicators used, as well as in the definitions of incident or progressive disease.

Studies have measured CAL and PD on all teeth, all teeth in two quadrants, the worst teeth in each sextant, and selected index teeth. Measurements have also been made on one, two, four and six sites per tooth. The use of partial-mouth examinations may lead to underestimation of both the prevalence and the severity of the disease (Hunt 1987, Kingman & Albandar 2002, Kingman et al. 1988). Some cross-sectional and longitudinal studies have used tooth loss, the ultimate end point of periodontitis, as an additional outcome variable in the context of risk assessment, as well as to measure the effectiveness of treatment (Chen et al. 2001, Krall et al. 1997, Machtei et al. 1997,

Machtei et al. 1999). Inconsistencies create difficulty in comparison of epidemiological data, estimates of prevalence, and assessment of risk factors in the initiation and progression of disease.

The case definition for periodontitis should state or consider (Burt 2005):

- what depth of CAL at any one site constitutes evidence of disease
- how many such sites need to be present in a mouth to establish disease presence
- how PD and BOP are incorporated in the case definition
- examiner variation

A high proportion of people have at least one site with a 2 mm CAL (Albandar et al. 1999). Because this level of CAL being so common, it is not suitable for use in a cross-sectional study (Burt 2005). The Extent and Severity Index (Carlos et al. 1986) which refers to the number of teeth in the mouth with CAL ≥1 mm as the extent and severity is the mean CAL for those teeth, have been proposed as being more appropriate (Burt 2005).

Recommendation for a two level periodontitis case definition has also been put forward (Tonetti et al. 2005). The levels are:

1. Presence of proximal attachment loss of ≥3mm in ≥2 non-adjacent teeth.
2. Presence of proximal attachment loss of ≥5mm in ≥30% of teeth present.

The rationale for using these proposed criteria was that:

- the definition is sensitive and specific
- the likelihood of including attachment loss from trauma or loss of adjacent teeth is minimized by using proximal sites and non-adjacent teeth,

- a 3mm threshold was based upon studies of incremental attachment loss measurement, where the error of the recording method was calculated at 2.5 mm.

Nonetheless, the authors also indicated that the proposed criteria are designed to identify risk factors and not for the assessment of prevalence of periodontitis across populations and/or age groups.

Another extent and severity threshold used was proposed in 1999 (Armitage 1999) where extent is characterised as localized if ≤30% of the sites are affected and generalized if >30% of the sites are affected. Severity can be described for the entire dentition or for individual teeth and sites, on the basis of CAL, as slight at 1-2mm of CAL, moderate at 3-4mm of CAL and advanced (severe) at ≥5mm CAL.

Periodontitis was defined according to extent and severity following analysis of data from the third National Health and Nutrition Examination Survey (NHANES III), (Albandar et al. 1999).

Advanced (severe) periodontitis was defined as

- two or more teeth (or 30% or more of the teeth examined) having ≥5 mm PD,
- four or more teeth (or 60% or more of the teeth examined) having ≥4 mm PD, or
- one or more posterior teeth with grade II furcation involvement.

Moderate periodontitis was defined as

- one or more teeth with ≥5 mm PD, or
- two or more teeth (or 60% or more of the teeth examined) having ≥4mm PD, or
- one or more posterior teeth with grade I furcation involvement and accompanied with ≥3 mm PD.

Mild periodontitis was defined as

- one or more teeth with ≥3 mm PD, or
- one or more posterior teeth with grade I furcation involvement.

Finally, any person not fulfilling any of above criteria was defined as not having periodontitis.

A recent survey carried out in Australia used two case definitions for prevalence of periodontitis (Roberts-Thomson & Do 2007). Measurements were made at the mesio-buccal, mid-buccal, and disto-buccal aspects of all teeth present, except for third molars. The first definition was based on that developed by the US Centre for Disease Control and Prevention (CDC) and the American Academy of Periodontology (AAP) to describe prevalence of moderate and severe periodontitis in health surveys. Moderate periodontitis was defined as either two sites between adjacent teeth having LOA of ≥4 mm, or at least two such sites having PD ≥5 mm. Severe periodontitis has been defined as having at least two sites between adjacent teeth where LOA is ≥6 mm or more, with at least one of these sites having a PD ≥5 mm. The second case definition used the United States National Centre for Health Statistics (NCHS) case definition for periodontitis, defined as at least one periodontal pocket with a PD ≥4 mm and LOA of ≥3 mm at the same site.

4.2.3 Validity and reproducibility in probing

Accuracy in measurement of PD and CAL with a periodontal probe depends on identifying the location of the connective tissue attachment. Various factors determine how a probe tip advances and where it finally stops when inserted into the periodontal pocket. Firstly, the shape and the diameter of the probe itself determine the pressure of the instrument against the periodontal tissues at any given probing force (Keagle et al.

1989). The periodontal probes mostly used today in practice and clinical research are slightly tapered metal cylinders with horizontal marks, with a rounded tip 0.4–0.5 mm in diameter, and measurements on a millimetre scale. Several studies have indicated that periodontal probes easily fail to identify the apical termination of the junctional epithelium, or the coronal level of the connective tissue attachment, by a variable margin of error. Probe tips penetrate differently in diseased and healthy pockets. In disease the probe tip may enter the connective tissue apparatus when probed (Fowler et al. 1982, Listgarten 1976). After treatment the probe may lie between the junctional epithelium and the tooth, at a distance of approximately 0.7 mm coronal to its apical termination (Fowler et al. 1982). Hence overestimating the attachment loss in disease and underestimating the attachment loss in health. However in smokers, due to a reduced inflammatory response, the probe tip may to penetrate less easily and approach closer to the actual attachment than in non-smokers (Biddle et al. 2001). Other potential sources of error from probing could be due to variability in angulation, indistinct reference points used, obstructions such as calculus, parallax error in reading and probing force.

Splints have been used in some trials to secure probe insertion pathways and to provide vertical reference points for depth readings. In spite of this, reliability from probing using a stent and a constant force probe could only result in 60% of the individual point probing measurements being reproduced (Watts 1987). Measurement of each site twice using a ‘doublepass’ method has been suggested to improve reproducibility of probing, especially in untreated patients where the presence of subgingival calculus may interfere with probe insertion (Osborn et al. 1992). A study on reproducibility of probing based on a larger number of repeated PD measurements revealed that about only 63% of repeated measurements were recorded to be the same PD (Goodson 1986). In comparison, about 95% of the repeated measurements were within 1mm of each other, 99% of the repeated

PD measurements were within an interval of 2mm (Goodson 1986). Thirty to forty percent of periodontal pockets that are re-probed with a manual probe after 1–3 weeks may show a positive or negative deviation in clinical attachment level or probing depth of ± 1 mm (Isidor et al. 1984, Mombelli et al. 1989). The standard deviation of a single measurement of an average periodontal pocket has been reported to be in the range of 0.8–1 mm (Abbas et al. 1982, Badersten et al. 1984, Haffajee et al. 1983, Mayfield et al. 1996).

The effect of force on probing is another variable that has to be considered. Early studies showed that for periodontal probing forces varied considerably between examiners, and when different regions of the mouth were probed (Freed et al. 1983). Use of force controlled probes has been proposed to reduce these possible sources of error (Mombelli 2005). By recording probe penetration into a periodontal pocket as a function of probing force it can be demonstrated that PD depends upon the force applied to the instrument (Mombelli et al. 1992). Deviations in measurement of PD are more likely to occur if one uses light forces rather than heavy probing forces. Thus, if high reproducibility is the primary goal, one should use a higher probing force. However, this may not improve validity as the probe might actually be in the connective tissue (Mombelli 2005). Probing with controlled forces not exceeding 0.25 N is recommended. Studies on periodontally healthy subjects demonstrate that occasional BOP can occur even in the absence of disease (Lang et al. 1991). In subjects with a reduced but healthy periodontium, a nearly linear relationship has been found between the percentage of sites that bleed on probing and probing force (Karayiannis et al. 1992). These studies suggest that the reason for bleeding in the absence of disease is due to trauma from probing with high force. It is quite obvious that the reproducibility of BOP can be improved by either increasing or lowering the probing force level. Eventually either all or no sites will bleed respectively.

4.3 Prevalence

4.3.1 General trends

The old model of periodontal disease assumed that susceptibility to periodontitis was virtually universal. However, only 5 to 20% of any population suffers from severe periodontitis (Burt 2005). This clustering of serious disease is a pattern that is apparent in treated patients (Kornman 2001, Lindhe & Nyman 1984), in epidemiological studies in populations in developed countries (Albandar et al. 1999, Powell & McEniery 1988, Srikandi & Clarke 1982), as well as in populations who do not receive modern dental care (Baelum 1987, Baelum & Fejerskov 1986, Baelum et al. 1988).

The prevalence of periodontitis is complicated as it will depend on the case definition used. In the American studies based on NHANES III, if periodontitis is defined as having at least one site with CAL ≥2mm, then around 80% of all adults are affected (Albandar et al. 1999). In the age group 55 to 64, this figure rises to 90%. When the case definition is that there is at least one site with CAL ≥4mm then the prevalence in those aged 55 to 64 years drops to around 50%. If a CAL of ≥6mm is used, then the prevalence is about 20%. Using pockets of ≥4mm as a case definition, 30% of adults met that criterion on at least three to four teeth. The following table presents the prevalence of periodontitis as reported by a major survey from America (Albandar et al. 1999) (See Table 8).

Table 8. Prevalence of Periodontitis based on The National Survey of Oral Health in U.S. Employed Adults and Seniors, 1985–1986. Data presented according to age group and severity *				
	Periodontitis			Health
Age (Years)	Mild	Moderate	Advanced (severe)	
30-34	17%	1%	1%	78%
35-54	19%	9%	3%	69%
55-74	30%	14%	5%	51%
75 and over	32%	18%	3%	46%
Overall	**22%**	**10%**	**3%**	**66%**

* Data modified from that presented in Albandar et al. (1999) according to specific age groups

Early Australian surveys utilised the clinical index, 'Community Periodontal Index of Treatment Needs' (Ainamo et al. 1982), as the basis for determination of periodontal disease prevalence. The results of these studies are presented in Table 9.

Table 9. Prevalence of periodontal conditions in Australia based on 'Community Periodontal Index of Treatment Needs'						
Reference	**Age (in years)**	**Sample Size**	**Healthy**	**Gingivitis or calculus**	**% shallow Pockets**	**% deep Pockets**
Srikandi & Clarke 1982	17-64	680	4%	11%	60%	25%
Srikandi et al. 1987	15	461	2%	78%	20%	0%
Powell & McEniery 1988	15-19	257	37%	60%	2%	1%
	35-44	223	11%	77%	8%	4%
	55-64	110	15%	66%	4%	8%
	65+	97	5%	68%	16%	11%

The recent National Survey of Adult Oral Health (NSAOH) presented the prevalence of periodontitis according to two case definitions. The prevalence of moderate periodontitis

was 20.5% while the prevalence of severe periodontitis was 2.5% according to the CDC/AAP case definition (Roberts-Thomson & Do 2007). Periodontitis was strongly related to age, with a prevalence of 7.4% among people aged 15-34 years and 60.8% among those older than 75 years old. NSAOH also presented the prevalence data according to the NCHS case definition. According to this definition the prevalence of periodontitis was 19% among Australian adults. There was some similarity among the older generations, whereas the 15-34 years old sample group had a prevalence of 12%. Table 10 shows a summary of prevalence according to gender and age groups.

4.3.2 Determinants of periodontitis

A risk factor is an 'environmental exposure, aspect of behaviour, or an inherent characteristic which is associated with a disease' (Burt 2005). The association is implied to be causal (Burt 2005). Two recognised risk factors for periodontitis are smoking and diabetes. Risk determinant is a term reserved for risk factors that cannot be modified (Burt 2005, Papapanou & Borrell 2005). The risk determinants of periodontitis are age, gender, race and socioeconomic status (SES). There are also other background factors of environmental and systemic origin such as osteoporosis, obesity, and rheumatoid arthritis that may determine the expression of periodontitis. These factors show a casual relationship with periodontitis.

In general, periodontal destruction increases with age (Albandar et al. 1999, Roberts-Thomson & Do 2007). The current consensus is that the greater periodontal destruction in the elderly reflects lifetime disease accumulation rather than an age-specific condition (Burt 2005, Albandar 2002, Borrell & Papapanou 2005). The prevalence of those with

Table 10. Prevalence of periodontitis in Australia as reported by NSAOH according to the different definition and age group (Roberts-Thomson & Do 2007)

Definition	Age at the time of survey (years)		All ages	15-34	35-54	55-74	≥75
CDC	**All People**	**% of people**	**22.9**	**7.4**	**24.5**	**43.6**	**60.8**
		95% CI	21.3-24.7	5.4-9.9	21.9-27.4	40.2-47.0	52.6-68.5
	Male	% of people	26.8	9.9	30.4	48.7	62.6
		95% CI	24.1-29.6	6.8-14.1	26.3-34.9	43.5-53.9	50.4-73.5
	Female	% of people	9.0	4.7	18.6	38.5	59.5
		95% CI	17.2-21.0	3.1-7.1	15.9-21.6	34.4-42.7	48.9-69.3
NCHS	**All People**	**% of people**	**19.0**	**12.0**	**23.2**	**23.5**	**25.9**
		95% CI	17.2-21.0	9.2-15.6	20.5-26.1	20.8-26.4	18.4-35.0
	Male	% of people	22.5	15.7	28.3	25.3	23.3
		95% CI	19.7-25.7	11.1-21.7	24.1-32.9	21.6-29.4	14.2-35.9
	Female	% of people	15.4	8.1	18.0	21.7	27.6
		95% CI	13.7-17.3	5.8-11.2	15.3-21.1	18.1-25.6	18.6-39
4+mm	**All People**	**% of people**	**19.8**	**13.1**	**23.9**	**23.7**	**26.0**
		95% CI	17.8-21.8	10.2-16.7	21.2-26.9	21.1-26.7	18.6-35.1
	Male	% of people	22.8	15.9	28.6	25.5	23.3
		95% CI	19.9-26.0	11.3-21.9	24.4-33.2	21.8-29.7	4.2-35.9
	Female	% of people	16.7	10.1	19.0	21.9	28.0
		95% CI	14.9-18.6	7.4-13.5	16.4-22.4	18.4-25.9	18.-39.3

Key: CDC: CDC/AAP definition; **NCHS:** NCHS definition; **4+mm:** prevalence of people with at last one probing pocket depth of 4mm

moderate and severe periodontitis increases with age (Roberts-Thomson & Do 2007, Burt 2005, Albandar 2002, Borrell & Papapanou 2005) but maybe only up to a certain point (Albandar et al. 1999). The results of the NHANES III show that the prevalence of moderate and severe periodontitis peaks between the ages of 75yrs to 85yrs. The explanation for this trend might be that the decrease in the prevalence of severe attachment loss in the elderly might be a survival phenomenon, meaning that those most susceptible to severe periodontitis may have already lost teeth or their lives.

Males in general have more severe periodontitis across all age groups (Albandar 2002, Burt 2005, Roberts-Thomson & Do 2007). However males also tend to have more calculus and plaque deposits, poorer oral hygiene (Albandar 2002). The reason for the difference in disease experience between the genders is not clear, but it may be due to less motivation towards positive oral health behaviour rather than any genetic factor (Burt 2005). Females have better oral hygiene practices (Christensen et al. 2003, Hugoson et al. 1998) and show greater utilization of oral health care services (Dunlop et al. 2002, Roberts-Thomson & Stewart 2003).

Similarly, lower SES has been related to more severe disease. The relationship between SES levels, gingival health and periodontal disease is thought to be a function of better hygiene among the better educated, more positive attitudes toward oral hygiene, and more frequent dental visits (Albandar 2002, Burt 2005). The prevalence of periodontitis found in the NSAOH was correlated with the level of education, eligibility for public dental care, and having private dental insurance as indicators of SES. Leaving school before Year Nine, being eligible for public dental care and not having private dental insurance were associated with a higher prevalence of periodontitis (Roberts-Thomson &

Do 2007). This indicates that the association between lower SES and more severe disease may exist in Australia as well.

Some surveys have shown a higher prevalence of periodontitis in developing countries in comparison to industrialised countries but these differences are not as apparent when oral hygiene is taken into account (Baelum et al. 1996). In addition, some national surveys have shown differences in periodontal status between different races within the same country (Albandar et al. 1999). For example, there was a greater prevalence of periodontitis in blacks and Mexican-Americans in the NHANES III (Albandar et al. 1999). In NSAOH, while there were elevated rates of tooth loss, tooth wear and decay among the indigenous people sampled, there was no statistically significant difference in prevalence between indigenous and non-indigenous people. This may be due to limitations in the sample size of the indigenous group who made up about 1.5% of those sampled.

Studies published over the last two decades have provided evidence that diabetes mellitus is a risk factor for periodontitis. The observations are consistent for both Type-1 and Type-2 diabetes. Evidence from cross-sectional and longitudinal studies suggests that, irrespective of the case definition used for periodontitis, subjects with diabetes have a higher prevalence, extent, and severity of periodontitis (Grossi et al. 1994, Bridges et al. 1996, Firatli 1997, Tervonen & Karjalainen 1997, Taylor et al.1998a, b, Lalla et al. 2004). Diabetes has been associated with an increased risk of periodontitis at a young age (Cianciola et al. 1982), with adults (Bridges et al. 1996, Moore et al. 1999, Tervonen et al. 2000, Campus et al. 2005), as well as the elderly (Collin et al. 1998). There is also evidence for a dose effect with a greater severity of periodontitis being associated with poorly controlled diabetes (Tervonen & Oliver 1993, Tsai et al. 2002, Safkan-Seppala

and Ainamo 1992). In addition, greater periodontal destruction may be observed in those with a long duration of disease (Taylor et al. 1996, 1998, Grossi & Genco 1998, Lalla et al. 2004). Some authors have argued for a two-way relationship between diabetes and periodontitis where periodontitis may have an effect on glycaemic control (Lalla et al. 2000, Soskolne & Klinger 2001, Taylor 2001). While it is biologically plausible, this effect is minimal and it is questionable if it is clinically significant (Janket et al. 2005).

The association between smoking and periodontitis has been identified by cross-sectional, case control studies and longitudinal studies (Bergstrom & Preber 1994, Martinez-Canut et al. 1995, Albandar et al. 2000, Bergstrom et al. 2000a, 2000b). The strength of association between smoking and periodontitis varied in these cross-sectional studies depending on the criteria used to define periodontitis and the adjustment made for plaque levels (Grossi et al. 1994, Grossi et al. 1995, Tomar & Asma 2000, Calsina et al. 2002, Axelsson et al. 1998). In general, after adjustment for levels of plaque accumulation, smokers tend to have deeper PD (Bergstrom 1989, Calsina et al. 2002, Haffajee & Socransky 2001a, Linden & Mullally 1994), greater attachment loss (Calsina et al 2002, Grossi et al. 1994, Axelsson et al 1998, Haffajee & Socransky 2001b, Linden & Mullally 1994), more bone loss (Grossi et al. 1994, Bergstrom 2004) and fewer teeth (Axelsson et al. 1998). A study based utilising data from the NHANES III revealed that about one half of periodontitis cases were attributable to having either a current or former smoking habit (Tomar & Asma 2000). In this study current smokers were four times more likely to have periodontitis when compared to non-smokers after adjusting for age, race, income and educational levels (Tomar & Asma 2000). The result of this study compares well to the result of a meta-analysis of six studies which concluded that smokers are almost three times as likely to have more severe periodontitis compared to non-smokers (Papapanou 1996). Interestingly similar to that seen with diabetes, a dose–

response effect has been demonstrated in several studies (Grossi et al. 1994, 1995, Martinez-Canut et al. 1995, Bergstrom et al. 2000b, Bergstrom 2004) with respect to the cigarette smoking. Although smoking cessation does not reverse the periodontal destruction of the past, the rate of bone and attachment loss slows after patients cease smoking. This trend is reflected clinically with disease severity being intermediate to that of current smokers and never smokers (Bergstrom 2004).

While the exact mechanism is uncertain, a potential link between obesity and periodontitis has been suggested. A hyper-inflammatory state resulting from the over-expression of inflammatory cytokines, aberrant lipid metabolism and insulin resistance has been proposed as resulting in enhanced periodontal tissue breakdown (Saito et al. 1998, Nishimura & Murayama 2001, Saito & Shimazaki 2007). Several studies have shown a positive association between obesity and periodontitis (Al-Zahrani et al. 2003, Buhlin et al. 2003, Saito et al. 2001, Wood et al. 2003). These studies, in general, have used the BMI as the measure for obesity, comparing those with a normal weight, as defined by BMI <25, to those overweight or obese, as defined by BMI >25 and
BMI >30 respectively. In contrast, one study carried out in Thailand failed to find an association between obesity and periodontitis (Torrungruang et al. 2005). The waist-to-hip ratio has also been used as a measure of obesity in some studies (Wood et al. 2003, Al-Zahrani et al. 2003, Saito et al. 2001). A significant association between both BMI and waist-to-hip ratio and periodontitis in younger adults was found, but curiously no association was found in middle-aged or older adults (Al-Zahrani et al. 2003). Another study reported that BMI, waist-to-hip ratio, visceral fat, and fat-free mass were associated with periodontitis after adjusting for age, gender, history of diabetes, current smoking, and SES (Wood et al. 2003). Since all the above studies were cross sectional and the majority of studies were based on one of two population samples, either the NHANES III

group or a Japanese population, additional research on the relationship between obesity and periodontitis is indicated.

4.4 Morbidity and mortality

Periodontitis may lead to recession, attachment loss, sensitivity, migration and drifting of teeth, pain and other signs and symptoms but the obvious end point or consequence of periodontitis includes tooth loss. Overall, periodontitis is thought to account for 30 to 35% of all tooth extractions (Papapanou 1996). A survey undertaken of 1250 subjects in Brisbane, Australia estimated that thirty two extractions were required because of periodontitis which translated to a mean of 0.02 teeth per subject (Powell & McEniery 1988). Tooth loss in treated populations of periodontally susceptible patients has been determined in longitudinal clinical studies (Table 11). The rate of tooth loss in these studies of compliant patients is low. Conversely, even in these studies there appears to be a distinct subset of patients who are at greater risk of tooth loss than others. With respect to untreated patients, the attachment loss per year has been calculated for populations based in developing countries. The rate of tooth loss of non-compliant patients in the clinical studies has also been investigated. Longitudinal studies have shown that, for populations in developed countries with adequate personal and professional dental care, attachment loss progresses by a mean of 0.05 to 0.1mm per year, per tooth (Loe et al. 1978). Comparatively, people in developing countries with no access to dental care had a mean rate of progression of about 0.3mm per year, per tooth (Loe et al. 1986). This was similar to the rates of progression for non compliant patients in a clinical study of 0.3 to 0.33mm per year (Harrel & Nunn 2001). Periodontitis may also have systemic consequences via systemic inflammation on diabetic control (Janket et al 2005), CVD

(Beck et al. 1996, Genco et al. 2002, Kinane & Lowe 2000, Mattila et al. 2005) and preterm low birth weight (Dasanayake 1998, Lopez et al. 2005, Offenbacher et al. 1996).

Table 11. Tooth loss in treated patients			
Study	**Number of patients**	**Average/minimum maintenance duration (years)**	**Tooth loss (%)**
Hirschfeld & Wasserman 1978	600	22	7.1
McFall 1982	172	12	9.8
Konig et al. 2002	142	10	7.9
Fardal et al. 2004	100	9.8	1.5
Checchi et al. 2002	92	6.7	2.0

5. POTENTIAL LINKS BETWEEN OSA, INFLAMMATION AND PERIODONTITIS

5.1 Overview

Periodontitis is an inflammatory condition. Recent evidence indicates that atherosclerosis has an inflammatory basis. The link between periodontitis and systemic inflammation, and in turn CVD, has been demonstrated by:

- case control and cross-sectional studies that show an association or increased risk of cardiovascular symptoms amongst subjects with periodontitis,
- cross-sectional and treatment studies that have analysed systemic inflammatory markers in patients with periodontitis without and with periodontal treatment, respectively,

- studies that have shown induction of atherogenic lesions by periodontal pathogens in animal models (Lalla et al. 2003, Li et al. 2002).

5.2 Cardiovascular risk and inflammatory markers

A review of the literature described 42 published studies of the association between CVD and periodontitis but whether or not periodontitis is causal for CVD is as yet unclear (Beck & Offenbacher 2005). Of the nine case control studies reported, only one resulted in a non-significant positive trend after adjusting for confounders (Mattila et al. 2000). These case control studies compared various indices of oral health in controls and cases with coronary heart disease (Emingil et al. 2000, Mattila et al. 2000, Mattila et al. 1989, Persson et al. 2003) and stroke (Dorfer et al. 2004, Grau et al. 2004, Grau et al. 1997, Syrjanen et al. 1989). Outcomes used were MI (Emingil et al. 2000, Mattila et al. 1989, Persson et al. 2003), coronary heart disease (Mattila et al. 2000) and ischaemic stroke (Syrjanen et al. 1989), combination of stroke or transient ischaemic attacks (Grau et al. 2004, Grau et al. 1997, Dorfer et al. 2004)

Beck & Offenbacher (2005) also reported that 16 longitudinal studies examined the association between periodontitis and CVD. However, eight of those studies were from the same two databases. Some of these prospective cohort studies were analysed as part of a systematic review (Janket et al. 2003). The meta-analysis was performed on nine studies that fitted the following inclusion criteria: studies that have a sample size of greater than 100 subjects, studies that must ascertain exposure before outcome and studies with data that could be used for statistical analysis, for example, to formulate a relative risk as well as confidence intervals. Six of these studies reported positive associations (Beck et al. 1996, DeStefano et al. 1993, Genco et al. 1997, Mattila et al.

1995, Morrison et al. 1999, Wu et al. 2000) while three did not (Howell et al. 2001, Hujoel et al. 2000, Joshipura et al. 1996). The final summary relative risk was 1.19, indicative of a higher risk of future CVD events in individuals with, compared to those without periodontitis. A significant and stronger association of periodontitis with incidence of CVD was observed among subjects aged 65 years or younger (RR 1.44). When the outcome was restricted to stroke, the RR was 2.85.

The authors conceded that the validity of their meta-analysis is based on its component of individual studies, and there was some variation between those studies (Janket et al. 2003). The variations were in the population which ranged from health professionals (Howell et al. 2001) to the native American Indians (Genco et al. 1997); outcome measures which included fatal and non fatal stroke, death, fatal and non fatal MI; the predictor measurements which included PD, alveolar bone loss, tooth loss, self reported history of periodontitis; and adjustment for confounders. They reasoned that certain individual studies underestimated the association between periodontitis and CVD, while some overestimated it. They concluded that the sophisticated statistical methods that they used to obtain a weighted average (which other meta-analyses did not), made the results of their study valid.

Cross-sectional studies have investigated the relationship between periodontitis and coronary heart disease, stroke, and systemic markers for heart disease such as CRP (Slade et al. 2000, Wu et al. 2000), fibrinogen (Kweider et al. 1993), and IL-6 (Loos et al. 2000). The exposure measures used to measure periodontitis and the outcome measures again varied among some of the studies. Most of the cross-sectional studies have reported at least one significant positive association after adjusting for confounders. There has been wide range of odd ratios reported from 1.04 to 2.09 (Beck & Offenbacher 2005). Case

control studies have investigated the total number of peripheral blood leukocytes in periodontitis patients, the level of serum CRP in healthy controls versus patients with Periodontitis, and plasma fibrinogen levels. A review of these studies concluded that the strength of the association and the difference between cases and controls have been modest at best, even when statistically significant (Loos 2005).

Intervention studies of the effect of periodontal therapy have resulted in conflicting results when comparing inflammatory markers. There appears to be a general tendency towards reduction in CRP levels after periodontal therapy (D'Aiuto et al. 2004, Ebersole et al. 1997, Iwamoto et al. 2003, Mattila et al. 2002, Montebugnoli et al. 2005, Pussinen et al. 2004, Taylor et al. 2006), although there are exceptions (Ide et al. 2003, Yamazaki et al. 2005). However, periodontal treatment has not resulted in statistically significant reductions in other inflammatory markers such as IL-1, IL-6 and TNF-α in studies (Ide et al. 2003, Montebugnoli et al. 2005, Yamazaki et al. 2005). Exceptions being a study of 94 patients undergoing nonsurgical periodontal therapy which showed a statistical significant reduction in IL-6 (D'Aiuto et al. 2004) and an intervention study examining the effect of full mouth extraction of all remaining teeth in 67 patients (Taylor et al. 2006) which also showed statistically significant changes in inflammatory markers. The discrepancy between the two latter studies and those that found no statistically significant changes may be due to the small sample size in the former.

5.3 Potential biological mechanisms

A model for a potential link between periodontitis, inflammation and CVD was described in 1996 (Beck et al. 1996). Periodontal infection forms the basis of this model that proposes that there is, in susceptible individuals, an underlying hyper-inflammatory

response to stimuli that is manifest by an excessive production of pro-inflammatory cytokines and lipid mediators by monocytes and other cell types. This hyper-inflammatory trait may be induced by genetic, behavioural and environmental exposure and may serve as a common antecedent to both cardiovascular and periodontal risk. The presence of oral bacteria and the resultant bacteraemia may add to the host's burden of systemic inflammation, thus increasing either the risks or severity of existing CVD. Inflammatory mediators produced locally in response to periodontitis may essentially be 'dumped' into the systemic circulation to have a distant effect (Loos et al. 2005). The same report proposes increased levels of systemic inflammatory markers are proof of bacteraemia from periodontal disease, and that this bacteraemia could be a reason for the association of periodontal disease with CVD.

There is as yet, no study evaluating a potential link between OSA and periodontitis.
Since OSA has been shown to affect systemic inflammation and also to increase the risk of other systemic disease, we can speculate that OSA could potentiate the effect of any risk factors and increase the risk of periodontitis in patients. Whether there is a bi-directional effect such that periodontitis influences the incidence or severity of OSA is unknown.

6. SUMMARY OF THE LITERATURE

Both OSA and periodontitis are common disorders with common risk factors and risk indicators. Periodontitis is associated with systemic inflammation and increased cardiovascular morbidity and mortality. The magnitude of this effect is unknown but is estimated to be small.

It is evident from the literature that OSA is also associated with systemic inflammation. Although the precise mechanism is uncertain, the underlying systemic inflammation from OSA may be due to the hypoxia/reperfusion injury from intermittent hypoxia due to OSA. OSA is an independent risk factor for hypertension. OSA has also been shown to be associated with increased cardiovascular morbidity and mortality, independently of its effects through hypertension. It is possible that increased systemic inflammation may directly contribute to the pathogenesis of CVD and be responsible for the increased cardiovascular morbidity and mortality. Similarly, the increase in systemic inflammation may affect the expression of periodontitis in those with OSA. If so, the prevalence and/or the severity of periodontitis should be greater in those with OSA than in those without OSA.

There are no studies, as yet, that have examined the relationship between OSA and periodontitis. An association between the two conditions may indicate one of three possibilities: (i) OSA contributes to systemic inflammation and increases the expression of periodontitis; (ii) periodontitis may be an important mediator of inflammation in OSA; (iii) periodontitis may be a confounder via an unknown mechanism in the relationship between OSA and cardiovascular morbidity.

There is a need to examine the relationship between the two conditions because of the implications of such an association. A large number of studies would be required to fully elucidate this relationship. Any study that examines this relationship must take into account the risk factors that are common to both conditions. The first step should be a carefully designed cross sectional study that examines whether there is indeed an association between the two conditions.

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PART B: SCIENTIFIC PAPER

Obstructive Sleep Apnoea and Periodontitis: A Novel Association?

Authors:

Kogulan Gunaratnam, BDS, BSc[1]

Barbara Taylor, BDS, MDSc, FRACDS[2,3]

Bradley Curtis BDS, MPH, G.Cert, FICD[4]

Peter Cistulli, MBBS, PhD[5,6,7]

Institutional affiliations:

[1]Discipline of Periodontics, Faculty of Dentistry, University of Sydney, Sydney, Australia

[2]Department of Periodontics, Sydney Dental Hospital, Sydney, Australia

[3]School of Dentistry and Health Sciences, Charles Sturt University, Wagga Wagga, Australia

[4]Community Oral Health and Epidemiology, Faculty of Dentistry, University of Sydney, Sydney, Australia

[5]Department of Respiratory Medicine, Royal North Shore Hospital, St Leonards, Australia

[6]Faculty of Medicine, University of Sydney, Sydney, Australia

[7]Woolcock Institute of Medical Research, Sydney, Australia

Corresponding Author:

Address correspondence to: Peter Cistulli, Department of Respiratory Medicine, Royal North Shore Hospital, St Leonards, NSW, Australia. Ph: +61-2-99268674, Fax: +61-2-99066391, email: cistullip@med.usyd.edu.au

Disclosure Statement

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

ABSTRACT

Study objective: 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. Hence the aim of the study was to determine the prevalence of periodontitis in a group of patients diagnosed with obstructive sleep apnoea.

Design: Cross sectional study

Settings: Clinical sleep laboratory and dental hospital setting

Patients: Sixty six (54 males and 12 females) treatment naïve patients with OSA, diagnosed by polysomnography.

Measurements and Results: A standard periodontal examination was undertaken to derive a number of quantitative variables regarding the presence and extent of periodontal disease. 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 variables were compared against periodontal variables, significant correlations were found between 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, and whether it is relevant to the known associations between OSA, inflammation, and cardiovascular morbidity.

Keywords: Obstructive sleep apnoea; periodontitis; prevalence

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] and cardiac arrhythmias.[8]

There is evidence of local upper airway[9,10] and systemic inflammation[11] arising from 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.[11] Several studies have demonstrated that patients with OSA have increased plasma markers of systemic inflammation, notably increased levels of inflammatory cytokines,[12-14] adhesion molecules,[15-17] and activation of circulating neutrophils.[16] 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.[18] Intermittent hypoxia occurring in OSA may stimulate transcription factors such as nuclear factor-κβ and increase production of cytokines.[19] 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.[18] 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 specific bacteria that trigger an inflammatory response in the supporting tissues of teeth.[20] This can result in destruction of the supporting tissues of the teeth, in those susceptible, that is clinically evident as the progressive loss of periodontal attachment, pocket formation, loss of alveolar bone and, ultimately, tooth loss.[20] Established risk factors for periodontitis include smoking[21, 22] and diabetes.[21-23]

The prevalence of periodontitis depends on the definition used. That of moderate and severe periodontitis in Australia[24] is estimated to be between 19 to 23% of the population which is similar to that reported in other developed countries.[22, 25,26] The prevalence and the severity of periodontitis increases with age and male gender.[24, 25] Factors such as socioeconomic status (SES), education, and ethnicity may also be linked to an increased prevalence of periodontitis.[27-29]

The relationship between periodontitis and systemic diseases has been investigated with conflicting results in, for example, rheumatoid arthritis[30,31] and osteoporosis.[32,33] There has also been evidence for[30,32] and against[31,33] a greater prevalence of periodontitis in those with rheumatoid arthritis and osteoporosis. While diabetes is a risk factor for periodontitis,[21-23] the relationship between the two conditions may be bi-directional.[34] Periodontitis may have a mild effect on the outcome and markers of cardiovascular disease.[35,36] 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.[37] 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.[38]

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. Patients with an apnoea-hypopnoea index (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. Clinical periodontal variables could be altered by recent periodontal treatment.[39] This could lead to inaccurate periodontal diagnosis. Hence, we excluded patients who had periodontal treatment within the previous three months.

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. 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),[40] 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.[41]

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 at individual sites were rounded to the nearest millimetre.

OSA variables for each patient were obtained by standard polysomnography prior to the periodontal examination.[42] 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 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 one 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 (KG was compared to another periodontist (BT)). This result is similar to the reported reproducibility in the literature.[43]

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).[24] 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.[24] According to the CDC/AAP definition, periodontitis is defined as the presence of two or more interproximal sites with ≥4mm CAL, not on the same tooth, or two or more interproximal sites with PPD ≥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 ≥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.[44, 45] 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 majority of this sample group could be considered overweight (BMI >25kg/m^2) or obese (BMI >30kg/m^2). For example, 55

(82%) patients having a BMI greater than 25kg/m² while 31 patients (47%) had a BMI of over 30kg/m². The mean BMI for the group was 30.5 kg/m² ($\pm$ 6.3kg/m² SD). The minimum BMI noted was 18.3kg/m² with a maximum of 51.2kg/m².

Table 2 shows results for the measured sleep variables. A wide of range in OSA severity from mild to very severe was noted within the sample. However, the majority of patients could be considered to have moderate to severe OSA (AHI >15/hr).[42] 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.[24]

Spearman correlation coefficients for the key periodontal and OSA variables were calculated. 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.[24] There was about a four-fold increase in the overall prevalence in the recruited group in comparison to the national average.[24] The prevalence of periodontitis depends on the definition used. Although other definitions are available,[46, 47] those used in this study were chosen in order to be consistent with the two definitions used in NSAOH and facilitate 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 an association between periodontitis and OSA or due to OSA and periodontitis sharing several overlapping aetiological factors. Exploring the latter, smoking[21, 22] and diabetes[21-23] are established risk factors for periodontitis. Associations have also been shown between periodontitis and age,[24, 25] gender,[24, 25] plaque levels,[21,22,26] obesity,[48,49] SES and education.[27-29] Thus these features could contribute to an increase in the prevalence of periodontitis in our sample. The prevalence of patients with diabetes in our sample group was higher than the national average.[50] However, the absolute number of patients with diabetes was small (6 subjects) and consistent with the reported association between OSA and diabetes.[51] In contrast, the level of cigarette smoking in our sample group was similar to the national level if never smokers are considered.[50] The prevalence of current smokers was lower

than the national average (9% vs. 21%).[50] Taken together, the effect of diabetes and smoking on the increased prevalence of those with periodontitis in our group appears to be minimal.

There were other characteristics of our sample group that were different to the general population. The subjects recruited to this study could be assumed to have belonged to a higher SES[52] 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.[53] The rate of dental attendance and maintenance in our group was much higher than the general population, as reported by NSAOH.[24] 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.[21,22,26] Past association studies have shown that all these factors should reduce the prevalence of periodontitis.[21,22,26] However the prevalence of periodontitis was greater in our sample group despite these factors.

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.[24, 25] However as seen in the Australian survey,[24] the magnitude of difference in prevalence between the two gender groups is small and is unlikely to explain the increased prevalence in our sample.[24]

Cross sectional studies investigating the association between periodontitis and obesity have shown conflicting results with positive association[48,49] as well as no association[54] between different measures of obesity and periodontitis. However, obesity is an established risk factor for OSA.[55] 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.[50] In comparison, 53% of adults in the Australian population can be considered overweight or obese.[50] 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 in explaining the increased prevalence of periodontitis observed in our study. Hence the possibility of a true association between OSA and periodontitis merits consideration. Such an association could be explained by a number of potentially inter-related pathways: (i) Periodontitis could be a previously unknown confounder in the relationship between OSA and cardiovascular disease that contributes to an increased inflammatory burden; (ii) OSA may increase the presence and severity of periodontitis by contributing to increased systemic inflammation; (iii) Periodontitis may be contributing to the increased systemic inflammation noted in OSA patients. However, we did not find any significant correlations between OSA indices and periodontal measures, suggesting that a causal association is unlikely. The only significant correlation was between CAL and TST. Regression modelling revealed TST and age to be predictive for CAL. However, the biological basis for a relationship between markers of periodontal disease and TST is unclear.

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, we deliberately excluded patients with a history of known periodontitis diagnosis or treatment within the last 3 months. Secondly, we used a

historical (NSAOH)[24] rather than concurrent control group. However, 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 unlikely.

In conclusion, our pilot study suggests that the prevalence of periodontitis may be higher in patients with OSA. The prevalence was greater despite the age group and the definitions used. 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

ACKNOWLEDGMENTS

We thank the staff at the Royal North Shore Dental Clinic for their help the periodontal examination. We thank the sleep technologists at the Department of Respiratory Medicine, Royal North Shore Hospital for their help with the data collection. We also thank Nathaniel Marshall PhD for his critical review of the manuscript

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**
AHI (per hour)	36.55 (25.77)	29.05 (5.7 - 137.2)
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)
Minimum SaO_2 (%)	79.2 (12.3)	84 (43 - 96.5)
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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