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JOHANNA SAHLMAN

Obstructive Sleep Apnea in Adults

Evolution, and Related Inflammation in Early Stages of Disease

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ABSTRACT

Obstructive sleep apnea (OSA) is a condition where there are repetitive breathing pauses due to upper airway obstruction during sleep. It decreases the patient's quality of life by causing both night-time (e.g. snoring and restless sleep) and daytime symptoms (e.g. daytime sleepiness and impaired congnitive function). Based on the frequency of breathing pauses, OSA is divided into mild, moderate or severe disease. Thus far, the research has mainly been focused on more symptomatic subjects with moderate-to-severe OSA. In addition to immediate symptoms, these more severe forms of OSA have been observed to have an association with cardiovascular and cerebrovascular co-morbidities and impaired glucose metabolism. Obesity is considered as a major risk factor for all these conditions. Low-grade inflammation has been proposed to be one underlying mechanism which explains the increased risk of co-morbidities in patients with OSA. OSA, similar to many other chronic diseases, is a progressive disease. Even though mild OSA accounts for more than half of all OSA patients, there has been a lack of studies on the early stages of OSA or the evolution of the disease. Moreover, little is known about inflammation in mild OSA. Weight reduction is believed to have an impact on resolution of OSA and related metabolic disturbances. However, the effect of weight loss on the inflammation has not previously been studied in OSA patients.

The present work includes a retrospective and a prospective clinical study. The aims of the retrospective study were to evaluate the objective outcome (sleep related respiratory events; N=50 patients) and subjective outcome (symptoms; N=81 patients) after different treatment options for mild OSA. The prospective trial assessed the impact of mild degree OSA on circulating inflammatory biomarkers in overweight or obese patients (N=84) compared with control patients (N=40), and whether weight loss results in changes in these markers (N=59).

This study shows that mild OSA, if left untreated, is a progressive disease both in terms of sleep related respiratory events and symptoms. Upper airway surgery for mild OSA in carefully selected patients seems to reduce the risk of disease progression. Low-grade inflammation seems to be activated already in the early stages of disease. In overweight patients weight reduction achieved by lifestyle intervention is an effective treatment for mild OSA, and it also results in improvement of inflammation. This study demonstrates that even mild OSA should be actively treated to prevent progression of the disease, and to reduce the risk for related co-morbidities.

National Library of Medical Classification: WF143, WD 210
Medical Subject Headings: Sleep Apnea, Obstructive; Obesity; Inflammation

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TIIVISTELMÄ

Obstruktiivisella uniapneataudilla tarkoitetaan ylempien hengitysteiden täydellisen tai osittaisen tukkeutumisen aiheuttamia unenaikaisia hengityskatkoja. Tautiin liittyvät yöaikaiset oireet, kuten kuorsaus ja levoton uni, sekä päiväaikaiset oireet, kuten päiväväsymys ja alentunut toimintakyky, heikentävät potilaan elämänlaatua. Hengityskatkojen määrästä riippuen tauti jaetaan lievään, keskivaikeaan tai vaikeaan asteeseen. Yli puolella uniapneapotilaista tauti on lieväasteinen. Tästä huolimatta suurin tieteellinen mielenkiinto on kohdistunut keskivaikeaan ja vaikeaan tautimuotoon. Näihin liittyy myös selkeämmin lisääntynyt alttius sydän- ja verisuonisairauksille, aivoverenkiertohäiriöille sekä heikentyneelle sokeriaineenvaihdunnalle. Lihavuus on kaikkien näiden sairauksien vaaratekijä. Yksi selittävä tekijä liitännäissairauksien lisääntyneelle alttiudelle voi olla matalan tason tulehdusreaktio, jota on tutkittu hyvin vähän lieväasteisessa obstruktiivisessa uniapneataudissa. Painonpudotuksen vaikutusta tähän tulehdusreaktioon ei ole aiemmin tutkittu uniapneapotilailla. Obstruktiivinen uniapnea on monen muun pitkäaikaissairauden tavoin etenevä sairaus, mutta etenemisen kehittymistä lievästä vaikeampiin muotoihin on tutkittu vähän.

Tutkimuskokonaisuus muodostuu retrospektiivisesta ja prospektiivisesta aineistosta. Retrospektiivisessä osiossa selvitettiin lievän uniapneataudin vaikeusasteen muutosta erilaisten hoitovaihtoehtojen jälkeen unirekisteröintituloksen (50 potilaalla) ja oireiden perusteella (81 potilasta). Prospektiivisessa osiossa tutkittiin taudin vaikutusta tulehdusmerkkiaineisiin 84 ylipainoisella potilaalla. Lisäksi arvioitiin painonpudotuksen vaikutusta näihin merkkiaineisiin.

Tutkimustulokset tukevat olettamusta, että hoitamaton obstruktiivinen uniapneatauti on etenevä sairaus. Valikoiduilla potilailla ylähengitysteiden kirurgia esti taudin etenemisen. Jo lievään uniapneatautiin näyttää liittyvän elimistön tulehdusreaktion aktivoituminen. Lisäksi havaittiin, että elämäntapamuutoksella toteutettu painonpudotus vähentää tehokkaasti tätä tulehdusreaktiota. Tämä tutkimus osoittaa, että myös lievää uniapneatautia tulisi hoitaa taudin etenemisen ja liitännäisairauksien riskiä lisäävän tulehdusreaktion hillitsemiseksi.

Yleinen Suomalainen asiasanasto: uniapnea-oireyhtymä; lihavuus; tulehdus

”Nainen tarvitsee elämässään kahta asiaa:

huumoria ja punaiset korkokengät...

Tohtorin tutkinto on hyväksi,

muttei välttämätön.”

Riikka Pulkkinen: Totta, s. 195, Otava 2010

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Johanna Sahlman
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List of the original publications

This dissertation is based on the following original publications:

I Sahlman J, Pukkila M, Seppä J, Tuomilehtio H: Evolution of mild obstructive sleep apnea after different treatments. *Laryngoscope 117(6): 1107-11, 2007*.

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IV Sahlman J, Seppä J, Herder C, Peltonen M, Peuhkurinen K, Gylling H, Vanninen E, Tukiainen H, Punnonen K, Partinen M, Uusitupa M, Tuomilehto H: Effect of weight loss on inflammation in patients with mild obstructive sleep apnea. In press. *Nutr Metab Cardiovac Dis,* in press. (Epub Dec 28 2010)

Contents

AHI	Apnea-hypopnea index
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CVD	Cardiovascular disease
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
ESS	Epworth Sleepiness Scale
HOMA-IR	Homeostasis model assesment of insulin resistance
hsCRP	high-sensitivity C-reactive protein
IL	Interleukin
IL-1Ra	Interleukin-1 receptor antagonist
MetS	Metabolic syndrome
NREM	non-rapid eye movement
OA	Oral appliance
ORL	Otorhinolaryngology
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
pO_2	Partial pressure of oxygen
pCO_2	Partial pressure of carbon dioxide
PSG	Polysomnography
REM	Rapid eye movement
RFA	Radiofrequency ablation
SaO_2	Arterial oxyhemoglobin saturation in pulse oxymetry
SD	Standard deviation
SDB	Sleep disordered breathing
TNF	Tumor necrosis factor
T2DM	Type 2 diabetes mellitus
UA	Upper airway
UARS	Upper airway resistance syndrome
UPPP	Uvulopalatopharyngoplasty
VLCD	very low calorie diet

1 Introduction

Changes in sleep have implications for quality of life and level of functioning in everyday life. Obstructive sleep apnea (OSA) is a public health issue because up to one out of five adults experiences at least mild OSA (1). Mild OSA is the largest subgroup of this condition, accounting for more than half of all OSA patients. However, previous reports have mainly focused on those patients with moderate-to-severe OSA, because of more severe symptoms and the more indisputable association with co-morbidities. Since OSA may have a tendency to progress to more severe disease (2), an early intervention to prevent its worsening is well-justified. However, the literature is relatively sparse regarding the natural progression of mild OSA as well as long-term follow-up of therapies on early stages of OSA.

Recent reports have indicated that OSA is most likely a risk factor for cardiovascular disease and mortality (3-5). The underlying mechanisms explaining the association of OSA and atherosclerotic diseases remain incompletely understood, but it has been hypothesized that chronic subclinical inflammation could be one crucial factor (3,6). Thus far, no clear consensus exists on whether the association between OSA and certain inflammatory markers is causal or simply reflects confounding by other underlying factors, mainly excessive body fat. The vast majority of OSA patients are obese, and obesity, as such, is regarded as a chronic inflammatory condition (7,8). Moreover, very little is known about the role of inflammation in early stages of OSA and the effect of weight loss on inflammatory markers in patients with mild disease.

It was decided to evaluate the effectiveness of different treatment modalities on early phases of OSA, and to assess if there is an activation of the inflammatory system similar to the situation in more severe OSA disease. A prospective study was arranged to determine the impact of lifestyle intervention and weight loss on mild OSA and related low-grade inflammation.

2 Review of the literature

2.1 NORMAL SLEEP

2.1.1 Sleep

Sleep is more complex than it seems at first glance. It is "…a state of immobility with greatly reduced responsiveness, which can be distinguished from coma or anesthesia by its rapid reversibility" (9). The hypothalamus and brainstem are the areas which actively regulate sleep. Sleep is regulated also by homeostatic (pressure to sleep) and circadian systems (10). Sleep is divided into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep stages based on characteristics detected electroencephalographically, electrooculographically and electromyographically (11) (Figure 1). The NREM sleep is further divided into so called light sleep (stages 1-2) and into a deeper slow wave sleep (stage 3). The NREM sleep comprises the majority of total sleep time, the REM sleep accounts for only about 20-25%. In an adult, these two subtypes of sleep cyclically alternate during the night at about 90 minutes intervals. The REM sleep is characterized by rememberable dreams, high brain activity, decreased muscle tone, and increased heart rate and respiration. On the contrary, during NREM sleep, all functions in the human body slow down. Both REM and NREM sleep have a restorative function. However, the exact function of the sleep stages is not resolved yet (9,12). NREM sleep seems to have a role in energy conservation and nervous system recuperation. Rapid eye movement sleep has an important role in brain maturation and development early in life, and in emotional regulation throughout the whole life. It also causes periodic stimulation and local recuperation of the brain during this phase of sleep. Sleep probably has also an important role in memory consolidation (learning enhancement).

2.1.2 Normal ventilation process during sleep

The respiratory centre, which lies in the medulla oblongata and pons, receives and responds to chemical (O_2, CO_2 and hydrogen ions) and mechanical stimuli (from lungs and chest wall), and behavioral (brain cortex) information. The chemical information about the partial pressure of oxygen (pO_2) is sensed in the carotid and aortic bodies, and transmitted to the medulla via the ninth cranial nerve, the glossopharyngeal nerve. The partial pressure of CO_2 (pCO_2) is sensed by the carotid body and a medullar central chemoreceptor. Increases in pCO_2 and hydrogen ions mainly stimulate the respiratory center directly and this leads to a rapid increase in ventilation. The pO_2 has a stimulatory effect on ventilation usually only when pO_2 is less than 7.3 kPa (normal values 11-13 kPa). In addition to chemical control of breathing, the increased mechanical load of the respiratory system evokes changes in breathing by means of lung stretch receptors which send information to the medulla via the tenth cranial nerve, the vagus nerve. During wakefulness, the basic metabolic control mechanism can be overriden by voluntary and behavioral functions. The respiratory centre sends efferent impulses to respiratory muscles. During breathing, efferent motor output to the upper airway musculature stiffens the upper airway walls, thus preventing collapsing of this "tube" in response to the generation of subatmospheric intrapleural pressure generated by the respiratory muscles. (13)

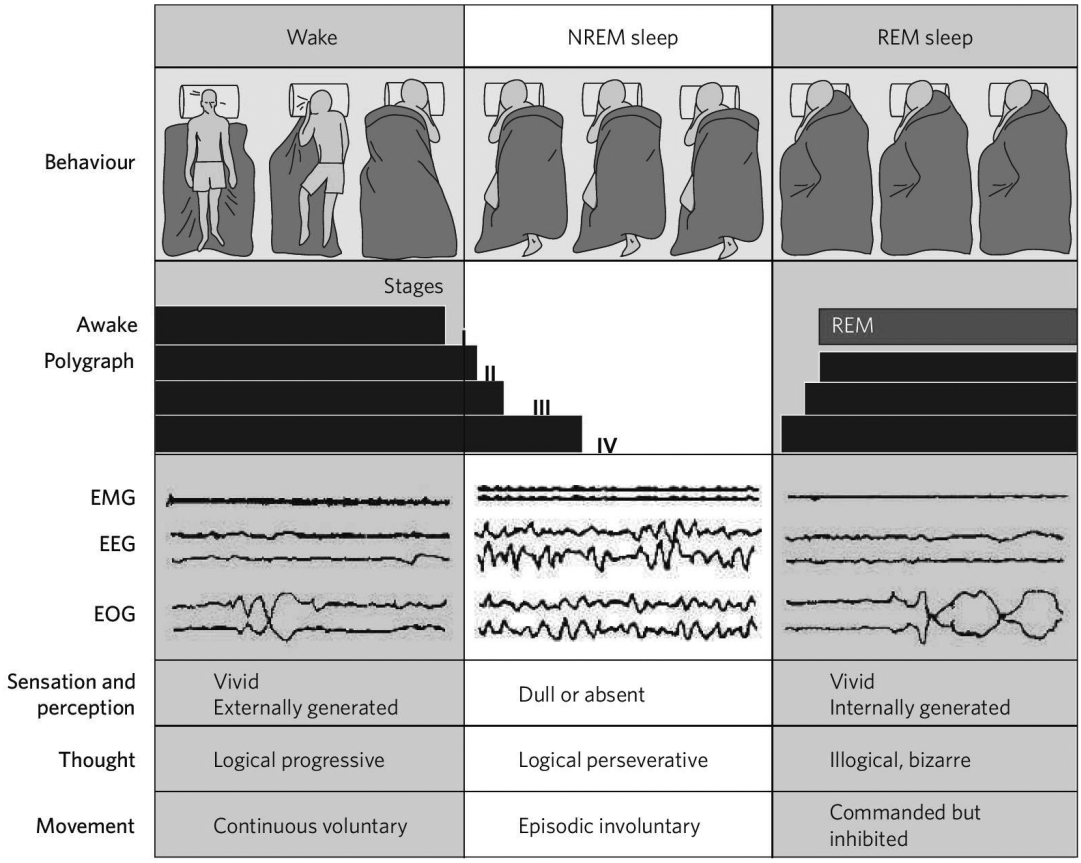


Figure 1. Behavioral states in humans. States of waking, non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM) have behavioral, polygraphic and psychological manifestations. In the row labelled behavior, changes in position can occur during waking and in concert with phase changes of the sleep cycle. Sample tracings of the three variables used to distinguish the state are shown: an electromyogram (EMG), an electroencephalogram (EEG) and electro-oculogram (EOG). The EMG tracings are highest during waking, intermediate during NREM sleep and lowest during REM sleep. The EEG and EOG are both activated during waking and inactivated during NREM sleep. Each sample shown is approximately 20 seconds long. The three bottom rows describe other subjective and objective state variables. Adapted by permission from Macmillan Publishers Ltd: Nature (Hobson J.A., 437(27):1254-1256), copyright 2005.

During sleep, ventilation is clearly dependent on the metabolic control system and the primary stimulus to ventilation during sleep is arterial pCO_2. During sleep, hypoventilation and CO_2 retention, increased airway resistance, apneas and suppressed reflexes, which protect airway patency and augment ventilatory drive in the face of increased mechanical loads, are normal findings (14). There is a decrease in the neural input from medullary inspiratory cells to phrenic and hypoglossal nerves resulting in decline in thoracic pumping and increased resistance of upper airways. The response to chemical stimuli decreases in brain. These result in CO_2 retention, and a reduced response to changes in CO_2 or O_2 in the body. On the other hand, reductions in CO_2 during sleep (because of excited ventilation) easily results in central apnea due to unmasking of hypocapnia-dependent threshold. Hypocapnia affects the motor input of the respiratory muscles thus predisposing to obstructive breathing episodes during sleep. During sleep, the increased mechanical load to ventilation (e.g. sighs) may lead to inhibition of inspiration due to the lung inflation reflex.

Sympathetic vasoconstriction is reduced during sleep and this may lead to narrowing of the upper airway due to vascular engorgement.

The abovementioned features are mainly occurring in NREM sleep during which breathing is under metabolic control due to the lack of cortical control (15). REM sleep results again in increased brain activity, and postural muscle atonia. These cause more collapse of the upper airway, increased dependency on diaphragmatic contraction and irregular breathing frequency, and variable and depressed response to chemical stimuli.

2.2 SLEEP APNEA

2.2.1 Historical aspects

In the literature, there are detailed descriptions of sleepy obese patients, who appear to have suffered from a sleep apnea syndrome and/or obesity-hypoventilation syndrome. The most famous of these sleep disordered patients in the literature is the fictional fat boy Joe in Dickens's book The Posthumous papers of the Pickwick club originally published in 1837 (16). Joe was a boy who consumed great quantities of food, had a red face, constantly fell asleep in any situation at any time of day and snored loudly. Since then, the association between obesity and breathing problems has been been widely acknowledged with ultimate description of the Pickwickian syndrome (first published in 1956) and obesity hypoventilation syndrome (first description in 1955) (17,18). The obesity-hypoventilation syndrome is the combination of obesity (body mass index [BMI] >30 kg/m2), daytime hypercapnia and nighttime hypoxemia (usually with OSA) which cannot be attributed to an alternative neuromuscular, mechanical or metabolic reason for the hypoventilation (too shallow or slow breathing) (19).

The first sleep recordings in Pickwickian patients were conducted in 1959 in Heidelberg, Germany, and in the next decade it was proposed that it was the disruption of sleep and not the CO_2-retention which was responsible for the daytime sleepiness in these patients (20). In addition, it was suspected that there might be obstruction of the airway due to retroposition of the tongue. At the end of 1960s this was verified by the concept that tracheostomy could eliminate apneic episodes (21). However, the cardinal symptoms and characteristics of OSA were not recognized until the 1970s. In 1981, new treatment tools namely continuous positive airway pressure (CPAP) and uvulopalatopharyngoplasty (UPPP) were introduced (22,23). Since then, the medical knowledge and publications of the disease, of its co-morbidities and treatment have increased widely and public awareness continues to grow.

2.2.2 Classification

Sleep apnea is a disease characterized by episodes of airflow cessation (apnea) and airflow reduction (hypopnea) during sleep (24). These episodes occur repeatedly throughout the period of sleep. The severity of sleep apnea is defined by the number of apneas plus hypopneas per hour of documented sleep [apnea-hypopnea index (AHI)]. Apnea is a ≥90% drop in the airflow for at least 10 seconds (11). There are several definitions of hypopnea and thus the criteria used has an effect on resultant AHI (25). At the moment, the criteria for a hypopnea in the American Association of Sleep Medicine scoring manual is either 30% or greater reduction in airflow for 10 seconds associated with at least 4% drop in O_2 saturation, or drop of ≥50% with ≥3% desaturation for 10 seconds.

Sleep apnea is divided into two major subtypes (11,24). In *central sleep apnea*, there is no inspiratory effort during the absent airflow. This generally results from instability of respiratory control, mainly a disturbance in the metabolic control system of ventilation, especially the CO_2 dependent (26). In *obstructive sleep apnea*, the efforts to inspire are present, but the airflow is blocked in the upper airways. If there is an initial central apnea

followed by an obstructive component, the entity is called *mixed type sleep apnea*. OSA is by far the most common type of sleep apnea. If a patient with OSA has also symptoms, the condition is called obstructive sleep apnea syndrome (OSAS). In one study, OSAS comprised 84%, mixed sleep apnea 15% and central sleep apnea a mere 0.4% all patients seeking help from the sleep clinic during one month (27).

OSAS is a condition that must be classified on a physiological basis [amount of apneas and hypopneas, and arterial oxyhemoglobin saturation as measured by pulse oximeter (SaO_2) during sleep] and on an evaluation of symptoms, especially sleepiness (28,29). Table 1 provides the diagnostic criteria for OSAS. The mildest form of OSAS is defined by AHI 5-14.9 events per hour, moderate sleep apnea as 15-29.9 events/hour, and severe as respiratory events of 30 or more events per hour (30). If the patient has disabling daytime sleepiness, OSAS falls into a higher category. Moreover, SaO_2 should be ≥85% and mean SaO_2 ≥90% in mild degree sleep apnea. In clinical practice, these criteria are further modified by age-, gender- and individual-related changes in these parameters, clinical status and co-morbidities.

Partial upper airway obstruction, which on the other hand is related to term upper airway resistance syndrome (UARS), is closely related to OSA. This entity is characterized by increased upper airway resistance with inspiratory flow limitation but without apneas, hypopneas or desaturation (31,32). However, these episodes of partial airway obstruction are common in both genders, especially in women, and are frequently associated with younger age and symptoms similar to OSA (33,34).

Table 1. The diagnostic criteria for adult obstructive sleep apnea syndrome (OSAS) (24)

Minimal criteria for OSAS: A, B and D or C and D

A. At least one of the following symptoms
Unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, or insomnia
Waking with breath holding, gasping or choking
Loud snoring and/or breathing interruptions during sleep
B. Polysomnographic monitoring demonstrates
Five or more apneas, hypopneas or respiratory effort related arousals per hour of sleep
Respiratory effort during these respiratory events
C. Polysomnographic monitoring demonstrates
Fifteen or more apneas, hypopneas or respiratory effort related arousals per hour of sleep
Respiratory effort during these respiratory events.
D. The disorder is not explained by another sleep disorder, medical or neurological disorder, medication or substance use.

2.2.3 Diagnostic Methods

Diagnosis and treatment decisions of OSAS are based on symptoms and signs, clinical findings, sleep recording and sometimes imaging. Under-recognition and under-diagnosis of this disorder are very common: it has been estimated that up to 90% of OSA cases remain undetected and even fewer receive treatment for OSA (35-37). Especially women and those with low BMI or with mild OSA are at risk of remaining undiagnosed and untreated.

Symptoms

Subjects with OSA experience both nocturnal and daytime symptoms (24,29). Nocturnal symptoms include snoring, breathing pauses, restlessness, choking, nocturia, heart burn and sleep fragmentation. Upon awakening, the mouth may be dry, headache ensues and the individual feels unrefreshed. Snoring, which according to Merriam-Webster Dictionary means "to breathe during sleep with a rough hoarse noise due to vibration of the soft palate", is the most obvious and frequent symptom of OSA occurring in almost all OSA patients (38). Habitual snorers are more likely to have AHI scores 15 or higher (39), and snoring intensity correlates with the severity of OSA (40). Snoring is socially disturbing and a common cause for OSA patients to sleep in separate bedrooms from their partners.

During daytime, OSA patients may experience excessive daytime sleepiness (EDS) (24,29). This cardinal symptom of OSAS may reflect the number of apneas: the higher AHI, the sleepier the subject is during daytime (41). However, this may not always be the case. Moreover, even simple snoring and mild OSA associate with daytime sleepiness as compared to the non-OSA population (39,42). The problem with EDS, and other daytime symptoms is that they may be contributed to many other conditions from depression to the arrival of a new baby.

In addition, inefficiency or deficits in cognitive and behavioural functions, in general health status and quality of life are found in sleep apnea patients (43-47). Usually the severity of OSA has an effect on these functions: patients with mild disease do not differ from normal controls (with the exception of quality of life) but those with more severe disease do display differences. The possible mechanisms leading to these deficits include daytime sleepiness, comorbid diseases, as well as sleep disruption due to arousals and hypoxemia (45,48).

Many screening tools, i.e. questionnaires, have been developed for detecting the abovementioned symptoms in adults. These can be time-consuming, but do offer the clinician a compact package of information on symptoms and quality of life. They are also a good tool for scientific purposes. The most widely used questionnaire on daytime sleepiness is the Epworth Sleepiness Scale (ESS) (49). The objective tests of sleepiness and vigilance – e.g. Multiple Sleep Latency Test (50) and Oxford Sleep Resistance test (51) – are time consuming and not widely utilized in the diagnosis of OSA. There are also self-report tools, such as the Berlin questionnaire and Snore Outcomes Survey, which focus on a set of symptoms and clinical features associated with sleep apnea (52,53).

Clinical findings

Even if there is a consensus that upper airway (UA) narrowing is a risk for OSA, the scientific evidence of the clinical findings predicting the presence of OSA have been found to be unreliable (54). However, it has been shown that BMI and neck circumference significantly correlate with AHI (55). Since the accuracy of BMI as a descriptor of obesity is limited (56,57), waist circumference or total body fat percentage may well be better measures, especially when estimating the risk for OSA related co-morbidities. The presence of skeletal abnormalities (e.g. high arched palate and retropositioned mandible) and voluminous soft tissues (large tongue and tonsils, prominent palate or uvula, and voluminous pharyngeal walls) could also be evaluated when searching for candidates for sleep recording (54,58). Alleviation of nasal obstruction may improve sleep quality and ease the use of CPAP (59,60). Thus, clinical examination is important to support therapeutic strategies and to indicate a need for a specific treatment, for example septoplasty or tonsillectomy.

None of symptoms or signs alone is sensitive or specific enough for detecting OSA, and there is a large spread of "typical" OSA findings within the general population. For example, even though habitual snorers are more likely to have OSA, snoring alone has a poor predictive value for the high prevalence of snoring in the general population (37,39,61-

63). On the other hand, in subjects with no sleep related symptoms, OSA can be found in about 3% of the subjects. However, simultaneous snoring, EDS and observed apneas combined with well known risk factors – male sex, age and obesity - should give rise to the suspicion of OSA. The sensitivity and specificity of the physician's subjective impression of the presence of OSA in a patient is about 60% (64).

Sleep recording

Thus, on the basis of symptoms and clinical findings, the presence of OSA may be suspected but the diagnosis is always confirmed by overnight recording during which sleep, respiratory effort, cardiovascular signals and muscle movement – or at least some of these parameters – are monitored. Full overnight polysomnography (PSG) recording in a sleep laboratory is the gold standard diagnostic tool for patients with suspected sleep apnea (30,65). Polysomnography includes measurements of at least oronasal airflow, chest and abdominal movements, electroencephalography, electro-oculography, electromyography, electrocardiography, oxyhemoglobin saturation, body position and movement, and behavior (65). Due to the high cost, demands on facilities and limited availability of full PSG, portable monitoring has become the most common diagnostic tool for OSA in Finland. These machines range from un-attended full PSG to single channel recordings. However, a practicable portable monitor should, at minimum, record airflow, respiratory effort and blood oxygenation (30). There are limitations associated with these portable monitors (66). They are recommended for patients with a high probability of OSA who do not have co-morbidities or any probable other sleep disorder. Moreover, assistance with sensors is needed. Finally, the analysis of raw data should be performed according to current standards by a trained person who is aware of the methodological limitations.

2.2.4 Epidemiology

Prevalence

Population-based studies have found that in working age population, the prevalence of OSA is high, 4% of men and 2% of women have at least mild OSA with daytime symptoms (39,67-70) The numbers are much higher if the daytime symptoms are ignored and only the AHIs are considered: then the prevalences are 24-26% for men and 9-28% for women (39,63). In Finland, there are approximately 150 000 OSA patients, of whom 85 000 have a mild, 50 000 a moderate and 15 000 a severe form of the disease (71).

Incidence

There are very few data on the incidence of sleep disordered breathing. Tishler et al concluded that the 5-year incidence is about 10% for AHI ≥15 and 16% for AHI≥10 (72). Newman et all reported an incidence of moderate sleep apnea (AHI >15/h) as 11% for men and five percent for women during a 5 year follow-up (73).

Natural evolution of OSA

Several studies have evaluated the course of OSA over time, but the data are conflicting. In the early 80's, a proposition of an orderly progression from snoring to OSA was published (74). Since then, many studies have reported a progression in OSA over time in those patients who initially have had only mild-to-moderate or no disease at all (2,43,73,75-81). However, there are also a number of clinical longitudinal trials which state that AHI does not increase over time in untreated OSA patients (82-86).

The predictors for changes in sleep-disordered breathing are not fully clear at present (2,72,73,77,80-82,84-86). It seems possible that increase in sleep related respiratory disturbance indices could occur primarily before old age, if it is going to happen at all. On the other hand, OSA in elderly people is likely to be different from the disorder in younger subjects: changes in bony structures, in neural- and neuromuscular control, increased diseases affecting breathing control, and changes in fat deposition probably influence the OSA likelihood (87). The deteriorating trend of OSA has been less clear in patients with high AHI at baseline. Moreover, change in body weight has been a significant predictor for AHI change (39,61,63,67,69,70,72,73,80,88). For example, Peppard et al. have reported that patients with mild OSAS have a 6-fold increase in risk for developing more severe disease if they gain 10% of their body weight. On the other hand, there are many smaller and older studies, which have not found any correlation between changes in body size and changes in sleep disordered breathing (76-78,83,86). Another possible explanation for disease progression has been upper airway trauma, which is caused by repeated apneas and snoring, see later in chapter "Pathogenesis".

2.2.5 Risk factors

Some degree of UA narrowing at the onset of sleep is a normal phenomenon (89), but various factors may conspire to accentuate it, such as obesity, soft tissue (e.g. tonsils) enlargement and craniofacial abnormalities. The extent of this narrowing varies from individual to individual, and from night to night, to some extent. However, it is well established that occluding features in the hard and soft tissues of the UA are risk factors for OSA.

Obesity

Obesity is an important risk factor for OSA, and it is increasingly prevalent around the world: 72% of adult men and 64% of women are overweight or obese in the USA (BMI ≥25 kg/m^2), and the corresponding figures for Finland are 66% for men and 53% for women (39,67,90,91). Some 60-90% of adults with OSA are overweight, and the relative risk for OSA in obesity is ≥10. Accordingly, the prevalence of OSA among obese patients has been reported to be as high as 30-98% (7). As mentioned above, it seems that weight gain not only increases the chance of developing OSA but it can also worsen the severity of a previously milder disease. Moreover, OSA may predispose to obesity. The possible underlying factors for this may include increased appetite caused by resistance to leptin and insulin (two hormones which inhibit eating and thus regulate body weight) and increased concentrations of ghrelin (appetite increasing hormone), all of which have been described in sleep apneics (7).

The location of fat may also be an important factor: excess fat have been reposted around the UA in both obese and non-obese patients with OSA (92), and neck circumference is a predictor of night-time desaturations (93). The total body fat distribution is also a factor with the central/visceral distribution appearing hazardous (61,94). Exercise has a protective effect against developing OSA (95).

Anatomical risk factors

Even though obesity is very common among sleep apnea patients, there are also a number of lean people who suffer from OSA and, on the other hand, obese subjects with no OSA. Why do some people develop collapse of UA sufficient to lead to apneas and others with similar body sizes do not? One factor may be an anatomically small pharynx which seems to predispose to upper airway collapse (7,96-98) (Figure 2).

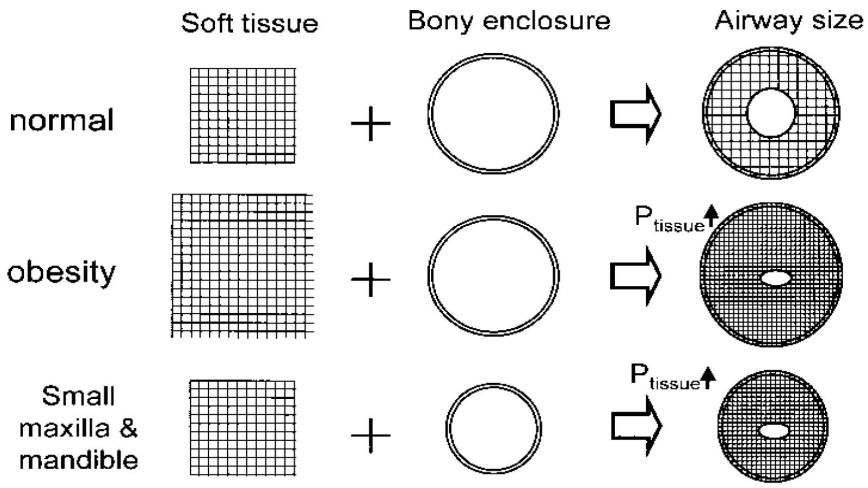


Figure 2. Schematic explanations for the mechanical model of the pharyngeal airway – combination of the bony framework and amount of soft tissue. Reprinted with permission from the American Thoracic Society. Copyright © American Thoracic Society. Watanabe, Isono, Takana et al, 2002: Contribution of body habitus and craniofacial characteristics to segmental closing pressures of the passive pharynx in patients with sleep-disordered breathing. American Journal of Respiratory and Critical Care Medicine, Vol 165(2), pp 260-265. Official Journal of the American Thoracic Society.

The volume of UA soft tissue structures is enlarged in patients with sleep apnea (e.g. large tongue, tonsillar or adenoidal hypertrophy and volume of lateral walls of the pharynx). This is attributable not only to excess fat but also to inherited factors (99). Blood engorgement and edema around the UA lumen may also play a role. The causal factor for UA obstruction may also be in the craniofacial morphology i.e. bony framework of UAs (100-103). Malocclusal traits as an indicator for mismatch between jaws, and low hyoid bone position have been shown to predispose to OSA. Moreover, in obese individuals, the risk of airway collapse is further elevated due to smaller airway cross-sectional area (larger soft tissues surrounding the upper airway, reduced upper airway size secondary to mass effect of the large abdomen, and decreased chest wall and tracheal traction) and a change in its shape to becoming more oval (the more anterior-posterior orientation of the long axis of the pharynx) (7).

Sex

The prevalence of OSA in women is less than in men, male-female ratio being about 3:1 (39,63,67,69,70). Pharyngeal anatomy may be one explanation: men have a longer airway length and a larger but more collapsible pharyngeal airway (104). The difference in prevalence is particularly clear when comparing premenopausal women to men, since in elderly women the prevalence of OSA increases (34,67,72,105). Female hormones augment pharyngeal muscle activity (106) and after menopause, hormone replacement therapy can have a protective effect against the development of OSA (67,107).

Age

The prevalence of sleep apnea increases with age (39,63,67,69,70,88,105). There is evidence that this trend declines after approximately 65 years of age. The peak prevalence is at about

55 years for men and about 10 years later for women. Weight loss with age or the underrepresentation of older age groups in the OSA study population may also be two reasons for this finding. On the other hand, the severity of OSAS may be milder in the elderly, at least in men.

Other risk factors

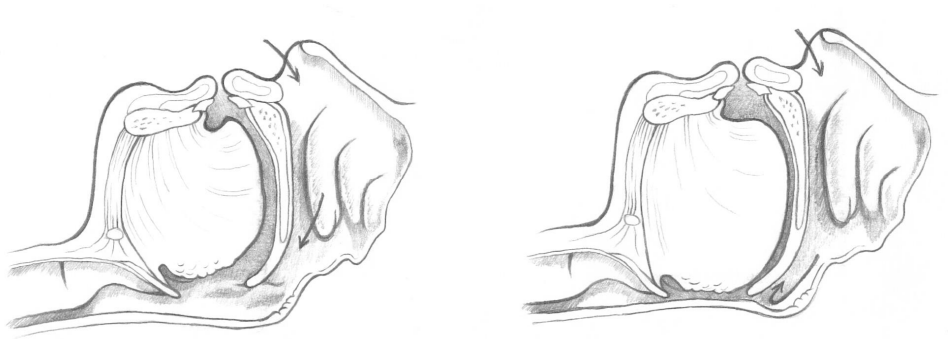
Alcohol ingestion reduces the activity of genioglossus and other dilator muscles that maintain the patency of upper airway (108,109). In addition, the elevation of arousal threshold and the response to chemical control of breathing may be factors contributing to the increased risk of OSA in many conditions. For example endocrinological abnormalities (e.g. hypothyreosis and polycystic ovarios) may increase apneic events (110,111). There are also studies showing sedating medications and smoking to be risk factors for OSA (112-114).

Heritability

It has been claimed that OSA aggregates in families (115). The risk of OSA may be 2-4-fold greater in relatives of OSA subjects when compared to controls and about 40% of AHI variance may be explained by familial factors. Symptoms of OSA and AHI levels aggregate in families independent of other important risk factors (e.g. BMI), and family-based interactions of physiological and anatomical abnormalities may partly account for this association. Both upper airway soft tissue and bony framework characteristics have been demonstrated to aggregate in families (99,116,117). Similarly, there is evidence, mainly from animal studies, that genetic factors can influence the expression (e.g. ventilatory control patterns) and sequalae of OSA (118). However, the genetic background of OSA is largely unknown at present.

2.2.6 Pathogenesis

The basic mechanism responsible for apnea-hypopnea events is the collapse of UA which occurs repeatedly during sleep (Figure 3) (96). These episodes lead to hypoxia and hypercapnia, which cause a stress reaction in the body, and increased ventilatory effort against an occluded airway. Ultimately, arousal from sleep occurs, which restores the airway and ventilation. Then the individual returns to sleep, but the cycle begins again. These arousals lead to sleep fragmentation, they cause changes in sleep architecture and thus result in lighter and non-restorative sleep (119,120).



A. B.

Figure 3. Normal (A) and obstructed (B) upper airway during sleep

The upper airways consist of the nose, pharynx, larynx and extrathoracic trachea, of which the pharynx is the collapsible segment. The cross-sectional area of the UA is determined not only by hereditary and acquired factors but also by static (surface adhesive forces, neck and jaw posture, tracheal tug and gravity) and dynamic forces (upstream resistance, Bernouli effect and dynamic compliance). These dynamic counteracting forces include the activity of the upper airway muscles which stiffen and dilate the airway, the negative intraluminal pressure caused by thoracic inspiratory muscles, and transmural pressure (difference between intraluminal pressure and pressure of surrounding tissues) (98). The muscle activity is modulated by proprioceptive and chemical feedback: the activity of UA muscles is normally increased as the negative pressure in the lumen increases, and by hypoxia or hypercapnia (121-124).

At sleep onset, the neural output to UA muscles and thence the muscle activity falls and the airway lumen becomes prone to suffer occlusion (125). This instability of respiratory control (loss of cortical control and waking neural drive and rise of stimulating metabolic threshold) is one of the three pathophysiological characteristics in OSA (98). It has been shown that local anaesthesia (or maybe afferent denervation in OSA) of pharynx and repetitive intermittent hypoxia (such as in OSA) can lead to suppression of these proprioceptive and chemical dependent reflexes, which partly guarantee the patency of the UA. The other two mechanisms causing the apneas and hypopneas are failure to stabilize the UA in an appropriate manner (see the previous paragraph) and disorders of the respiratory pumps. Interestingly, there is an increased dilator muscle activation to keep the pharynx open in OSA patients during awake periods but this is attenuated at the initiation of sleep (126). Moreover, airway collapses are opposed by hyperactivation of pharyngeal dilator muscles. During normal sleep or general anaesthesia, the OSA patient's pharynx collapses without negative pressure in contrast to normal controls who need negative pressure (suction) for this to happen (127). Usually this UA narrowing is multilevel, the retropalatal region being the most common site to become obstructed (125,128).

Due to swings in intraluminal pharyngeal pressure, there are tissue vibration and violent eccentric muscle contractions against an occluded airway and thus UA tissues are subjected to mechanical trauma. The increased activity level may lead to adaptive changes in both structure and function of muscles (129). These adaptive changes may crate a vicious cycle, promoting further compromise of the upper airway via more occluding soft tissues, increased injury and reparative attempts (blood engorgement, edema, fibrosis, inflammation). These changes are more pronounced in severe degree OSA (130). Moreover, inflammatory cells and pro-inflammatory mediators may provoke muscle weakness (131,132). If this affects also the pharyngeal muscles, then inflammation would predispose to airway collapse. Denervation and inflammation has been found both in UA mucosa and muscle (133). This harmful effect of inflammation (along with mechanical load) has been proposed as a mechanism for increased risk of OSA in obese individuals: obesity is an inflammatory condition (134). Increasing age predisposes the individual to pharyngeal collapse (135).

2.2.7 Treatment

Treatment of OSA is aimed at reducing the collapsibility of UA during sleep by overcoming the imbalance of forces acting on the UA. In general, the treatment modalities are intended to a) raise the pharyngeal pressure above the closing pressure, b) decrease the closing pressure or c) increase the upper airway muscle activity (128). The methods include lifestyle modification, continuous positive airway pressure (CPAP), oral appliances (OAs) and surgical options. The choice between the different modalities of treatment depends on the patient, the predisposing factors for OSA and the severity of the disease. Multiple interventions may be appropriate in some patients.

Lifestyle modification

Sleep hygiene and behavior which worsen OSA should be checked in every OSA patient, and recommendations how to improve these should be offered. For example, sleep deprivation and sleep fragmentation (24/7 society, young children at home), inebriation, smoking and use of sedatives may increase apnoeic episodes (43,112,119,136). For patients with supine position dependent OSA, positional therapy (e.g. a backpack with a ball inside to prevent supine sleeping) can provide some help in terms of improving AHI, sleep quality and daytime symptoms (137-139). However, CPAP is superior to positional therapy in decreasing AHI and desaturation level (138). There are no reports on the long term efficacy of positional treatment or on its impact on co-morbidities. This treatment modality could be considered as benefitting those mild degree OSA patients who have positional disease.

There have been some publications about how to strengthen upper airway muscles in order to decrease apneic episodes during sleep (140). The methods have included electrical neurostimulation, didgeridoo playing and oropharyngeal exercises. These may have some benefit but the evidence is very vaque.

Since obesity is the major predisposing factor for OSA, it is tempting to assume that weight loss should be recommended for all overweight patients with OSA. In general, the first line therapy for overweight and obesity is behavioral: lifestyle intervention with weight reduction (141). This can be augmented by special diets, medication or bariatric surgery. The beneficial effects of dietary weight loss on OSA, sleep architecture and daytime somnolence have been known for decades (142). However, only three well executed studies have assessed the impact of a behavioral method to achieve weight loss, the study by Tuomilehto et al. being the one which resulted in the present thesis (143-147). In the study populations of overweight or obese OSA patients, these papers have indicated that intensive supervised lifestyle intervention is more effective than general lifestyle and diet counselling in terms of treatment success. In the mild sleep apneics in the study of Tuomilehto et al., two thirds of patients in the intervention group were objectively cured of OSA, i.e. AHI<5, the figure for control group being only one in three. In the report of Foster and co-workers, remission of OSA was three times more common in the intensive lifestyle intervention group compared to the control group. Johansson et al. reported that at one year, 10 % of mostly mild-to-moderate degree OSA patients had been cured and 48% no longer needed CPAP. All of the abovementioned studies support the contention that the greater the weight loss, the greater the reduction of AHI. For example, in the Swedish report it was found that a 10 kg weight loss was associated with an average decrease of five events/hour in the AHI. This is confirmation of earlier studies, e.g. the meta-analysis by Greenburg and co-workers in which a mean 17.9 kg/m^2 decrease in BMI achieved by bariatric surgery resulted in mean AHI decrease by 71 % (43,148). However, weight loss does not result in a decline in AHI to the same proportion that weight gain elevates AHI: 10% weight loss/26% fall in AHI versus 10% weight gain/32% increase in AHI (80). Maintaining the achieved weight after dietary counselled weight loss is very challenging (149). However, in the studies by Tuomilehto, Foster and Johansson, the improvements in AHI were still sustained at 1-2 year(s). This beneficial effect of lifestyle intervention on OSA may persist in spite of weight gain (Figure 4) (146). There are recent findings to suggest that in patients with OSA, about 50% of the overall response to weight loss may be related to a reduction in fat and in passive mechanical properties (150). The remaining half seems to be attributable to concomitant improvement in neuromuscular properties.

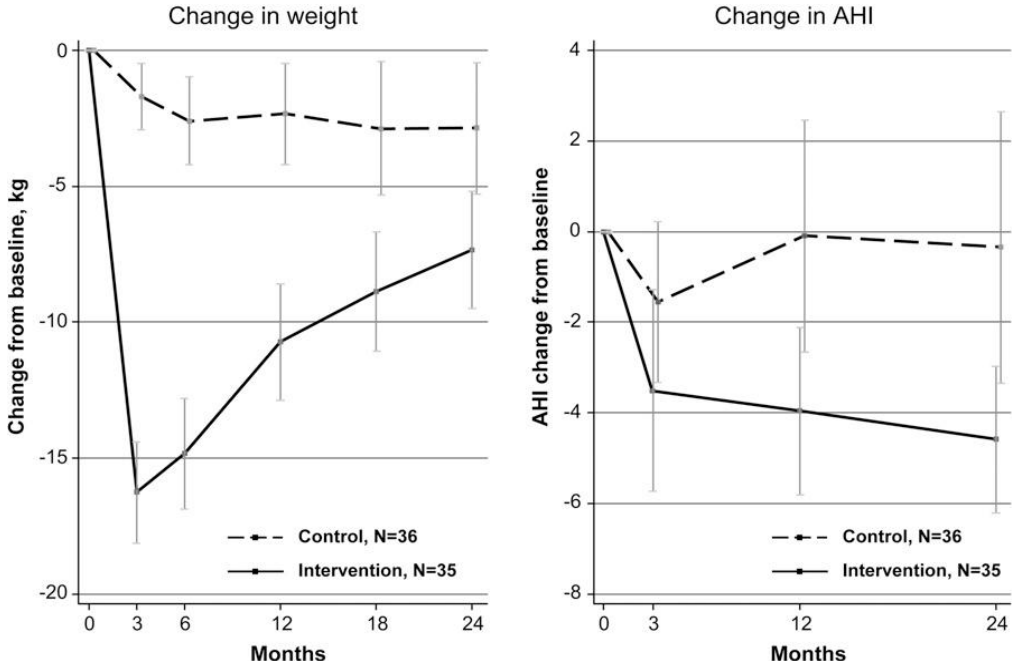


Figure 4. Mean changes in weight and in the apnea-hypopnea index (AHI) achieved by lifestyle and dietary intervention compared with usual weight loss attempt over the 24-mo follow-up period. A study among overweight or obese patients with mild obstructive sleep apnea. Vertical bars indicate 95% CIs. Reprinted with permission by American Society of Nutrition. Tuomilehto et al., The American Journal of Clinical Nutrition 2010;92(4):688-96.

While weight loss can lead to substancial decreases in OSA severity, it often does not eliminate the disease altogether (43). Particularly, this is evident among patients with severe degree of OSA (144,148). Thus it is important to remember to perform the follow-up sleep study, and offer alternative treatment options when needed. However, CPAP treatment does not improve the results of weight loss program which supports the use of weight reduction as an initial treatment for obese patients with mild disease, who are motivated to lose weight (151). There is some evidence that OSA related daytime sleepiness decreases and quality of life increases by lifestyle intervention (143,145,147).

CPAP

Continuous positive airway pressure is the cornerstone of OSA treatment. It prevents UA obstruction by delivering a stream of compressed air (produced by a flow generator) via a hose to an interface (usually a nose mask) and this air pressure acts as a pneumatic splint to prevent collapse of the pharyngeal airway (22). This treatment modality reduces sleepiness and improves quality of life (152). Treatment with positive airway pressure reverses the negative cardiovascular consequences of OSA: it improves control of hypertension (152), reduces the risk of fatal and nonfatal cardiovascular events (4), reduces heart rate (153) and night-time bradyarrhythmias (154), improves vascular dysfunction (155), and early signs of atherosclerosis (156), and in patients with heart failure, it improves cardiac systolic function (157). The evidence for the effectiveness of the CPAP is stronger in symptomatic and/or moderate-to-severe AHI (152,158). In patients with mild-to-moderate sleep apnea, CPAP has improved snoring and subjective daytime sleepiness (159,160). However, regardless of the disease degree, The American Association of Sleep Medicine guideline states that CPAP is the treatment of choice for OSA (30). CPAP is long-term treatment that requires compliance. However, CPAP compliance is not optimal (65-80%), and use per night can be

suboptimal (161). Side-effects of this treatment option include leaks, skin problems, dry upper airway, stuffy nose, rhinorrhea, claustrophobia and inconvenience with CPAP (162). Thence, alternative treatment modalities have been developed.

Oral appliances

Madibular advancement devices increase the phayngeal space by protruding the mandible and advancing tongue. They increase airway size in the retroglossal region as well as in the retropalatal area, predominantly in the lateral dimension (163,164). A Cochrane report recommended oral appliance (OA) therapy for patients with mild symptomatic OSA, and those patients who are unwilling or unable to tolerate CPAP therapy (165). Even though this treatment modality alleviates symptoms and respiratory disturbances, CPAP is more effective in improving respiratory indices (165). The authors also concluded that after 1-year, OA is as good as corrective upper airway surgery in improving symptoms, and better than surgery at reducing AHI. The side-effects of OAs include jaw and teeth discomfort, salivation and occasionally joint discomfort.

Surgery

Surgery for OSA aims to relieve obstruction by increasing the size of the airway, bypassing the obstruction or removing an obstructing lesion. There are three major anatomic regions of potential UA obstruction: nose, palate and base of tongue (166). Surgery can involve soft tissues (soft palate, tonsils, tongue base), skeletal framework or it can consist of tracheostomy. In children, adenotonsilectomy is the first line treatment and highly effective for small and/or normal weight children (167,168).

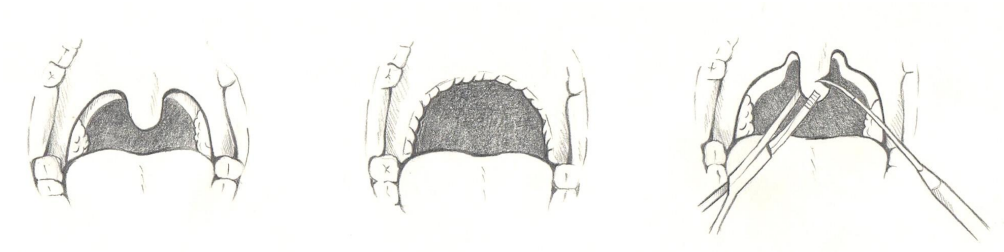
At present, indications for surgery in adults include OSA which is not better treatable by other options or there has been a failure with other options, and there is an anatomic airway abnormality. Contraindications include morbid obesity, severe unstable illness, older age and unrealistic expectations of outcome (166). The fact that the majority of OSA patients have multilevel obstruction of UA (125,128) means that the curing effect of a single operation is highly questionable. There have been suggestions that multilevel surgery should be performed when needed (169). However, the scientific evidence for this claim is based mainly on single procedures, and current knowledge from randomised controlled studies does not support the widespread use of surgery in adults with OSA (170). However, the treatment response may vary from patient to patient depending on the obstruction, and carefully selected patients may benefit from a procedure. In the United States of America, less than 0.2% of the adults with OSA undergo surgery for this disease (171). Isolated palate surgery composes majority of all these procedures. In general, the beneficial effect of surgical treatment seems to vanish with time. The impact of surgery on cardiovascular outcomes is not known. There is some evidence that surgery may decrease CRP levels independent of bodyweight in adults with OSA (172).

Tracheostomy. Since the dawn of OSA surgery, tracheostomy has been the only definitely curable operative treatment (173). This bypasses the UA and thus eliminates the obstructive episodes during night. However, it is not widely used nowadays because of its invalidizing nature.

Nasal surgery. Isolated nasal surgery (septoplasty, polypectomy, conchal operation) for OSA has a low success rate, but it may have an impact on sleep quality, daytime sleepiness, and it may help those individuals with CPAP (174,175). However, a patent nasal airway is important for minimizing mouth breathing, because an open mouth worsens upper airway obstruction by forcing the lower jaw to rotate downward and backward, pushing the tongue into the posterior pharyngeal space (176).

Surgery of the soft tissues. Uvulopalatopharyngoplasty or an equivalent palatal procedure has been introduced to stiffen the soft palate and thus open the retropalatal region (Figure

5). However, the success rate of UPPP has been reported to be as low as 40-50%, especially in those patients with UA narrowing elsewhere than only in the retropalatal area (177). Thus, persistent upper airway narrowing in the nonresected portion is the probable cause for treatment failure. Soft palate radiofrequency ablation (RFA) is well tolerated but not curative for sleep apnea (166,178,179). When administered also into the tongue base, its effectiveness may be improved. The genioglossus advancement, tongue base surgery and hyoid suspension for hypopharyngeal obstruction have now lost their attractiveness due to poor long-term results (180).



A. B. C.

Figure 5. Examples of pharyngeal surgery. A. Normal pharynx, B. uvulopalatopharyngoplasty (UPPP) and C. uvulopalatoplasty.

Surgery of the jaws. Maxillomandibular advancement has been found to be the most effective surgical option after tracheostomy for OSA, and sometimes it can be as effective as CPAP for severe OSA in terms of AHI and ESS (181,182).

Bariatric surgery. If one considers all levels of obesity, then it seems that the numbers of individuals with severe obesity (BMI >40 kg/m2) are increasing most rapidly (183). Since the conventional lifestyle and weight reduction interventions have often proven to be ineffective in long-term follow-up in this group, the number of patients undergoing bariatric surgery is increasing rapidly. It has favorable effects not only on obesity related metabolic and cardiovascular diseases and mortality but also on symptoms related to OSA (184-186). In OSA patients who have undergone bariatric surgery, the disease was cured or alleviated in 85% of cases. The basic concept of bariatric surgery is to decrease the amount of energy ingested daily by performing an operation which either makes the stomach smaller (restrictive surgery) or results in malabsorption by bypassing part of the absorptive alimentary tract. A combination of these two procedures, laparoscopic gastric bypass, is the most common type performed in Finland nowadays (141).

Drug therapy

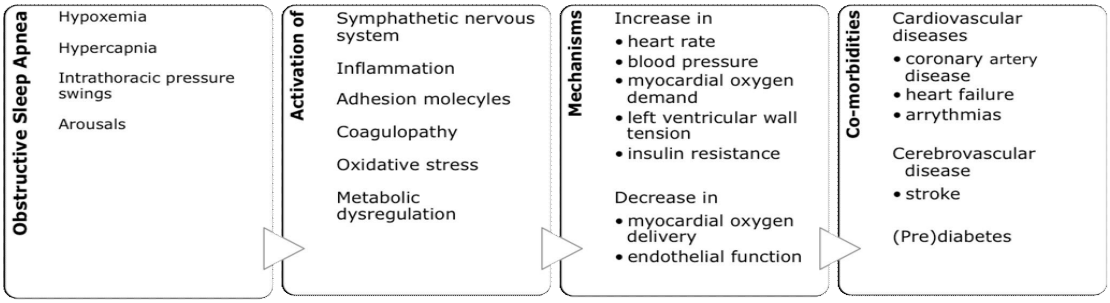
A variety of drug therapies has been tried to treat OSAS. Regimens which increase UA muscle tone, ventilatory drive or cholinergic tone during sleep have been investigated in small studies, as well as those which decrease airway resistance, UA surface tension or proportion of REM sleep. There is no convincing evidence that any drug therapy is successful (187). For those patients who suffer persistent daytime sleepiness on CPAP treatment and no co-existing remediable cause is identified, a safe wake-promoting agent, modafinil, can be considered (188).

Whatever the treatment, a follow-up PSG or unattended cardiorespiratory recording is routinely indicated to acertain the effect of the method, and whether some other therapy is still needed.

2.2.8 OSA and related conditions

OSA results in disturbances of two major homeostatic systems – oxygenation and sleep – and thus it is not surprise that OSA is linked to many common diseases and these have significance at the level of individual and from a public health perspective. The close association of obesity and OSA complicates the differentiation of these effects, i.e. whether the co-morbid condition is secondary to OSA or to some other risk factor(s). The mechanisms that may lead to increased risk of cardiovascular, cerebrovascular and metabolic disorders among OSA patients are presented in Figure 6.

Figure 6. Possible mechanisms leading to increased risk of cardiovascular diseases in obstructive sleep apnea



Cardiovascular diseases

Cardiovascular diseases (CVD) are highly prevalent, associated with excessive morbidity and mortality (40% of all deaths in Finland in 2009 and 34% in the USA in 2007), and responsible for huge economic costs (189,190). The Finns are among the highest risk population for coronary artery disease [CAD] in Europe (191). In particular, severe OSA in young and middle-aged men is associated with a risk of CVD (CAD, stroke and heart failure) (192,193), and CPAP therapy had reduced cardiovascular events, even if it is only the mild form of the disease, if the patients have other risk factors (4,194).

OSA presents autonomic, hemodynamic and respiratory challenges to the heart and vascular system. These challenges are accentuated in a diseased myocardium. Especially hypoxemia, arousals from sleep and intrathoracic pressure swings are responsible for cardiovascular consequences (195). Moreover, many OSA patients have additional traditional risk factors for CVD, e.g. obesity and high cholesterol levels.

Pathophysiological mechanisms (196,197). There are several pathophysiologial mechanisms which mediate the harmful effects of hypoxemia: directly i.e. the decreased myocardial oxygen delivery may result in ischemia; indirectly i.e. hypoxia increases expression of inflammatory mediators and genes which code for vasoconstrictive and platelet aggregating substances, and suppress the production of vasodilatators and deaggregators. Re-oxygenation leads to the production of free oxygen radicals (oxidative stress). These mechanisms may evoke endothelial dysfunction, vascular inflammation and remodelling.

Hypoxia, arousals and changes in ventilation may increase sympathetic activity. During normal NREM sleep sympathetic tone declines and parasympathetic tone rises, and vice versa during REM sleep. During apneic episodes, hypoxia leads to a sudden reduction in sympathetic tone, which then surges up in parallel with the rise in blood pressure and heart rate. In sleep apnea, with recurrent apnea, overall sympathetic activity tends to increase. The adverse effects of increased sympathetic activity include elevated ventricular load, myocardial hypertrophy, tachycardia and arrhythmias.

The increased intrathoracic pressure during apneas results in an increase in the transmural pressure and left ventricular stress. Many of these mechanisms can be found to persist during wakefulness: sympathetic activation, reduced heart rate variability, release of vasoconstrictive agents and systemic inflammation. Vascular wall (endothelial) damage and its dysfunction is responsible for this increased risk of atherosclerosis in OSA patients. The endothelial damage is believed to be a result of hypoxemia/hyperoxia cycles, altered autonomic control and oxygen free radicals. Loss of endothelial nitric oxide, increased blood coagulability and fibrinogen levels and impaired vasodilatation also have an impact on the CAD in OSA patients.

Hypertension. There is convincing evidence that OSA is an independent risk factor for hypertension (198-200). AHI and sleep time below 90% oxygen saturation are associated with greater odds of hypertension in a dose-response fashion. Persons with mild OSA have approximately two times the odds of suffering hypertension at four-eight years follow-up compared to those with no OSA. It seems that middle aged subjects with OSA are more likely to develop hypertension than older individuals (201). From the opposite perspective one can state that blunted decline in nocturnal blood pressure and drug-resistant hypertension seem to be linked with OSA (197,202). Several studies suggest that both CPAP (203-205) and OAs result in a reduction in blood pressure (206,207). The effect of CPAP on hypertension is variable, those with severe OSA, resistant hypertension and good CPAP compliance are most likely to benefit. On the other hand, anti-hypertensive agents are safe in terms of OSA (187).

Coronary artery disease. The causal relationship between CAD and OSA is not so clear as it is between hypertension and OSA. However, OSA may represent an additive or synergistic risk factor for the development of CAD (192,208,209). Importantly, patients with OSA without overt CVD show early structural and functional signs of atherosclerosis (210). In cross-sectional studies in the general population, the subjects with OSA have either a similar or only slightly increased risk for overt CAD compared to subjects without OSA. The risk seems to be higher in clinical based samples. In community-based follow-up studies, there has been a modest increase in CAD risk in men (193). This risk is probably higher in younger patients with more severe disease similar to the risk of hypertension. OSA is overrepresented in CAD patients (192,211,212). Moreover, in those patients who already have CAD and OSA, episodes of nocturnal ischemia are more common than in those with no overt CAD (213). Furthermore, ischemia is more likely to occur during hypoxic, apneic and REM-sleep episodes. Effective treatment of OSA reduces the CAD risk (4,209). Even a small reduction in blood pressure over the long term can decrease the incidence of CVD and cerebrovascular disease (214), and CPAP use decreases blood pressure, thus CPAP should have a protective effect against CVD also in hypertensive patients.

Stroke. The risk for stroke seems larger than the risk for CAD events in OSA patients (192). Moreover, OSA (even mild) is associated with about a 3-fold risk of cerebrovascular events in those patients who have also CAD (215,216). In a recent paper, Redline and co-workers described a community-based sample where men with moderate-to-severe OSA had an almost a three-fold risk for stroke compared with control subjects (217). Interestingly, untreated mild-to-moderate sleep apnea displayed an association with stroke: an increase of one unit of AHI increased the risk of stroke by 6%. The effect of treatment of OSAS with CPAP on cerebrovascular events is unclear at the moment (216).

Heart failure. OSA predicts the development of heart failure in men (193). In a cross-sectional analysis of a large community study, the odds ratio for self-reported heart failure was 2.38 in patients with sleep-disordered breathing vs controls (192). The prevalence of sleep apnea is about 50% in patients with chronic heart failure, with the central type sleep apnea being more common (218). At the moment the impact of OSA treatment is unclear (but probably beneficial) (218).

Rhythm disorders. OSA is characterised by brady-tachycardia cycles: during hypoxemia caused by obstructive apnea, the vagal response leads to bradycardia; at the apnea termination, a transient tachycardia occurs due to triggering of sympathetic system (196). Recent observational studies have also shown increased nocturnal dysrhythmias (especially atrial fibrillation) in patients with OSA in dose-dependent manner, but there is no solid evidence for a beneficial effect of CPAP on these rhythm problems (153,154,197,219-221).

Metabolic syndrome and diabetes

Metabolic syndrome. The relative role of obesity and OSA in the pathogenesis of metabolic alterations is unclear but there is a link (possibly obesity itself) between OSA and metabolic abnormalities. The metabolic syndrome (MetS) is a cluster of risk factors for diabetes, CVD and mortality in the general population (222). It includes disturbances in glucose metabolism (insulin resistance), abdominal obesity (excess visceral fat), dyslipidemia (hypertriglyceridemia and decreased high-density lipoprotein) and hypertension, the exact definition depending on the authority issuing the guideline (223). Metabolic syndrome is common in OSA patients, the risk being about five-fold compared with controls, and more than 2/3 of newly diagnosed MetS patients have OSA (224-226). In many studies, the degree of OSA has been predictive of MetS prevalence (224,225,227-229). In fact, a recent report suggested that OSA could be the second most important determinant after obesity for MetS (230).

Diabetes. As could be expected on the basis of connection between OSA and MetS, the link between OSA and impaired glucose metabolism (glucose intolerance, insulin resistance and type 2 diabetes mellitus [T2DM]) is quite convincing. Most epidemiological and clinical cross-sectional studies have observed that OSA is associated with impaired glucose metabolism, independent of body size, and this association becomes ever clearer with increasing AHI and hypoxemia (225,231-236). However, prospective studies on OSA patients have reported conflicting results on the development of diabetes, and thus the causality is still unclear (234,237,238). In patients with T2DM, the prevalence of OSA is high, > 75% (239,240). Moreover, increasing severity of OSA has been associated with poorer glucose control thus supporting OSA treatment in these patients (240). The association between sleep apnea and T2DM may be bidirectional: firstly, hypoxemia and fragmented/deprived sleep have a negative effect on glucose metabolism (231,241,242). Inflammatory cytokines released from adipocytes (e.g. interleukin [IL]-6 and tumor necrosis factor [TNF]-α), reactive oxygen speaces, increased sympathetic activity and alterations in hypothalamic-pituitary-adrenal function (e.g. reflected in blood cortisol) may be mechanisms mediating this relationship (225,231,241-243). Secondly, diabetes may impair the reflex responses to hypoxia and hypercapnia which promote periodic breathing and hypoxemia thus leading to deeper desaturations (244-246). The suspected beneficial effect of CPAP treatment on metabolic problem is still not proven (247,248). It seems that the patient profile (e.g. degree of obesity) and CPAP compliance may have an impact on the outcome.

Other conditions

Even mild OSA has been linked with depressive symptoms (249,250). The risk for traffic accidents is also increased in OSA patients, and CPAP treatment seems to improve driving performance (251,252).

Mortality

In the three epidemiological studies published so far, participants with moderate-to-severe OSA have had a 1.5-3-6 fold greater risk of all-cause mortality compared to those without

OSA (5,253,254). The risk for cardiovascular mortality is even more elevated. The risk is largest in those subjects with severe OSA and men 40-70 years of age, and hypoxemia was independently associated with mortality. In clinical samples, similar findings of elevated CVD related and all-cause mortality have been demonstrated (4,255,256).

2.2.9 OSA and health economics

Sleep apnea incurs costs to the patient, to his/her employer and to society as a whole. Direct costs include those related to the management of OSA and associated medical conditions. OSAS patients are heavy consumers of health-care resources: the medical costs of patients with (undiagnosed) OSA are twice those of matched controls, with women and the elderly being the most expensive OSA subjects, and even mild sleep apnea is associated with increased healthcare utilization (257-260). Daytime sleepiness and sleep problems per se are linked with increased health care utilization as well (261,262). The indirect costs are mainly related to reduced working capability and increased risk of accidents. Sleep apnea increases the risk of sickness absence and disability pension before and after OSA diagnosis (263,264). As before, this risk is higher in women compared to men. The cost-effectiveness of CPAP treatment has been demonstrated to be favorable (265,266).

2.3 INLAMMATION

2.3.1 Definition of inflammation and cytokines

Inflammation. Inflammation (Latin, inflammare, to set on fire) is the major local protective process to tissue injury and is thus an integral part of immunity. The immune response is aimed at eliminating injurious stimulus and the consequences of the injury (e.g. necrotic cells caused by bacterial infection), and to start the healing process to guarantee the survival of the individual. The immune response can thus protect an individual against diseases. The response is generated by the immune system which consists of an army of both rapid deployment troops for the first response (innate immunity) and well equipped special forces with their sophisticated, comprehensive and powerful combat abilities (adaptive immunity) (267). Changes in circulating leukocytes (white blood cells), plasma proteins and blood vessels are essential in inflammation. There is also a systemic reaction known as the acute-phase response, characterized by changes in acute-phase proteins (the best known of these proteins is C-reactive protein [CRP]), inflammatory cytokines, biochemical parameters, body-temperature, nutrition and behaviour (268). (269,270)

Triggers for acute inflammation include microbes, tissue necrosis, hypoxia, foreign bodies and immune reactions. Normally, in the acute response to a harmful stimulus, i.e. acute inflammation, the immune responses wane with time due to antigen elimination, short half-lives of mediating compounds, and appropriate control and negative feedback mechanisms built into this system. On the other hand, if this does not happen and chronic inflammation ensues, these inflammatory mechanisms are capable of damaging normal cells and endothelium and actually cause diseases. In chronic inflammation, both tissue injury and attempts to repair the damage are being implemented. Moreover, chronic inflammation may begin insidiously, as a low-grade response. Diseases with etiological origins in immune-mediated inflammatory processes include autoimmune diseases (e.g. rheumatoid arthritis) and allergic diseases (e.g. asthma). The non-immune mediated inflammatory diseases include atherosclerosis, where toxic endogenous lipid components may induce the process. In these kinds of systemic inflammation, the inflammatory process is not confined to a particular tissue but involves the endothelium as well as other organ systems. (269,270)

Cytokines. Cytokines are short-acting proteins which are produced after a triggering event by many activated cell types (e.g. macrophages, endothelial cells, even adipocytes) and act as hormone-like soluble mediators modulating the functions of other cells (270,271).

They are essential in inflammation by recruiting leukocytes to the tissues where an injurious agent is present (e.g. TNF-α). Moreover, cytokines participate in the regulation of cell growth and activation, tissue repair and morphogenesis. The effect of a single cytokine on different target cells can be diverse (272). The first cytokines were found to mediate communication between leukocytes and thus were named interleukins. Other important cytokine groups include interferons, TNF-α and cell type specific growth factors. Even though multiple cytokines may have similar functional effects and they can partly replace and regulate each other, cytokines act in a highly regulated cascade: for example, TNF-α stimulates IL-1, IL-1β regulates its own receptors and the IL-6 response, and IL-6 inhibits TNF-α (268). IL-6 is also the main activator of CRP production in the liver. Sometimes there are failures in cytokine regulation and this inappropriate cytokine production triggers or worsens a disease.

Although there is very complex networking of cytokines, they can be classified into pro-inflammatory cytokines (e.g. TNF-α, IL-1β, IL-6), which augment the inflammatory response, and anti-inflammatory cytokines (e.g. IL-10 and IL-1 receptor antagonist [Ra]), which attenuate inflammation. The exact function will depend on the specific cytokine but in general, pro-inflammatory cytokines induce inflammation by endothelial activation, by stimulating chemokine and cytokine secretion, by leukocyte stimulation, and they induce acute phase reactions. They may also stimulate tissue repair through the fibroblasts. In the pathogenesis of CVD, pro-inflammatory cytokines have an essential role because there is dysfunctional endothelium. When present in large amounts, these cytokines have systemic actions such as fever, cachexia, lost of blood pressure, disseminated intravascular coagulation, hypoglycaemia, which can be extended into septic shock, and sleepiness. (271,273,274)

The exclusively anti-inflammatory cytokines include IL-1Ra and IL-10. IL-1Ra is structurally similar to IL-1 and binds to the same receptors, but it is biologically inactive and thus prevents IL-1 from transmitting a signal into the cell. In other words, it is a natural antagonist or regulator of IL-1's biological effects. It has an important role in the suppression of the IL-1 induced atherogenesis in the vascular wall, and of β-cell destruction in the pancreas (275,276). IL-10 is the major inhibitor of inflammation e.g. by down-regulating the production of pro-inflammatory cytokines and modulating or terminating the inflammatory responses (277). (271,272)

Disease launching properties of cytokines can be targeted in the development of treatment options for these diseases. TNF-inhibitors and anti-IL-6 agents have been used for the treatment of autoimmune disorders such as rheumatoid arthritis. One of these agents, etanercept, has decreased the degree of sleepiness in obese sleep apneics which is not surprising in view of the sleep promoting property of IL-6 (278). Anakinra, a human recombinant form of IL-1Ra, has been evaluated in the treatment of rheumatoid arthritis, as well. (271)

2.3.2 Assessment of inflammation

In (acute) inflammation, the physical signs of pain, redness, swelling, heat, dysfunction, fever and tiredness represent the visible markers of disease. Estimation of changes in CRP can be a useful way to evaluate the presence, intensity and type (bacterial vs. viral) of inflammation and response to treatment (279,280). In terms of clinical inflammation, CRP values less than 10 mg per liter are unimportant, and most normal subjects have values less than 2 mg/L (268). On the other hand, CRP concentrations in this gray zone of 2-10 mg/L have been linked with low-grade inflammation. For example, CRP concentration > 3.0 mg/l is associated with an increased risk for CVD (281). High-sensitivity CRP (hsCRP) refers to the measurement of CRP using methods with sufficient sensitivity to quantify CRP throughout its normal range. HsCRP concentrations (< 10 mg/L) are quite stable in the same individual across 24 hours and are thus a good tool for estimating low-grade inflammation (282).

Cytokine measurements could be used as markers of inflammation as well. However, they are seldom used in clinical practise due to their short half-lives, high costs, limited availability and lack of standardization of the measurements (268). On the other hand, circulatory levels of cytokines represent the average value of all cellular sources, and thus the blood concentration of a single cytokine does not necessarily provide relevant details about the activity level of the whole cytokine cascade, or the intracellular activity (272,274). Moreover, obesity and other co-morbidities, exercise, medications and hereditability can all affect cytokine and CRP levels.

2.3.3 Inflammation in OSA, obesity, cardiovascular diseases and (pre)diabetes

Inflammation and OSA

Inflammatory compounds, and many other neurotransmitters, are integral part of sleep regulation in normal physiological conditions and in diseases (283,284). For example, the pro-inflammatory cytokines IL-1, TNF-α and IL-6 have sleep promoting abilities: they enhance sleep, if injected; if inhibited, the amount of sleep is reduced. The concentration of these cytokines varies in the brain with sleep propensity; they act on sleep regulatory neuronal circuits and their levels are altered in conditions with enhanced sleepiness. On the contrary, the two anti-inflammatory cytokines IL-10 and IL-1Ra are able to inhibit sleep.

Alterations in the levels of inflammatory compounds have been reported in OSA with intermittent hypoxia being one potential mechanism mediating these changes. Hypoxia functions as a danger signal for the immune system by inducing the synthesis of inflammatory cytokines and the expression of adhesion molecules in different cell types and tissues (eg. vascular endothelium) due to oxidative stress (274). Accordingly, hypoxemia of high altitude has been reported to induce an increase in circulating concentrations of cytokines in healthy subjects (285). On the other hand, sleep deprivation caused by repetitive microarousals in sleep apnea may explain part of the elevation in the levels of pro-inflammatory cytokines (278,286,287).

However, it remains inconclusive whether the changes in circulating inflammatory biomarker levels are due to OSA per se or to some other underlying factors such as excess weight and co-morbidities. Thus, conflicting results have been found in all of the biomarkers of inflammation which have been studied: **1)** both reports of increased levels of TNF-α, IL-6 and CRP independent of body weight (288-293,293-306) and **2)** papers reporting that the increase in these biomarkers, if found, is mostly dependent on excess weight (or the groups were not matched for body weight) have been published (288,305,307-317). The IL-1(β) levels do not seem to be elevated in patients with OSA, although the plasma levels of IL-1β may increase after an apeneic event (288,295,296,315).

Many of the above studies have shown that pro- inflammatory biomarker levels correlate with the severity of OSA. However, most of the studies have included a heterogeneous group of patients with different degrees of OSA, and very few studies have included a subgroup analysis especially with mild degree OSA patients. In these few studies, the levels of pro-inflammatory biomarkers have not seemed to differ significantly from the levels measured in control subjects (290,292,294,303,310,312) except for the CRP level in a Chinese study (318).

There are very few studies on the levels of anti-inflammatory cytokines in adult sleep apnea and in these reports, the subjects have suffered from moderate-to-severe OSA. The intracellular levels of IL-10 in OSA patients depend on leukocyte type, some cells displaying increased production, but all in all, it seems that a pro-inflammatory state predominates (274). The circulating levels of IL-10 decrease as the sleep apnea worsens (296). OSA patients with moderate-to-severe have also decreased IL-10 levels compared to

controls. Treatment of sleep apnea does appear to elevate the IL-10 concentrations (319) but changes in weight may have an impact on this improvement.

As could be expected, the effect of CPAP or surgery on inflammation in OSA patients is also unclear, with both pro- and con-studies having been published (290,292,294,295,312,315,315,320). On the other hand, the effectiveness of CPAP treatment on inflammation may increase with greater hours of use (321-324). However, the clinically significant effects of CPAP on subclinical inflammation in OSA, particularly in overweight patients, still need to be established: In recent randomized controlled studies, CPAP was claimed not to have any effect on IL-6, TNF-α or CRP levels in patients with moderate-to-severe OSA (325,326). On the other hand, Drager et al reported a significant decline in CRP concentrations in patients with severe OSA (156). Additionally, CPAP treatment did not improve hypercytokinemia or insulin resistance in obese patients with OSA, and the withdrawal of CPAP was not associated with an increase in the inflammatory markers (312,327). Moreover, the poor compliance of mild OSA patients with CPAP provides more support for choosing weight loss or other therapy in this group of patients. On the other hand, there are no studies where the effect of weight loss has been investigated on this issue either.

Inflammation and obesity

Obesity is a condition where there is excessive adipose tissue (increased size or number of adipocytes) which develops as a consequence of an imbalance between energy intake and energy expenditure (328). The BMI is the most widely used measure of obesity (141). It is calculated by dividing the individual's weight in kilograms by the square of the individual's height in meters (kg/m^2). Overweight is defined as BMI 25.0-29.9 kg/m^2 and obesity as BMI ≥30.0 kg/m^2. White adipose tissue is considered not only to be an energy storage site but also an active endocrine organ releasing a large number of proteins (adipokines) which regulate many systemic processes such as food intake, metabolism and inflammation (329). In addition, adipose tissue secretes many inflammatory mediators including cytokines (e.g. IL-6, TNF-α, IL-10 and IL-1Ra) (330,331). In white adipose tissue, it is the macrophages that are essential for the production of cytokines (332).

Thus, it is not surprising that obesity can be viewed as a low-grade inflammatory condition. The primary cause of obesity associated inflammation is not clear, a role for hypoxia and macrophage infiltration due to adipocyte death has been postulated (333,334). However, it is clear that high BMI and weight gain, and especially a large amount of visceral fat, have a connection with elevated circulating levels of the pro-inflammatory biomarkers (335-337). Accordingly, cytokine production in visceral fat has been shown to be greater than in subcutaneous fat (338,339). The increase in cytokine levels by weight gain seems to be larger in those individuals who were more obese at baseline, this being independent of other inflammatory diseases (337). This could have a connection with the fact that obese subjects have carried a higher total adipocyte number than lean individuals since childhood (340). Weight loss has a lowering effect on the levels of both pro-inflammatory (341,342) and anti-inflammatory biomarkers (343). Obesity is a risk factor not only for OSA, but also for many diseases such as CVD, diabetes and cancer (344-346), and inflammation may be one linking mechanism.

Inflammation in cardiovascular and cerebrovascular diseases

Atherosclerosis, which in the form of CVD and cerebrovascular diseases continues to be an important cause of morbidity and mortality around the world, is a dynamic and progressive disease of the inner layer of the arterial wall. A subclinical malfunction in this inner layer, endothelial dysfunction (pro-atherogenic and pro-inflammatory state), is the fundamental cornerstone of this disease (347,348). The normal endothelium regulates

vascular tone (constriction vs. dilatation) and is the site of interaction between the vessel wall, vasoactive compounds and cellular mediators in the blood. For example oxidative stress, inflammatory mediators or hypercholesterolemia can launch this dysfunction, and this will lead to a lack of nitric oxide. Atherosclerosis is characterized by the accumulation of lipids, extracellular components, leukocytes, adhesion of platelets and proliferation of smooth muscle cells in these lesions (349,350). Inflammation is considered as one of important mechanisms in the pathogenesis and also in clinical manifestations of atherosclerosis (e.g. acute myocardial infarction due to plaque rupture). In terms of OSA, this inflammation is enhanced by the oxidative stress evoked by hypoxia/reoxygenation cycles (274). Hypoxia functions as a danger signal for the immune system by inducing the synthesis of inflammatory cytokines and promoting the expression of adhesion molecules in different cell types and tissues (eg. vascular endothelium) due to oxidative stress. Cytokines, which are mainly secreted by macrophages and T-cells in atherosclerotic lesions, are one of the most important promoters and mediators in these processes. For example, IL-6 is expressed in atherosclerotic lesions and is predictive of future cardiovascular events (351). Elevated levels of other pro-inflammatory molecules such as TNF-α, IL-1 and CRP can be detected in the peripheral circulation in affected individuals. Moreover, atherosclerosis can be inhibited, or at least decelerated, by anti-inflammatory compounds, for example IL-10 (352). An increased risk of CVD has been reported if the lifelong total burden of infections is high (353). In the past years, there has been an on-going debate about whether CRP can be used as a risk-marker for CAD. It seems that in patients with intermediate risk, adding CRP into a risk prediction model may be beneficial (281). Increased hsCRP (> 3.0 mg/l vs < 1 mg/l) is associated with CVD events but CRP is only a marker of inflammation and not the direct cause of CVD (354).

Cytokine activation has also been connected with heart failure (355).

Inflammation in the metabolic syndrome and (pre)diabetes

It seems that the inflammatory condition, which is associated with excess weight as stated above, is an essential finding in both the metabolic syndrome and T2DM (356,357). Insulin resistance is a key element in both of these conditions: there is a failure of insulin to inhibit glucose output from liver, and to promote glucose uptake in fat and muscle cells (358). Moreover, in T2DM, there is a pancreatic islet β-cell dysfunction, which is partly caused by inflammation. In both of these conditions, there is an increase in the concentrations of many pro-inflammatory biomarkers such as IL-1, CRP, IL-6 and TNF-α. For example, TNF- α and IL-6 mediate insulin resistance, and blockage of their signalling improve insulin sensitivity at least in animal models (359,360). Thus anti-IL-1 therapies are promising new treatments for T2DM (357). It is noteworthy that the level of the anti-inflammatory cytokine IL-1Ra is increased in obesity, pre-diabetes and diabetes (343,361-363). It has been shown that increasing components of the metabolic syndrome are associated with higher levels of inflammatory biomarkers. Moreover, the levels of these biomarkers can predict the later development of T2DM (364).

2.4 BACKGROUND TO THE PRESENT STUDY

The progression of OSA is very important in terms of public health: 1) in patient's perspective a more severe degree of OSA usually causes more symptoms, and it is a more severe risk factor for co-morbidities. 2) Even now the number of snorers and OSA patients who seek medical help is high. Thus, the focus has been on treating more symptomatic patients and moderate-to-severe OSA. Based on the current knowledge researchers would demonstrate that even early stages of OSA should be treated more actively than we do nowadays. However, to succeed, we would need more infrastructure, medical staff and money to do that work. The aim of the present study was to investigate the natural

evolution of mild OSA and furthermore, the possible chronic inflammation related to the early stages of OSA.

Inflammation has proved to have an essential role in obesity and in the pathogenesis of important co-morbidities of OSA. However, there are not so many papers on inflammation in (mild) OSA. Thus, it seemed reasonable to clarify the connection between OSA and inflammation and, on the other hand, to try to treat OSA in a way that would also alleviate the inflammation. Weight loss, which is known to reduce inflammation and lower the risk of OSA-related co-morbidities, thus seemed to be logical choice for implementing this kind of therapeutic intervention.

3 Aims of the Present Study

The aims of the present study were

1. To investigate the evolution of mild OSA after different treatment modalities. (Study I).
2. To assess the evolution of symptoms related to mild OSA after surgical intervention with a long term follow-up. (Study II).
3. To investigate the possible association between mild degree OSA and a range of inflammatory biomarkers and also to evaluate whether this potential activation is linked to the extent of respiratory events. (Study III).
4. To determine the impact of lifestyle changes aimed at weight reduction on inflammatory biomarkers in overweight patients with mild OSA. (Study IV).

4 Material and Methods

4.1 THE RETROSPECTIVE FOLLOW-UP

The retrospective part of the thesis was originally conducted to evaluate the evolution of OSA and the outcome of different treatment modalities of mild OSA.

4.1.1 Patients and methods

In the follow-up studies I and II, medical records of adult patients who had visited the Department of Otorhinolaryngology (ORL) at Kuopio University Hospital due to suspicion of sleep disordered breathing between 1998 and 2004 were reviewed. Data on ORL-status, sleep recording, treatment modality, sleep questionnaire, medical conditions and medications were retrieved (Appendix 1). This sleep questionnaire (Appendix 2, questions 1-22) has been used in the Department of ORL since 1995 for all patients presenting with suspicion of sleep disordered breathing. The same questionnaire, supplemented with an inquiry into the patients' opinions about the treatment they had received in the period since their last visit (questions 23-28 in Appendix 2), was mailed to all those patients in 2005, for whom there was the previously mentioned data and a postal address was available. The inclusion criteria for study I were age 18 years or older and mild OSA (AHI 5-15/h) verified by full PSG or cardiorespiratory recording prior to any treatment. For the study II, an additional criterion was that they had to have filled in the questionnaires at baseline and in 2005.

Study I retrospectively investigated the outcomes of different treatment options for mild OSA in terms of AHI. The patients (in alphabetical order) who fulfilled the inclusion criteria were contacted by the study nurse by telephone. The first 50 patients who agreed to participate in the study visited the study nurse at the outpatient unit and underwent overnight cardio-respiratory recording in 2005. Three groups were created: a) the untreated group including those patients who underwent passive interventions such as lifestyle counseling by an otorhinolaryngologist, a single consultation with a nutritionist or a pulmonologist, instructions for positional therapy, or a short term unsuccessful CPAP therapy due to poor compliance; b) the operative group i.e. those who had underwent any upper airway surgical procedure due to sleep apnea; c) the CPAP group including patients who were actively using CPAP treatment at the time of inquiry.

Study II investigated retrospectively the changes in the symptoms of the patients after surgical treatment versus passive treatment for mild OSA. Those patients who were regularly using CPAP were excluded from this study.

4.2 THE PROSPECTIVE TRIAL

The original randomized, clinical follow-up trial was conducted to determine the effects of lifestyle intervention with weight reduction in patients with mild OSA. Studies III-IV which examined the biomarkers of low-grade inflammation in OSA and the effects of lifestyle intervention on these markers were subanalyses of that larger trial.

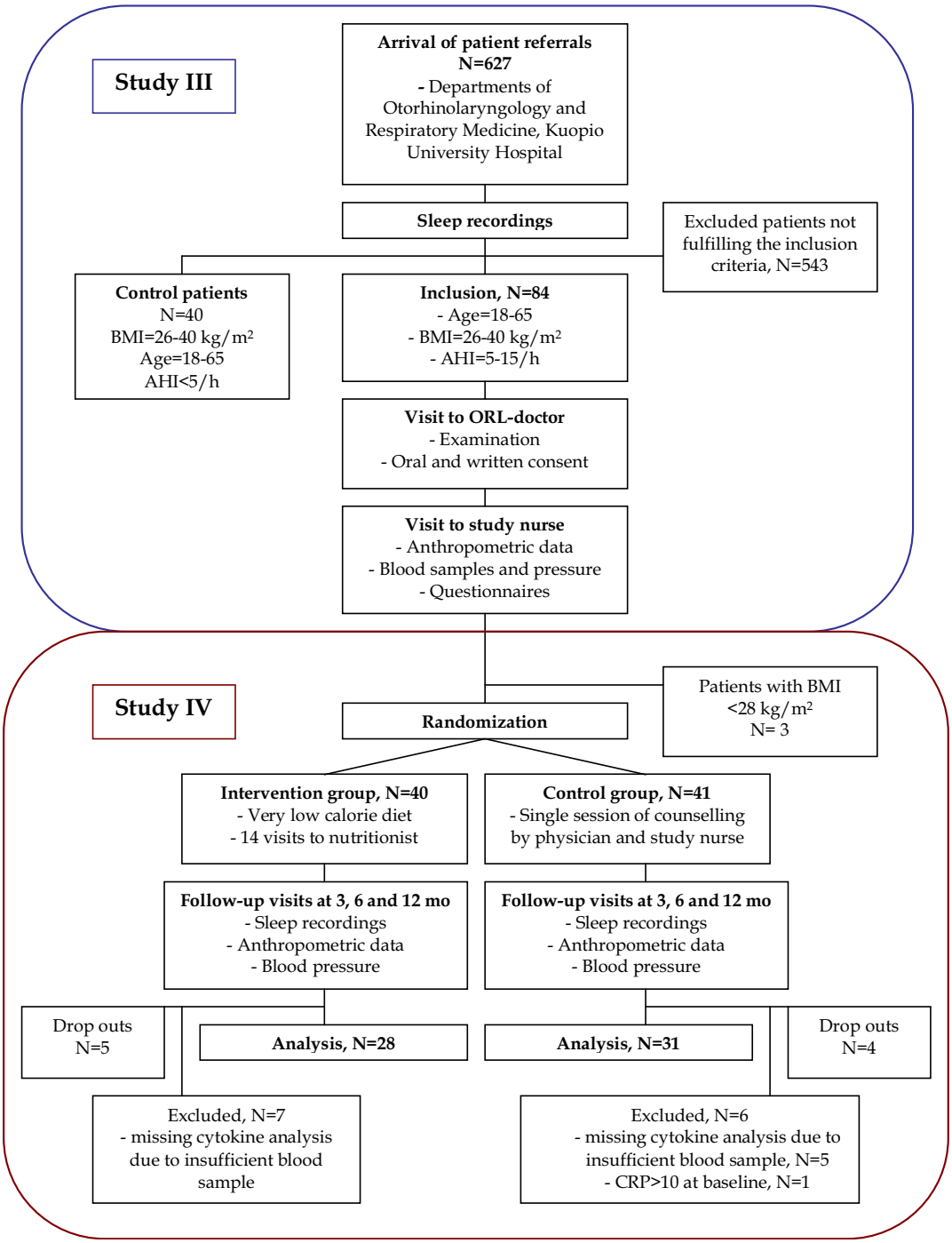


Figure 7. Studies III-IV flowchart

4.2.1 Patients

The recruitment for the original prospective study started in October 2004, and ended in December 2006. The participants were consecutively recruited from the adult patients referred to the outpatient clinics of the Department of Otorhinolaryngology or Respiratory Medicine of Kuopio University Hospital, in Kuopio, Finland because of suspicion of sleep disordered breathing. Their weight, height and upper airways were checked, and previously diagnosed diseases and prescribed medications were recorded. The patients were eligible for participation if they were of working age (age 18-65 years), were overweight or obese (BMI 26[28]-40 kg/m^2), and had mild OSA (AHI 5-15/h). The exclusion criteria were active treatment of OSA of any kind, chronic kidney or liver disease, untreated thyroid disease or pregnancy. Moreover, all those patients whose blood samples were inadequate for cytokine analyses, were excluded from analyses in studies III-IV. After the visit to the study physicians and the confirmation that the patients fulfilled the inclusion criteria, the subjects were allocated in order of appearance randomly into two study groups by a study nurse. A block randomization with a block size of 16 was used. At the beginning, there was a plan to recruit one hundred patients for the study during the two years but this goal was not reached. The study nurse did not take part in the intervention part of the study, nor did the study nutritionist see the patients before the first group session for the intervention group. No stratification was used in the allocation of the participants into the two groups. The flowchart for studies III-IV is shown in Figure 7. Forty patients who were not eligible for the study due to AHI less than 5/h served as a control group for all OSA patients in the baseline measurements.

4.2.2 Methods

Procedures and measurements

In the prospective controlled trial (studies III-IV) all the patients with OSA had a baseline visit and two follow-up visits with a physician, at three and 12 months. The 40 non-apneic patients, who served as control patients for the baseline measurements, were examined once at baseline. At all these visits, the clinical assessments for all patients were done by an otorhinolaryngologist and they included a complete ORL status, including examination of pharynx and larynx in Müller's manoeuvre with a fiber-endoscope. Moreover, special attention was paid to possible obstructing sites in the upper airway (deviated nasal septum, nasal polyps, large tonsils etc). The study nurse met the patients at the time points mentioned above as well as at the six months evaluation. The study nurse measured the height, weight, waist circumference between lower costal margin and iliac crest in the standing position, hip circumference at the broadest level, greatest sagittal measure of the stomach between ziphoid process and pubic symphysis, and horizontal measure of the stomach from axillary to axillary line at the broadest level. Blood samples were taken after overnight fast at 8.30-9.30 a.m. thirty minutes after insertion of an intravenous cannula and bed rest. BMI was calculated as weight (kg) divided by height squared (m^2). Body composition, measured with an InBody 3.0 bioimpedance device (Biospace; Seoul, Korea), and blood pressure were measured by a trained nurse in the Department of Clinical Physiology and Nuclear Medicine. The multifrequency bioimpedance method for measurement of body composition provides detailed information on fat mass, total body water and fat distribution within the whole body and segmental lengths. When compared with the dual-energy X-ray absorptiometry method, Inbody analysis has provided a good assessment of fat mass in healthy subjects (365). Blood pressure was measured from the right arm with the subject in the sitting position, and was determined three times, after 10

minutes of rest, using a standard sphygmomanometer. The mean value of the measurements was used as the result.

The patients filled out several questionnaires of which only the Patient data – questionnaire was utilized in the present studies III-IV (Appendix 3). The first eight multiple choice questions were identical with those in the Snore Outcomes Survey (53). Daytime sleepiness was assessed with the same questions than those in Epworth Sleepiness Scale (49). The respondents were also asked whether their bedfellows had noticed breathing pauses during their sleep and subsequently these were classified as "witnessed apneas." Moreover, questions about daytime napping, sleep quality and daytime functioning were asked. The questionnaires were filled out by the patients both at baseline and at the 1-year visit.

The overnight in-home sleep study was performed in accordance with accepted guidelines for diagnosis of OSA (66). Venla® cardiorespiratory recording device (Remote Analysis, Kuopio, Finland) was used for six non-apneic patients at baseline, and Embletta® (Embla, Broomfield, CO) for all the other patients. Both Venla® and Embletta® measured oronasal flow and pressure by thermistor and pressure sensors, thoracoabdominal respiratory effort by bands, snoring sounds by a microphone, SaO_2 and heart rate from a finger oxymeter, and body position by a sensor. The recordings were manually evaluated by a blinded, trained physician. Apnea was defined as a cessation (more than 90%) of airflow for more than 10 seconds with oxygen desaturation of more than 4%. Hypopnea was defined as a reduction (more than 30%) of airflow for more than 10 seconds with oxygen desaturation of more than 4%. The apnea–hypopnea index was defined as the number of apneas and hypopneas per hour, and mild OSA was defined as an AHI of 5–15 events/hour. Other parameters were assessed, for example, arterial oxygen saturation, time and percentage with arterial oxygen saturation below 90%, and heart rate. The sleep recordings were conducted at baseline, at the 3-month visit, and at the 1-year visit. The OSA was considered objectively cured when the AHI was less than 5 events per hour.

All the biochemical measurements were performed both at baseline and at the 1-year visit in the Laboratory of Clinical Chemistry in Kuopio University Hospital. The blood samples in EDTA tubes were centrifuged at 2100 g for 10 min. The tubes for serum samples were allowed to clot for 30-120 min after which the serum was separated. Cholesterol, high-density lipoprotein, triglycerides, alanine aminotransferase and glucose were determined from fresh serum samples, using an automated analyzer system (Konelab 60 analyzer; Thermo Fisher Scientific, Waltham, MA), and insulin was measured with a fluoroimmunoassay technique (Wallac; PerkinElmer, Waltham, MA). Insulin resistance measured by the homeostasis model assessment (HOMA-IR) was calculated as follows: HOMA-IR=fasting glucose (mmol/l) × fasting insulin (mU/l)/22.5 (366). Extra tubes of EDT-plasma and serum were stored at -70˚C, and inflammatory biomarkers from baseline and 1-year samples were analyzed in single runs using these tubes. Plasma levels of TNF-α, IL-1β, IL-6, IL-10 and IL-1Ra were analyzed with high sensitivity ELISA kits (R&D Systems, Minneapolis, MN, USA). Serum hsCRP was analyzed by Immage® (Beckman Coulter Inc, Fullerton, CA, USA) and a high sensitivity kit.

Intervention

At the beginning of the trial, the patients were informed about the general health risks associated with OSA and obesity (including information about harmful lifestyle factors, such as smoking and alcohol drinking). Both the doctor and the nurse stressed the importance of diet and exercise to the control group. No specific individualized programs were offered to the subjects in the control group.

The intensive lifestyle intervention lasted for one year, and consisted of 14 visits with the study nutritionist. At the beginning, patients in the intervention group were asked to keep

a 3-day food diary at baseline to estimate their nutrient intake. After screening, the intervention group participants started with a group-based very low calorie diet (VLCD) of 600–800 kcal/day (Nutrilett® [Nycomed Pharma, Oslo, Norway], Modifast® [Novartis, Basel, Switzerland], Nutrifast® [Leiras, Helsinki, Finland], or Naturdiet® [Vitamex, Norrköping, Sweden]) for 12 weeks. At the beginning of the intervention, previous attempts to lose weight were discussed and an individual goal was set for weight loss. During the VLCD period, follow-up visits were arranged every second week and the sessions were supervised by the nutritionist. Compliance with the program and supervision for any possible adverse events were monitored by individual interviews at each visit by the nutritionist. The weight was measured at every visit and the patients were asked about any lifestyle changes he or she had made. The nutritionist provided face-to-face counseling individually tailored to each patient in the intervention group and also took part in the group sessions. Each session lasted 60–90 minutes. In addition to VLCD products, the patients were allowed to have calorie-free drinks and vegetables in accordance with our outpatient clinic's weight reduction program. The clinical nutritionist provided dietary and lifestyle counseling at each visit, with the emphasis placed on diet, exercise, and modification of lifestyle in general, specifically focusing on eating behavior. After the VLCD program, the patients were advised to reduce fat to no more than 30% of total energy by increasing their intake of fruits, vegetables, poultry, fish, and lean meat, and by limiting dairy fats, fatty meat, sweets, pastries, and desserts. The subjects were recommended to increase their overall level of daily physical activity, and endurance exercise (such as walking, skiing, jogging, or swimming) was also recommended. After the VLCD, a physiotherapist supervised two of the group meetings, which focused on circuit-type resistance exercise to improve functional capacity. None of the study subjects in the intervention group had ongoing weight loss procedures, were enrolled into formal exercise programs, or were provided with personal trainers. During the intervention period, the rate of participation in these sessions varied from 70 to 80%.

Any possible adverse events related to the weight reduction program were assessed by the nutritionist at the visits which took place every second week. All study participants were also given the telephone number of the study nurse, if any questions or concerns about their health should emerge. All the results of the laboratory tests, blood pressure measurements, and electrocardiograms were checked by study physicians. It was decided that if any abnormal test results endangering the health of the study participants were observed, then participants would be informed and referred for appropriate medical care.

4.3 STATISTICAL METHODS

In studies I-II, differences between groups were assessed with one-way analysis of variance for continuous variables and Fischer's exact test or Kruskal-Wallis test for categorical or not normally distributed variables. Then the post hoc test for Kruskal-Wallis and Bonferroni post hoc tests were used to compare individual characteristics between treatment groups. In the study II, logistic regression models were used to compare the frequency of the symptoms by adjusting for age, sex, BMI, AHI, baseline status of respective symptom and the follow-up time.

Study IV was an explorative substudy of an existing randomized controlled trial. No separate sample size calculation was done for study IV. The results can be considered as explorative post hoc analyses regarding the effect of weight loss on inflammatory mediators in mild OSA patients with obesity.

Studies III-IV assessed differences between the groups by Fisher's exact test and logistic regression analysis with adjustment for age and sex for dichotomous variables, and t-test and analysis of covariance with the same adjustments for continuous variables. Due to the right-skewed distribution of the inflammatory markers, a logarithmic transformation was applied before analysis. Geometric means and standard deviations (SD) are reported for

these variables, i.e. the logarithmic values were converted back to the original scale via the antilog. Age, sex, total body fat percentage and baseline level of the respective variable were considered as confounding factors when analyzing the inflammatory markers. At baseline, co-morbidities (hypertension, CAD, hypercholesterolemia, diabetes, asthma and inflammatory diseases) and non-steroidal anti-inflammatory drug medication were also taken into account as confounding factors. Additionally, there was further adjustment for cardiovascular medication but because this analysis provided essentially the same result, these are not separately shown in the figures. The inflammatory marker analyses were performed at 12 months also by adjusting for lean body mass, waist circumference or BMI instead of fat percentage, and the results were similar. Thus, it was decided to use fat percentage because the accuracy of BMI as a descriptor of obesity is limited (56,57). Linear and multiple regression analyses were used to identify independent determinants for inflammatory markers.

In studies I-IV, 95% confidence intervals (CI) were calculated for the main results, and all the analyses were performed on an intent-to-treat basis. Differences were regarded as statistically significant if a two-sided P-value was less than 0.05. Data are expressed as the number of cases or mean with the SD. Patient characteristics and variables were analyzed with the Statistical Package for Social Sciences (software version 11.0.4-17.0 for Windows or Mac, SPSS Inc., Chicago, USA).

4.4 ETHICAL ASPECTS

The studies were approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (17.8.2004, decision number 127/04) and they were conducted in accordance with the Declaration of Helsinki (367). The patients were given oral and written information about the trial protocol and they provided written consent.

5 Results

5.1 RETROSPECTIVE STUDIES (STUDIES I-II)

The medical records of 592 patients were reviewed in the studies I-II. After excluding those patients with insufficient data, final diagnosis other than OSA, death during the follow-up, age <18 at the time of diagnosis and treatment, or unavailable contact information, 362 potential study subjects were traced. Forty-one percent of them (147 patients) had mild degree OSA.

Of these patients with mild degree OSA at baseline, 50 were invited to undergo an objective assessment for OSA by control polysomnography (study I). Eleven of them had been provided with CPAP prior to this study, 11 had underwent surgical UA operation due to OSA and 28 of them were considered as being untreated during the follow-up (Table 2). The UA surgeries consisted of two tonsillectomies, five UPPPs, two RFAs of the soft palate, one septoplasty and one nasal polypectomy. In patients with CPAP therapy, compliance with the CPAP was good, average use per night being 6.4 hours. The subjects in all groups were mainly male, middle aged, overweight/obese patients with mild OSA (see Table III in the original publication I). The patients in the CPAP group were significantly older than in the other two groups. At baseline, there was a significant difference (P=0.035) between groups in the presence of obstruction in the pharynx due to anatomical structures: 96.4% of untreated patients, 90.9% of patients in the operative group and 63.6% of patients in the CPAP group had obstructive features as verified by an otorhinolaryngologist. Otherwise, there were no statistically significant differences with respect to nasal obstruction, age, bodyweight, BMI, BMI change during follow-up, follow-up time, male/female proportion, smoking or AHI at baseline.

Table 2. Treatment modalities of study patients (n=50) in the study I.

		Treatment group, n (%)	
Treatment modality	**Untreated, n=28**	**Operative, n=11**	**CPAP, n=11**
No treatment	1 (3.6)		
A single session of lifestyle counseling	19 (67.9)	5 (45.5)	4 (36.4)
Dietitian consultation	3 (10.7)		
Pulmonologist consultation	4 (14.3)		
Instructions for positional treatment	7 (25.0)		
Dentist consultation		2 (18.1)	
Surgery		11 (100)	
CPAP			11 (100)
Terminated CPAP use	6 (21.4)	2 (18.1)	

CPAP=continuous positive airway pressure.

A letter with a follow-up questionnaire was mailed to all 362 individuals, of whom 287 (79 %) responded. However, patients with AHI>15/h, insufficiently filled questionnaires and those with CPAP treatment were excluded from the study II. Thus, 81 patients (40 in the operative group and 41 in the control group) with mild OSA were included in the analysis of subjective symptoms. In the operative group, nine RFAs, four tonsillectomies, four uvulectomie, 23 UPPPs and septoplasties were done. The patients in the operative group were younger at baseline (Table 3). Weight, BMI, and BMI change, follow-up time, male/female proportion, smoking habits, alcohol consumption, prevalence of CVD and metabolic diseases were similar in both groups. The mean follow up period was 2.9 (range 0.5-5.7) years.

Table 3. Characteristics of patients at baseline, study II.

	Group, mean (SD)		
Factors	**Control, n=41**	**Operative, n=40**	**P**
Gender, men/women	38/3	35/5	0.482
Age, years	52.2 (8.9)	46.0 (8.4)	0.002
Weight (kg)	90.1 (14.5)	85.4 (12.9)	0.129
BMI (kg/m^2)	29.1 (4.7)	27.6 (3.7)	0.119
AHI (events/hour)	9.3 (1.2)	9.2 (3.3)	0.855
Follow-up time	2.9 (1.2)	2.8 (1.4)	0.728

BMI=body mass index, AHI=apnea-hypopnea index. p value: Fisher's exact test or T-test for equivalence between groups.

5.1.1 Evolution of AHI in patients with mild OSA

The patients who were not actively treated experienced a statistically significant exacerbation of AHI during the mean follow-up time of 4.1 years (range 1.3-9.0; SD 1.9) (Figure 8). This was also statistically significant compared to the operative group, which did not experience a change in their AHI. It is also noteworthy that patients with CPAP treatment did exhibit an increase in AHI. Sixty-four percent of patients in the CPAP group developed at least moderate sleep apnea as measured by cardio-respiratory recording after a one night wash-out period from the use of CPAP. The value for the untreated group was 50%, and for operated patients 18%.

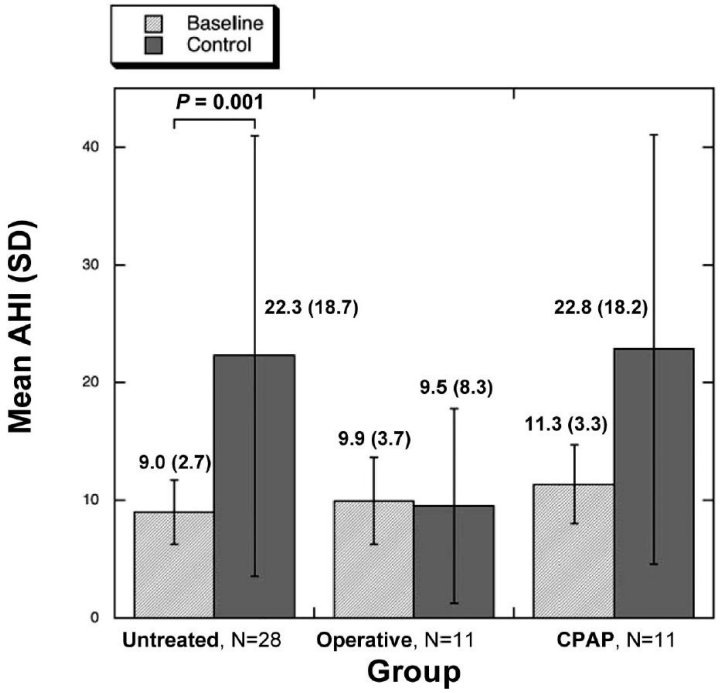


Figure 8. Mean apnea-hypopnea index (AHI) in untreated, operative and continuous positive airway ressure (CPAP) treatment groups at baseline and at control measurements. Reprinted with permission by John Wiley and Sons. Sahlman J et al., Laryngoscope 117(6):1107-11, 2007.

5.1.2 Evolution of the symptoms related to sleep apnea

At baseline, patients in the operative group were less alert in the morning (P=0.003) than those in the control (passive treatment) group. Otherwise, there were no significant differences in any of daytime or night-time symptoms between the two groups (Tables 4 and 5).

However, untreated patients had a worse progression of their sleep apnea symptoms compared to operated patients: there was no improvement in any of their daytime symptoms, and there was an increase in all night-time symptoms, except for snoring intensity. With respect to the daytime symptoms, daytime sleepiness and tiredness at work were significantly less prevalent among the operated patients than in the control patients. Odds ratio for daytime sleepiness and tiredness at work were 0.05 (95% CI 0.01-0.25, P<0.001) and 0.19 (95% CI 0.05-0.70, P=0.005), respectively, in the operated group compared with the untreated patients.

In terms of night-time symptoms, the operated group displayed less snoring, fewer apneas and less insomnia, and their sleep quality was better at follow-up. Adjusted odds ratio for frequent snoring was 0.15 (95% CI 0.03-0.75), for intensive snoring 0.06 (95% CI 0.02-0.22) and for better sleep quality 0.15 (95% CI 0.03-0.69) in the operated group as compared with the control group.

There was no difference between the surgical procedures in terms of reducing the proportion of symptomatic patients in either daytime or night-time items.

Table 4. Daytime symptoms of the study patients at baseline and follow-up (study II)

	Group, %		
Parameter	**Control, n=41**	**Operative, n=40**	**P**
Daytime sleepiness			
Baseline	87.2	95.0	
Follow-up	89.7	65.0	<0.001
Tired at work			
Baseline	55.0	61.5	
Follow-up	55.0	32.5	0.005
Not alert in the morning			
Baseline	38.2	76.5	
Follow-up	41.9	36.8	0.128
Falling asleep easily while watching TV			
Baseline	72.5	60.0	
Follow-up	80.5	52.5	0.128

P: likelihood-ratio test, adjusted for age, sex, body mass index, apnoea-hypopnea inex, baseline symptom status and follow-up time.

5.2 PROSPECTIVE STUDIES (STUDIES III-IV)

Study III involved 84 patients with mild OSA, and 40 controls recruited from those subjects who had AHI <5/h. Of these mild OSA patients, three were excluded from study IV since their BMI was less than 28 kg/m^2. Moreover, nine subjects dropped out later during the one year follow-up. The reason for dropouts were a dislike of the VLCD products in two cases, work-related schedule problems in six cases, and a death not related to OSA in one case. Moreover, 12 subjects had a missing cytokine analysis at 12 months due to an insufficient blood sample. One patient was excluded due to high hsCRP (>10) at baseline. Thus, study IV included those 59 sleep apnea patients (28 in the intervention group and 31 in the control group), who had both baseline and 12 mo cytokines measurements available and had participated in the prospective controlled trial for the 12 months (Flow chart in Figure 7).

In study III, patients in the non-apneic control group were younger (mean 45.6 years, SD 11.5) than patients with mild OSA (mean 50.4 years, SD 9.3), P=0.013 (see Table 1 in the original publication III). In study IV, OSA patients in the intervention group were heavier, Table 6. The analyzed sleep recording time was longer in the control group (434 min vs. 382 min, P=0.028). However, the time of over six hours also in the intervention group can be considered as more than adequate for a reliable analysis. Otherwise the groups were similar in terms of the other sleep apnea indices, chronic diseases and medications.

Table 5. Night-time symptoms of the study patients at baseline and follow-up (study II)

	Group, %		
Parameter	**Control, n=41**	**Operative, n=40**	**P**
Frequent snoring			
Baseline	80.0	94.9	
Follow-up	86.8	71.4	0.014
Intensive snoring			
Baseline	89.5	97.3	
Follow-up	75.0	35.0	<0.001
Witnessed apneas			
Baseline	35.3	50.0	
Follow-up	76.5	13.8	<0.001
Poor quality of sleep			
Baseline	41.9	54.8	
Follow-up	60.6	36.1	0.033
Frequent awakenings			
Baseline	58.5	60.0	
Follow-up	65.9	50.0	0.133
Insomnia			
Baseline	35.0	35.0	
Follow-up	41.5	22.5	0.022
Nocturia			
Baseline	36.8	36.1	
Follow-up	52.6	34.3	0.747

P: likelihood-ratio test, adjusted for age, sex, body mass index, apnoea-hypopnea inex, baseline symptom status and follow-up time.

During the 1-year of follow-up the mean change in weight was -10.7 kg (10.4 % of the initial weight) in the intervention group, and -2.9 kg (3.2 %) in the control group (P<0.001). A marked difference was found in all anthropometric measurements (BMI, fat % and waist circumference) between the two study groups, although some significant improvements took place also in the control group. The intervention group achieved more marked metabolic improvements, and the insulin level improved more in the intervention group compared with the control group (P=0.021). There were no statistically significant differences in the prevalence of smoking or chronic diseases between groups at 1-year. (Table 7).

Table 6. Patient characteristics at baseline, study IV. The data present proportions given as percentages (%) or mean values with standard deviations (SD).

	Group, (SD)		
	Control, N=31	**Intervention, N=28**	**P**
Men, %	71	82	0.270†
Age, years	51.8 (9.0)	52.5 (8.8)	0.576‡
Weight, kg	91.4 (10.5)	102.0 (12.9)	0.001
BMI, kg/m^2	31.5 (2.5)	33.5 (3.0)	0.007
Total body fat, %	29.0 (7.0)	30.1 (6.9)	0.035
Waist circumference, cm	105 (6.3)	113 (9.2)	0.035
Plasma fasting glucose, mmol/l	6.1 (1.7)	6.5 (2.7)	0.632
Serum insulin, mU/l	10.8 (4.6)	13.9 (7.3)	0.085
HOMA-IR	2.9 (1.7)	4.3 (3.9)	0.114
Plasma total cholesterol, mmol/l	4.7 (1.0)	4.6 (0.7)	0.491
Plasma HDL cholesterol, mmol/l	1.1 (0.3)	1.0 (0.2)	0.296
Plasma triglyserides, mmol/l	1.8 (1.0)	1.7 (1.2)	0.829
Plasma ALT, U/l	34 (25)	39 (20)	0.571
Systolic blood pressure, mmHg	129 (13.7)	133 (10.6)	0.158
Diastolic blood pressure, mmHg	80 (8.5)	81 (8.2)	0.713
Current smoker, %	25.9	7.4	0.074
Hypertension*, %	35.5	53.6	0.163
Coronary artery disease*, %	3.2	3.6	0.864
Diabetes*, %	9.7	14.3	0.579
AHI, events/h	9.6 (3.0)	10.0 (3.0)	0.502
Mean SaO_2, %	94 (1.2)	94 (1.5)	0.349
SaO_2 below 90%, %	1.4 (3.3)	3.0 (5.5)	0.162
ESS	10.0 (5.1)	10.2 (4.9)	0.824
Mean heart rate, beat/min	58 (7.5)	59 (7.8)	0.379

*P: P value from logistic regression analysis for dichotomous variables, ANCOVA for continuous variables; adjustment for age and sex. BMI=body mass index, HOMA-IR=the homeostasis model assessment of insulin resistance, HDL= high-density lipoprotein, ALT=alanine aminotransferase, AHI=apnea hypopnea index, SaO2= oxygen saturation. †Adjusted for age. ‡Adjusted for sex. * self reported*

Table 7. Changes in anthropometric, biochemical and cardio-respiratory recording parameters after the 1-year intervention. The data present mean changes with standard deviation (SD). Study IV.

	Group, change (SD)		
	Control, N=31	**Intervention, N=28**	**P**
Weight, kg	-2.9 (6.5)**	-10.7 (6.1)***	<0.001[a]
BMI, kg/m^2	-1.01 (2.2)**	-3.53 (2.0)***	<0.001[a]
Total body fat, %	-0.75 (3.2)	-5.11 (3.5)***	<0.001[a]
Waist circumference, cm	-3.70 (6.6)**	-11.6 (6.4)***	0.001[a]
Plasma fasting glucose, mmol/l	-0.44 (1.5)	-0.75 (2.5)	0.827
Serum insulin, mU/l	-1.00 (3.6)	-6.54 (7.4)***	0.021
HOMA-IR	-0.43 (1.3)*	-2.45 (4.0)**	0.057
Plasma total cholesterol, mmol/l	0.01 (0.7)	-0.18 (0.8)	0.693
Plasma HDL cholesterol, mmol/l	0.09 (0.2)**	0.12 (0.2)**	0.588
Plasma triglyserides, mmol/l	-0.21 (0.7)	-0.57(1.2)*	0.053
Plasma ALT, U/l	-9.58 (21.1)*	-15.6 (18.9)***	0.150
Systolic blood pressure, mmHg	-0.66 (7.9)	0.74 (10.7)	0.279
Diastolic blood pressure, mmHg	0.14 (6.2)	-0.26 (6.7)	0.874
AHI, events/h	-0.7 (7.6)	-3.7 (6.0)**	0.297
Mean SaO_2, %	-0.05 (1.4)	0.87 (1.3)**	0.062
SaO_2 below 90%, %	0.62 (3.9)	-1.77 (4.3)	0.316
ESS	-2.2 (3.0)***	-3.3 (4.0)***	0.187
Mean heart rate, beat/min	0.87 (5.3)	-3.06 (5.9)	0.090

*P= p value from ANCOVA adjusted for age, sex, body mass index and baseline level of respective variable for difference between groups. Asterisks indicate whether the change between follow-up and baseline was significant in the respective group: *P<0.05, **P<0.01 and ***P<0.001; paired samples T-test. BMI=body mass index, HOMA-IR=the homeostasis model assessment of insulin resistance, HDL=high–density lipoprotein, ALT=alanine aminotransferase, AHI=apnea-hypopnea index, SaO_2=arterial oxygen saturation, ESS= Epworth sleepiness scale [a]Not adjusted for body mass index.*

Total AHI decreased (-3.7/h, SD 6.0, P=0.003) and mean SaO_2 increased (0.87, SD 1.3, P=0.003) in the intervention group during the follow-up, but the differences between the groups were not statistically significant (Table 7). Also the other sleep parameters displayed a trend towards improvement in favor of the intervention group. Daytime sleepiness decreased significantly in both groups, the difference between the groups being non-significant.

Table 8 presents the inflammatory biomarker concentrations in the mild OSA group and the non-OSA control group at baseline. The level of TNF-α was higher and IL-1β lower among OSA compared with control patients. The two anti-inflammatory cytokines, IL-10 and IL-1Ra were higher in patients with mild OSA than in controls. There were no differences in the baseline concentrations of inflammatory markers between those patients

who continued in the supervised lifestyle intervention group and those in the single session lifestyle counseling group, i.e. the control group

Table 8. Baseline inflammatory biomarker concentrations in patients with and without mild obstructive sleep apnea (OSA), Study III

	Group		
	Mild OSA, N=84	**Non-OSA, N=40**	**P**
TNF-α	1.54 (1.75)	1.17 (1.58)	0.004
IL-1β	0.19 (1.51)	0.23 (1.31)	0.004
IL-6	2.36 (1.90)	2.14 (2.01)	0.893
hsCRP	1.67 (2.53)	1.30 (2.53)	0.087
IL-10	1.28 (2.34)	0.70 (1.51)	<0.001
IL-1Ra	478 (1.65)	330 (1.97)	0.003

P: ANCOVA on logarithmically transformed variables adjusted for age, sex, body mass index, fat%, chronic diseases and non-steroidal anti-inflammatory medication.

The biomarker levels in whole study III population were examined in relation to OSA severity (AHI and night-time oxygen saturation) at baseline. The hsCRP levels were higher in patients with AHI 5-10/h and AHI>10/h compared with subjects with AHI <2/h (P=0.049 and P=0.009, respectively). IL-1β showed a decline in conjunction with AHI (P<0.001). The concentration of IL-6 was found to be higher in patients who spent more time at SaO_2 <90 % during their sleep. The levels of both anti-inflammatory cytokines, IL-10 and IL-1Ra increased with the amount of sleeping time spent at SaO_2 <90 % (P=0.016 and P<0.001, respectively)(See Tables 3 and 4 in the original publication III).

5.2.1 Changes in pro-inflammatory biomarkers

During the 1-year follow-up, levels of IL-6 and hsCRP decreased significantly in both groups (Table 9). The decreases tended to be greater in the intervention group, but the differences between the groups did not reach statistical significance. The change in AHI was a significant determinant of change in hsCRP levels: β=0.080, 95% CI 0.019, 0.141, P=0.011. Insulin seemed to be related to IL-6 levels, (β=0.082, 95% CI 0.001, 0.163, P=0.049 for IL-6), but in multivariate analysis, the association vanished and only smoking remained as a significant predictor of IL-6 level (β=1.256, 95% CI 0.131, 2.382, P=0.029). Moreover, the improvement in total body composition variables (mainly BMI) exhibited several borderline significant (P=0.06) associations with hsCRP and IL-6. An hsCRP concentration > 3.0 mg/l, which is known to associate with increased risk for cardiovascular risk, was found only in three patients out of those 14 patients who had hsCRP > 3.0 mg/l at baseline (seven patients in both groups had a high value at baseline, and two patients in control group and one patient in the intervention group had an elevated level at 1-year). No significant differences were found either for TNF-α or IL-1β levels between the groups. However, improving nocturnal SaO_2 was associated with decreasing TNF-α: change of SaO_2 and change of SaO_2 <90% in the same model: β=-0.536, 95% CI -0.834, -0.239, P=0.001 for ΔSaO_2, and β=-0.139, 95% CI -0.237, -0.041, P=0.007 for Δ SaO_2 <90%.

5.2.2 Changes in anti-inflammatory biomarkers

There was a statistically significant reduction in the levels of IL-1Ra in the intervention group compared with the control group (Table 9). The decrease in IL-1Ra was best

explained by improving insulin metabolism (β=11,748, 95% CI 1.260, 22.237, P=0.029). Weight loss was associated with a change in IL-Ra in the linear regression but in the multiple regression analysis, this finding disappeared. A significant reduction of IL-10 occurred in the control group over the follow-up period. This was probably due to the higher baseline levels, the reason for which remains unknown. The changes in IL-10 levels were associated with improvements in body composition.

In the whole study population, no associations were found between the levels of immune mediators and excessive daytime sleepiness measured by ESS.

Table 9. The 12 month changes in inflammatory biomarker concentrations in patients with mild OSA by treatment group. Study IV

	Group		
	Control, n=31	**Intervention, n=28**	**P**
TNF-α	0.25 (1.14)	-0.32 (1.44)	0.145
IL-1β	0.10 (0.27)	0.18 (0.70)	0.788
IL-6	-0.73 (2.00)*	- 1.51 (1.55)***	0.079
hsCRP	-0.68 (1.67)**	-1.17 (1.67)***	0.067
IL-10	-0.45 (0.83)**	-0.25 (1.03)	0.962
IL-1Ra	-38.6 (238)	-147 (207)**	0.001

*Padj: ANCOVA on logarithmically transformed variables adjusted for age, sex, fat% and baseline level of respective variable. Asterisks indicate whether the change during the 12 months was significant in the respective group: *P<0.05, **P<0.01 and ***P<0.001, paired samples T-test.*

6 Discussion

The present study shows that untreated patients with mild OSA experience significant symptoms related to this disease. Furthermore, the study supports the belief that OSA is a progressive disease. In carefully selected patients, upper airway surgery can prevent the exacerbation of both symptoms and AHI. Obesity is a major risk factor for OSA, and weight loss is recommended in all clinical guidelines. However, until recently, there have been no well-conducted studies on the effect of weight loss in the treatment of OSA (143-147). This study demonstrated that there is an activation of the inflammatory system in overweight patients with mild OSA. Furthermore lifestyle intervention with weight reduction was observed to improve the signs of low-grade inflammation. These findings suggest that active treatment should be provided already in the early stages of OSA to prevent the progression of the disease and to reduce the risk for co-morbidities.

6.1 EVOLUTION OF MILD OSA

In studies I-II, the untreated patients experienced an increase of AHI and OSA related symptoms independent of changes in weight. The results of these present studies on AHI are well in line with the earlier proposal that OSA is preceded by simple snoring, followed by rapid increase in respiratory events and a plateau phase (368), as well as with the studies in which a progression of snoring or OSA have been reported (2,73,75-81). However, there are also reports which state that AHI does not deteorirate over time in untreated patients (82-86). If one considers these studies, then three included an elderly population, and thus support the proposal that the deterioration happens before old age (82,84,85). It is noteworthy that the trials reporting no change in AHI included relatively small number of patients (17-58 patients) while there were five large studies (160-2968 patients) among those which all concluded that OSA does deteriorate with time. Our study did not include simple snorers and thus we can not conclude if OSA is a continuum of snoring. If this would be the situation, the treatment of simple snoring would become important. Taken together, it seems that age, time, body weight change and mild-to-moderate OSA at baseline are the most important determinants of changes in OSA severity (2,73,80,81,83,85). Moreover, it has been demonstrated that untreated patients have more severe oxygen desaturations and an increased intensity of snoring. The evolution of OSA symptoms has not been studied extensively previously: there do not seem to be significant changes in daytime sleepiness as measured my ESS (2,86) and multiple sleep latency test (83) in untreated patients even though the ESS scores were usually higher at the follow-up.

In the present study, operative treatment was found to represent a good and effective alternative for the treatment of mild OSA, when used selectively. However, this study did not elucidate criteria for operative treatment. The role of operative treatment in OSA is controversial due to the paucity of randomised controlled studies and the lack of long-term outcome reports. However, surgery has been recommended for mild-to-moderate OSA in non-obese patients (369). As reviewed earlier, the best result of surgical treatment on OSA has been achieved with operations targeted to treat retropalatal obstruction compared to retrolingual obstruction with or without retropalatal obstruction (177). This is in accordance with the present findings that case-to-case selection of nasal or retropalatal obstruction is beneficial in the long run.

The finding of non-significant worsening of AHI in patients on CPAP treatment is in line with earlier reports that CPAP improves but does not cure OSA. However, it has to be used every night because the benefit is not sustained, though the AHI level may remain decreased after one night without CPAP (370,371). Due to the short washout period in the

present study, the results on AHI for the CPAP group could have been even worse if measured after a longer washout period. The available evidence supports the use of CPAP as a first-line treatment for individuals with high AHI and moderate-to-severe sleepiness associated with obstructive sleep apnea (152). However, it has been reported that CPAP treatment is effective in improving sleep quality and decreasing symptoms, especially subjective sleepiness, in subjects with mild OSA (159,160,372-376).

6.2 OSA AND INFLAMMATORY BIOMARKERS

There are only a few publications which have examined the inflammatory biomarkers in the early stages of OSA. Moreover, there are no publications at all on the effect of weight loss on inflammatory markers in OSA.

This present study showed that the inflammatory system is activated in patients with mild OSA as compared with individuals without OSA. The most important new information emerging from this study was that both anti-inflammatory marker levels, IL-1Ra and IL-10, were elevated in overweight or obese patients with mild OSA. This increase was higher in those subjects with higher AHI and more severe night-time desaturations. Successful weight loss therapy resulted in a decrease of the level of IL-1Ra, and the improving insulin resistance best explained this decrease. These results concerning insulin metabolism and IL-1Ra are understandable because it is known that IL-1Ra levels are elevated in those individuals who will later develop diabetes (361), and, on the other hand, this cytokine improves glycemic control in by improving the IL-1 induced beta-cell dysfunction (276,377). In the perspective of OSA patients' general health, it is also important that both IL-10 and and IL-1Ra have been shown to have a beneficial effect on the risk of suffering atherosclerosis and coronary events (275,378-380).

With the respect to the pro-inflammatory cytokines, this investigation supports the earlier reports of the association between OSA severity and levels of pro-inflammatory CRP, IL-6 and TNF-α, i.e. the pro-inflammatory activation seems to be weaker than that in more severe disease (6,288,290,291,293,295,296,298,301-303). In this present study concentrating on early stages of OSA, there were no significantly elevated levels of CRP or IL-6 as compared to normal subjects (290,307,310,312). However, even a minimal number of apnea-hypopnea events seemed to correlate with CRP. This supports the proposal that in more severe disease with higher AHI, the CRP level is elevated. Moreover, an association was detected between elevated TNF-α and AHI. The lower levels of IL-1β in the group of sleep apneics compared with the controls may be explained by the simultaneous high concentration of IL-1Ra, which negatively regulates IL-1 signaling, and IL-10, which inhibits the production of IL-1. This high activity of the anti-inflammatory biomarkers may explain the lower concentrations of pro-inflammatory markers in mild OSA as compared to those encountered in more severe disease.

Weight loss resulted in reductions in CRP and IL-6 concentrations even though there was no difference between the supervised and traditional lifestyle guidance group. Both of these biomarkers are known to be associated with obesity and to decrease in response to weight loss (336,341,342). It has also been proposed that it is the excessive fat and not OSA per se, which is responsible for the elevation of CRP and IL-6 in overweight patients with OSA (6,288,307,312,316). However, this present study revealed that in patients with mild OSA, the degree of AHI and the change in AHI achieved by weight loss were significant determinants of the CRP levels.

Finally, the interaction of pro- and anti-inflammatory cytokines is complex and multidirectional. Anti-inflammatory cytokines can inhibit the production (IL-10 inhibits IL-6 and IL-1) or the effect (IL-1Ra inhibits IL-1) of pro-inflammatory compounds (381,382). In addition, IL-10 is known to enhance the production of IL-1Ra. In the light of these previous and the present data, it seems that there is an active ongoing struggle to counteract the pro-inflammatory processes, and that the body still has capacity to succeed in this effort, even

in overweight patients with mild OSA and co-morbidities. Moreover, this activation seems to vanish with weight loss, partly due to improvement of metabolism and partly due to improving night-time breathing. Thus, mild OSA can be considered as a condition similar to pre-diabetes: patients have same risk factor (obesity), a similar activation of low-grade inflammation, and lifestyle intervention can stop the evolution to full-blown disease with its increased risk of serious co-morbidities. On the basis of this study, it seems that obesity, mild OSA and inflammation are interacting but it is impossible to show the mutual causality – that would need a larger and better selected population (subjects with no co-morbidities and also a group of lean subjects).

6.3 CLINICAL ASPECTS

We demonstrated that mild OSA patients experience the disease as being detrimental to their quality of life, and if left untreated, the disease progresses to become more severe with time as measured by both AHI and the severity of symptoms. These patients should not be left untreated. Thus, the clinical guidelines of American Academy of Sleep Medicine for OSA are very important: the questions regarding OSA should be incorporated into routine health evaluations, a physician should keep this disease in mind, and if diagnosed, "OSA should be approached as a chronic disease…" (30).

Largely on the basis of Kuopio sleep apnea study, lifestyle intervention with weight reduction is now included in the Finnish "Current Care" evidence based treatment guidelines of OSA in adults, but more effort should certainly be exerted to introduce it in widespread clinical practice (29). Intensive lifestyle and weight loss program in a group supervised by a clinical nutritionist could be a good option. This type of first-line treatment is also recommended for obesity (141). In Finland, a good way to reach the overweight or obese individuals could be through the primary health care systems provided by communities and employers. However, the knowledge about the association of OSA and comorbidites, and the beneficial effect of weight loss needs to be increased.

Weight loss resulted in improvement of insulin and cholesterol metabolism and also lowered alanine aminotransferace levels. This is very important, since most OSA patients are at a high risk of suffering cardiometabolic complications or even already have these diseases. Thus, all physicians working with these diseases need to be alerted to ask about snoring, breathing pauses and EDS, and to remember OSA as a possible risk of these diseases and as a cause of poor treatment results.

This study raises the question of whether an early and successful intervention with weight loss could normalize the elevated levels of inflammatory cytokines, and whether this would benefit the patients in terms of reduced cardiovascular risk, particularly obese patients with OSA. It is not yet clear, if the up-regulation of anti-inflammatory cytokines in mild OSA is sufficient to have some protective effect against the cardiometabolic disorders in patients with OSA. More prospective studies are warranted to assess the prognostic relevance of these biomarkers in different study populations.

6.4 LIMITATIONS OF THE PRESENT STUDY

The numbers of patients in the present studies were not large, which has also been the case in most other studies investigating mild OSA. This probably results from the relative disinterest in this subgroup of OSA, because more emphasis has been paid to the more severe forms of OSA due to the exacerbated symptoms and the more obvious co-morbidity risk. The problem is statistically exaggerated when patients are divided into smaller subgroups within a study.

In the retrospective part of the study, those patients who were more symptomatic and/or dissatisfied with their OSA at the time of inquiry, may have been more likely to complete the questionnaire and return it. This may have resulted in selection bias.

The prospective part of this thesis was based on a sub-analysis of an on-going study. The original intent was to investigate the effect of weight loss on mild OSA and the study was not specially designed to analyze the changes in inflammatory biomarkers. The number of patients was reduced because of unsuccessful biomarker analysis. However, this is the first study in this field and thus will serve as a good reference for further studies. Although the results regarding the changes in inflammatory mediators are novel especially in terms of the anti-inflammatory compounds, they need to be replicated in larger studies, and by examining healthy normal weight patients with mild OSA to quantify the true impact of the disease on these changes. Furthermore, a longer follow-up time of one year would give more reliable objective outcome information on the sustainability of reduced weight and improved OSA.

The diagnosis of OSA was based on overnight in-home cardio-respiratory recording. This limits the further analysis on how the symptoms and inflammatory markers relate to sleep structure, for example to the arousal index. Night-to-night variability in AHI can play a role in the findings of study. However, in the home environment, one night testing has been shown to be reliable (383).

7 Conclusions

The findings of the present study were

1. Mild OSA has a natural tendency to worsen with time. Active treatment can prevent progression of the disease. (Study I).
2. Obstructive sleep apnea patients experience symptoms detrimental to quality of their life. If left untreated, both night-time and daytime symptoms become worse. Upper airway surgery may be a good treatment option in selected cases. (Study II).
3. There is an activation not only of pro-inflammatory biomarkers but also anti-inflammatory compounds in overweight patients with mild OSA. Hypoxemia seems to have an effect on the concentrations of these biologically active compounds. (Study III).
4. In overweight patients with mild OSA, lifestyle intervention with weight reduction results in improvement of low-grade inflammation. (Study IV).

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Appendices

1. Retrospective data
2. The follow-up of obstructive sleep apnea patients in Kuopio University Hospital
3. The effect of weight loss and lifestyle guidance on obstructive sleep apnea

RETROSPECTIVE DATA Patient number _____

The follow-up of Obstructive sleep apnea patients in Kuopio University Hospital

NAME: **Sex:** 1. Male 2. Female
DATE OF BIRTH:

Height:_____ **Weight:**_____ **BMI:**_____

A. STATUS:

1. Septal deviation
1. No
2. Yes

2. Nasal polyps
1. No
2. Yes.

3. Neck
1. Normal
2. Thick

4. Pharynx
1. Normal
2. Obstructed

5. Tonsils
1. Non-obstructive
2. Large, obstructive
3. Removed

6. Uvula
1. Normal
2. Enlarged

7. Soft palate
1. Normal
2. Flobby/elongated

8. Larynx
1. Normal
2. Abnormal

9. Tongue 1. Normal 2. Large **10.** _____

B. SLEEP RECORDING:

Date:_____**Equipment:**_____
Total recording time:_____**h**_____**min. Snoring:**_____**h/(%)**
AHI:_____ **ODI4:**_____
Lowest saturation:_____%

Sleep apnea
1. Obstructive
2. Central
3. Mixed

Positional dependence
1. No
2. Yes

C. TREATMENT

1. No treatment
2. Lifestyle guidance
   a. ENT-doctor
   b. nutritionist
3. Operative
4. Pulmonologist consultation, CPAP
5. Neurologist consultation
6. Dentist consultation
7. _____

Operation
1. TE
2. Uvulectomy
3. TE+uvulectomy
4. UPPP
5. LUPP
6. BOX
7. Mandibular advancement
8. _____

D. QUESTIONNAIRE

Question	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15a	15b	15c	15d	15e	15f
Points																				

Question	15g	16	17	18	19	20a	20b	20c	20d	20e	20f	20g	20h	20i	20j	20k	20l
Points																	

21. Medical conditions: 1. No 2. Yes_____
_____
_____

22. Medication: 1. No 2. Yes_____
_____
_____

THE FOLLOW-UP OF OBSTRUCTIVE SLEEP APNEA PATIENTS IN KUOPIO UNIVERSITY HOSPITAL

NAME **Tel.**

DATE OF BIRTH **Date**

Height: **Weight:**

Please circle the most appropriate option

1. How many hours do you sleep per night?
1. 6 h or less 2. 6-8 h 3. more than 8 h

2. Has somebody told you to have breathing pauses when asleep?
1. No 3. Don't know 5. Always
2. Sometimes 4. Often

3. Are you tired during daytime?
1. Always 3. Don't know 5. No
2. Sometimes 4. rarely

4. Do you take a nap?
1. No 2. Yes

5. Are you more tired than your friends or co-workers during daytime?
1. No, much more awake than they are 4. Yes, more tired than they are
2. No, more awake than they are 5. yes, much more tired than they are
3. No difference

6. Have you ever fallen asleep when driving a vehicle?
1. Never 3. Twice 5. At least 5 times
2. Yes, once 4. 3-4 times

7. Have you ever been in an accident due to tiredness?
1. Never 3. Twice 5. At least 5 times
2. Yes, once 4. 3-4 times

8. Do you easily fall asleep at a lesson, or while watching a movie/TV etc.
1. Always 3. Sometimes 5. Never
2. Often 4. Rarely

9. Have you ever had complaints about your tiredness at school or at work?
1. No 2. yes

10. How soon do you fell asleep when going to bed in the evening?
1. In 10 min or faster 2. 10-30 min 3. more than 30 min

11. How do you sleep?
1. Very restless 3. Don't know 5. Very calm
2. Restless 4. Calm

12. How many times do you wake up during a night?
1. Not at all 3. Twice 5. Five times or more
2. Once 4. 3-4 times

13. In the last three months, have you had insomnia?
1. Almost every night 3. Sometimes 5. Never
2. Often 4. Seldom

14. Do you feel refreshed when you wake up in the morning?
1. Yes, very 3. Don't know 5. I feel extremely tired
2. To some extent 4. I feel tired

15. How often have you had these symptoms during night-time in the last years. Cross the appropriate choice.

		Always	Often	Sometimes	Never	Don't know
a	Snoring					
b	Teeth biting					
c	Urge to urinate					
d	Nightmares					
e	Sleepwalking/talking					
f	Sweating during night					
g	Choking					

16. Do you snore?

1. I don't snore
2. Rarely/ in certain positions
3. Most of the sleeping-time
4. All the time and loudly

17. Have you taken sleeping pills during the last three months?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Regularly

18. How much do you drink alcohol? (Days per week or month. How much?)_____

_____

19. Do you smoke?

1. Never
2. Ex-xmoker
3. Yes, 1-5 cigarettes/day
4. 6-10 /day
5. 11-20 /day
6. More than 20/day

20. Have you had the following symptoms? Cross the appropriate choice.

		I have now	I have had	Never	Don't know
a	**Morning headache**				
b	**Difficult to concentrate**				
c	**Nervousness**				
d	**Irritability**				
e	**Impotence**				
f	**Decreased libido**				
g	**High blood pressure**				
h	**Depression**				
i	**Coronary artery disease**				
j	**Heart attack**				
k	**Cerebrovascular disease**				
l	**Pulmonary diseases**				

21. Other medical conditions 1. No 2.Yes_____

_____

22. Medication_____

---

23. Shift work 1. No 2. yes

24. What kind of treatment have you had for sleep apnea? You may circle several choices if needed.

1. No treatment
2. Lifestyle guidance by a doctor
3. Lifestyle guidance by a nutritionist
4. Positional treratment
5. I had an operation
6. I have CPAP
7. Something else_____

25. If you have had an operation due to sleep apnea are you

1. Satisfied 2. Dissatisfied with the result

26. If you have (had) CPAP are you

1. Satisfied 2. Dissatisfied 3. Dissatisfied and terminated the use

27. Have you ever tried to lose weight due to sleep apnea?

1. No 2. Yes, but I regain the weight 3. Yes and I remain at the lower weight

28. How do you see your sleep apnea symptoms at the moment compared to your last visit to the ENT-department or before treatment?

Snoring	1. decreased a lot	4. increased a little bit
	2. decreased a little bit	5. increased a lot
	3. remained the same	6. don't know
Breathing pauses	1. decreased a lot	4. increased a little bit
	2. decreased a little bit	5. increased a lot
	3. remained the same	6. don't know
Daytime sleepiness	1. decreased a lot	4. increased a little bit
	2. decreased a little bit	5. increased a lot
	3. remained the same	6. don't know

THANK YOU FOR YOUR CONTRIBUTION!

Note! The questions 23-28 were asked only at the follow-up.

PATIENT DATA Baseline/12 months Patient nr. _____

THE EFFECT OF WEIGHT LOSS AND LIFESTYLE GUIDANCE ON OBSTRUCTIVE SLEEP APNEA

NAME: **Tel.**

Sex:_____ **Height:**_____ **Weight:**_____

Smoking 1. No 2. Yes

How much do you drink alcohol? How many days per week/month and how much?_____
_____

Medical conditions_____

_____

Medication_____

_____

In the past 4 weeks, when you have been asleep, to the best of your knowledge do you snore?

1. All of the time 3. Some of the time 5. None of the time
2. Most of the time 4.A little of the time 6. Don't know

In the past 4 weeks, how would you describe your snoring or how has it been described to you?

1. None 3. Moderate 5. Very severe
2. Mild 4. Severe 6. Don't know

My snoring wakes me from sleep and/or makes me tired the next day

1. Definitely true 3. Don't know 5. Definitely false
2. Somewhat true 4. False

During the past 4 weeks, how much did your snoring interfere with your normal sleep and your level of energy?

1. Not at all 3. Moderately 5. Extremely
2. A little bit 4.Quite a bit

Does your snoring annoy or bother your spouse/bed partner?

1. Extremely 3. Moderately 5. Not. at all
2. Quite a bit 4. A little bit 6. Don't know

Compared to one year ago, how would you rate your snoring now?

1. Much less 3. About the same 5. Much more than a year ago
2. Somewhat less 4. Somewhat more

How would your spouse/bed partner describe your snoring?

1. Extremely loud 3. Somewhat loud 5. No snoring at all
2. Very loud 4. Soft and quiet 6. Don't know

Please describe when you snore?

1. I don't snore 3. Only in certain positions 5. I snore all of the time
2. I snore very rarely 4. I snore most of the time

Have someone told you that you have breathing pauses when you sleep?

1. No 3. I don't know 5. Always
2. Sometimes 4. Often

Do you nap? 1. No 2. Yes

How long does it take to fall asleep in the evening?

1. Max. 10 minutes 2. 10-30 min 3. more than 30 minutes

How do you sleep at night?

1. Very restless
2. Restless
3. Don't know
4. Calm
5. Very calm

How many times do you wake up during the night?

1. Not at all
2. Once
3. Twice
4. 3-4 times
5. At least five times

In last three months, have you had insomnia ?

1. Almost every night
2. Often
3. Sometimes
4. Rarely
5. Never

Do you feel refreshed when you wake up in the morning?

1. Yes, very
2. To some extend
3. Don't know
4. I feel tired
5. I feel extremely tired

Do you have headache in the morning?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Regularly

In last three months, have you used sleeping pills?

1. Never
2. Rarely
3. Sometimes
4. Often
5. Regularly

Have you ever fallen asleep when driving a vehicle?

1. Never
2. Yes, once
3. Twice
4. 3-4 times
5. At least five times

Have you ever had a traffic accident due to tiredness?

1. Never
2. Yes, once
3. Twice
4. 3-4 times
5. At least five times

Has your working ability been decreased?

During last three months?	During last year?
1. Yes, _____days	1. Yes,_____days
2. No	2. No

How likely do you doze off or fall asleep in the following situations? Choose the most appropriate number.

Situation	**No change**	**Slight change**	**Change of dozing Moderate change**	**High change**
Sitting and reading	0	1	2	3
Watching TV	0	1	2	3
Sitting inactive in a public place (e.g.a theater or a meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the after-noon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3

Sitting quietly after a lunch without alcohol	0	1	2	3
In a car, while stopped for a few minutes in traffic	0	1	2	3

Johanna Sahlman

Obstructive Sleep Apnea in Adults

Evolution, and Related Inflammation in Early Stages of Disease

Obstructive sleep apnea (OSA) causes both daytime and night-time symptoms for the patient; in particular the more severe forms of OSA are also associated with an increased risk of cardiovascular and metabolic diseases. This thesis examines the evolution of mild OSA. The activation of low-grade inflammation, which is one of the mechanisms leading to abovementioned co-morbidities, as well as the effect of weight loss on inflammation are clarified in overweight patients with mild OSA. This study demonstrated that even mild OSA should be actively treated to prevent progression of the disease. Moreover, low-grade inflammation was found to be activated already in early stages of disease. Weight loss was a useful way to decrease the inflammatory burden.

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