Weight Reduction and Alcohol Abuse in Sleep Apnea Patients

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WEIGHT REDUCTION AND ALCOHOL ABUSE 
IN SLEEP APNEA PATIENTS

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"There is time for many words, and there is also a time for sleep”

Homer, *The Odyssey*
Obstructive sleep apnea syndrome (OSAS) has an estimated prevalence of 2 percent in women and 4 percent in men. OSAS is characterized by repeated obstructive events of the pharyngeal upper airway during sleep. OSAS, which often causes excessive daytime sleepiness, is both an individual and a societal problem with large personal suffering and societal costs. The most common cause of OSAS is overweight and obesity, an increasing burden worldwide. In Sweden, 43 percent of the adults are estimated to be overweight. Other causes to OSAS are anatomical narrowness with large tonsils and tongue, alcohol, smoking, and supine sleeping position. The prevalence of alcohol overconsumption is estimated to 10 percent in Swedish adults.

This thesis evaluates two aspects of OSAS; firstly, the prevalence of alcohol over-consumption, secondly the effects of dietary weight reduction in the obese OSAS patient.

In PAPER I we evaluated the overuse of alcohol and benzodiazepines among 98 OSAS patients at our ENT-department, which has not previously been reported. We screened the patients with a local questionnaire, but also objectively with blood and urine tests. A new laboratory marker, Carbohydrate-Deficient-Transferrin (CDT), reflecting the alcohol consumption the last two weeks, was used, in combination with benzodiazepine metabolites in urine. The prevalence of positive CDT was 8.5 percent, which is approximately the same level as estimated in the general population. The prevalence of benzodiazepine use was 3.2 percent. Only 2 persons denied study participation. None of the patients who screened positive for CDT had indicated overuse of alcohol in the questionnaire, and none was willing to accept contact with an abuse-clinic.

In PAPER II we performed a randomized pilot study between weight reduction and expectancy among 20 obese (Body Mass Index >30) OSAS males. There is a demand for randomized studies on weight reduction and the goal of the study was to evaluate our weight reduction program in obese OSAS patients. The diet consisted of 8 weeks low-calorie-diet (LCD) with a protein drink (Nutrilett®) in combination with weekly group meetings for support. The controls were asked to maintain their weight. Evaluations included changes in weight and Oxygen Desaturation Index (ODI4) measured with polygraphy. The results showed significant differences between the intervention and control group concerning changes in weight and ODI4. However, there was a large drop-out rate (45 %), which makes the results uncertain. On the other hand, this pilot study showed us how difficult it is to motivate obese OSAS patients to change their life-style.

In PAPER III and IV we continued to evaluate the effects of weight reduction with LCD in obese OSAS with a non-randomized prospective intervention study. We improved our selection methods to included better motivated patients compared to in study 2. The LCD was followed by an additional behavioral modifying group therapy for 2 years, which aimed to change dietary and exercise habits. A group of 33 patients (24 males, 9 females) were included, out of who 23 used OSAS-device (19 Continuous Positive Airway Pressure (CPAP), 4 Mandibular Retaining Device (MRD)). The evaluations included weight, bioelectrical impedance, polysomnographic respiratory and sleep parameters, metabolic status, blood pressure, excessive daytime sleepiness and ratings of quality of life. Such extensive information has not been reported previously for this patient group. The weight reduction at 6 months was in mean 18 kilos in 30 patients, a more impressive result than after 2 years, when it was 11 kilos in 23 patients. However, after 2 years nocturnal respiration, arousals, metabolic status (blood insulin levels and dyslipidemia), as well as daytime sleepiness, were still significantly improved compared to baseline values. Quality of life ratings showed significant improvements for the subscales ”vitality” and ”physical functioning”. Further, there was a significant positive correlation between the reductions in weight and apneas. There were no gender differences, neither between patients with CPAP/MRD-device compared to without. In conclusion, as we found clinically important improvements, we recommend treating well motivated obese OSAS patients with dietary weight reduction in group therapy.
The present thesis is based on the following papers, which will be referred to by their Roman numerals.

I. PIA NERFELDT, Peter Graf, Stefan Borg, Danielle Friberg
   *The prevalence of high alcohol and benzodiazepine consumption in sleep apnea patients studied with blood and urine tests*
   ACTA Otolaryngologica 2004; 124: 1187-1190

II. PIA NERFELDT, Bengt Y Nilsson, Joanna Uddén, Stephan Rössner, Danielle Friberg
   *Weight reduction improves nocturnal respiration in obese sleep apnoea patients - A randomized controlled pilot study*

III. PIA NERFELDT, Bengt Y Nilsson, Liliana Mayor, Joanna Uddén, Stephan Rössner, Danielle Friberg
   *Weight reduction improves sleep, sleepiness and metabolic status in obese sleep apnoea patients*
   Accepted for publication: Obesity Research & Clinical Practice (2008), doi:10.1016/j.orcp.2008.08.001

IV. PIA NERFELDT, Bengt Y Nilsson, Liliana Mayor, Joanna Uddén, Danielle Friberg
   *A two-year weight reduction program improves sleep and reduces sleepiness in obese sleep apnoea patients*
   Submitted
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HTOL</td>
<td>5-hydroxytryptophol Low, Sat.</td>
</tr>
<tr>
<td>AHI</td>
<td>Apnea Hypopnea Index (events per hour) MAST Test</td>
</tr>
<tr>
<td>AI</td>
<td>Apnea Index (events per hour) MCV</td>
</tr>
<tr>
<td>ALAT</td>
<td>Alanine-Amino-Transferase MRD</td>
</tr>
<tr>
<td>ASAT</td>
<td>Aspartate-Amino-Transferase MSLT</td>
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<tr>
<td>AUDI'</td>
<td>Alcohol Use Disorders MWT</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index (kg/m²) Identification Test</td>
</tr>
<tr>
<td>BNSQ</td>
<td>Basic Nordic Sleep Questionnaire OR</td>
</tr>
<tr>
<td>CDT</td>
<td>Carbohydrate-Deficient-Transferrin OSA</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous Positive Airway Pressure PLM</td>
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<td>CRP</td>
<td>C-reactive protein ODI₄</td>
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<tr>
<td>CVD</td>
<td>Cardio Vascular Disease PP analysis</td>
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<tr>
<td>ECG</td>
<td>Electro Cardio Gram PSG</td>
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<tr>
<td>EDS</td>
<td>Excessive Daytime Sleepiness RCT</td>
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<tr>
<td>EEG</td>
<td>Electro Encephalo Gram RDI</td>
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<td>EMG</td>
<td>Electro Myo Gram REM</td>
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<tr>
<td>EOG</td>
<td>Electro Oculo Gram RERA</td>
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<td>ESS</td>
<td>Epworth Sleepiness Scale RR</td>
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<tr>
<td>FASS</td>
<td>Farmaceutiska Specialiteter i SBU</td>
</tr>
<tr>
<td>Sverige i.e. The Swedish Medicines Compendium SDB</td>
<td>Sleep Disordered Breathing, equal to SRBD</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration in United States of America SDB</td>
</tr>
<tr>
<td>FOSQ</td>
<td>Functional Outcomes of Sleep Questionnaire u-Benz</td>
</tr>
<tr>
<td>gamma-GT</td>
<td>gamma-Glutamyl-Transferase UPPP</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio VAS-scale</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone Replacement Therapy after menopause ITT analysis</td>
</tr>
<tr>
<td>LCD</td>
<td>Low Calorie Diet</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

SLEEP

What is normal sleep? 1.
Why do we sleep? 2.
The spectrum of sleep disorders 2.

CLINICAL BACKGROUND OF OSAS

Prevalence of OSAS 5.
Etiology of OSAS 5.
Anatomy 5.
Gender 5.
Obesity 6.
Smoking, alcohol and reflux 6.
Pharyngeal neuromuscular impairment 6.
Hereditv 7.
Nasal congestion 7.
Symptoms of OSAS 7.
Diagnosis of OSAS 8.
Diagnostic criteria 8.
Diagnostic levels 9.
Comorbidity of OSAS 10.
Cardiovascular disease 10.
Hypertension 10.
Coronary artery disease 11.
Stroke 11.
Metabolic impairment 11.
Dyslipidemia 11.
Glucose intolerance 11.
Quality of life 12.
Traffic accidents 12.
Mortality 12.

Treatment of OSAS 13.
CPAP 13.
MRD 14.
UPPP 14.
Weight reduction as treatment of OSAS 15.

ALCOHOL AND BENZODIAZEPINE USE 17.
Alcohol 17.
Definition of alcohol use 17.
Prevalence of alcohol use 17.
Diagnosis of alcohol use 17.
Effects on sleep of alcohol use 18.
Benzodiazepine 19.
2. AIMS

3. SUBJECTS AND METHODS
   SUBJECTS
   PAPER I
   PAPER II
   PAPER III and IV
   METHODS
   PAPER I
   PAPER II
   PAPER III and IV
   BIA Bioelectrical impedance analysis
   SLEEP RECORDINGS
   STATISTICAL ANALYSIS
   ETHICAL APPROVAL

4. RESULTS AND COMMENTS
   PAPER I
   Results
   Comments
   PAPER II
   Results
   Comments
   PAPER III and IV
   Results
   Comments

5. GENERAL DISCUSSION

6. CONCLUSIONS

7. FUTURE PERSPECTIVE

8. POPULÄRVETENSKAPLIG SAMMANFATTNING

9. ACKNOWLEDGEMENTS

10. REFERENCES

11. ORIGINAL PAPERS
1. INTRODUCTION

SLEEP

What is normal sleep?
Normal sleep consists of two states, non-rapid eye movement (NREM) and REM sleep, as described in Principles and Practice of Sleep Medicine [1]. During REM sleep, the electroencephalogram (EEG) activity is desynchronized, muscles are atonic and dreaming is typical. A simple definition would be “a highly activated brain in a paralyzed body”. This is in contrast to the NREM sleep, when EEG activity is variably synchronized, and episodes of so called sleep spindles, K-complex and high-voltage slow waves are observed. Further, there is a low muscular tonus during NREM. It is subdivided into four stages according to sleep depth. Stage 1 is the lightest sleep with a low awakening threshold. Stage 4 is the deepest sleep level, characterized by slow waves, and the awakening threshold is highest. A simple definition of NREM sleep would be “a relatively inactive brain in a moveable body”. Figure 1 illustrates the different EEG appearances during sleep stages. The sleep stages alternate over the sleep period, with approximately 4-5 cycles each night, as seen in the hypnogram in Figure 2.

The proportion of different sleep stages vary between individuals, as well as over age. For example, infants have a higher proportion of REM than toddlers, and the amount of slow wave sleep decrease in adolescence. The normal sleep length is also individual, but most young adult report 7.5 hours during week nights and 8.5 hours during weekend nights.

Sleep can be described as a reversible behavioural state of low perceptual engagement and low responsiveness to the environment. But it is also a complex state of physiologic and behavioural processes [1].

Figure 1. The four stages of NREM sleep illustrated with EEG recordings. The arrow indicates a K-complex and the underlining shows two sleep spindles. Illustration from Principles and Practice of Sleep Medicine [1].
Why do we sleep?
There are still uncertainties concerning the effect of sleep and sleep deprivation. Sleep saves energy and brings recovery. For example, the deep sleep (stage 3 and 4) is known to be very important for the patient’s well-being, as the heart rate, blood pressure, ventilation, metabolism and brain temperature decrease, all of which are crucial for the cerebral recovery [2]. Although a sleep deprived individual easily can be identified in social events, neurological changes are found to be relatively minor and quickly reversible. Nevertheless, a global decrease in brain activity has been found with the use of positron emission tomography, and the decreased activity was correlated to increased sleep loss. The activity-reduction was larger in the cortico-thalamic network mediating attention and higher-order cognitive processes [3]. Among several other responses to sleep deprivation, a reduction in the body temperature has been described [4], as well as a decrease in growth hormone which has a circadian rhythmicity [5]. Further, the appetite down-regulating hormone leptin has been found to decrease, which could be a mechanism for increased food intake and weight gain after sleep restriction [6]. In addition, C-reactive protein (CRP), an inflammatory marker predicting increased risk for cardiovascular disease, has been reported elevated after sleep restriction [7]. Although there is no uniform evidence showing that sleep loss affects immune functions to a clinical level in humans [8], it has been argued that it may cause a collapse of the host defence against otherwise common bacteria. This has been shown in sleep deprived rats, which died within approximately two weeks [9].

The spectrum of sleep disorders
The international classification of sleep disorders (ICSD-2) lists 85 sleep disorders in the following eight major categories:

1. The insomnias
2. The sleep-related breathing disorders (including Obstructive Sleep Apnea Syndrome)
3. The hypersomnias not caused by a breathing disorder
4. The circadian rhythm sleep disorders
5. The parasomnias
6. The sleep-related moving disorders
7. Isolated symptoms, apparently normal variants and unresolved issues
8. Other sleep disorders

Figure 2. The progression of sleep stages during the night in a normal subject illustrated with a hypnogram. The x-axis shows the time of the night and the y-axis sleep stage. Illustration from Principles and Practice of Sleep Medicine [1].
CLINICAL BACKGROUND OF OSAS

This thesis is based on studies of adult patients with Obstructive Sleep Apnea Syndrome (OSAS). OSAS is a large public health problem, especially in view of the neurocognitive and cardiovascular sequel associated with this disorder, with extensive impact on human suffering and society costs. OSAS is both common and dangerous. Overall, there is still a large number of undiagnosed and untreated patients, and with the rising number of obese persons all over the world, the prevalence of OSAS is increasing. This thesis is focusing on weight reduction as treatment of obesity in OSAS. Further we have evaluated the prevalence of alcohol abuse, which is also shown to increase in the western world, adding to the burden of OSAS.

OSAS is characterized by episodes of complete or partial pharyngeal obstruction during sleep. The intermittent obstruction of the pharynx during sleep causes apneas and arousals, which result in impaired sleep quality and an often obvious daytime sleepiness [10]. If the patients have apneas but no subjective symptoms, they suffer from Obstructive Sleep Apnea (OSA), as the criteria for the syndrome are not fulfilled. Figure 3 shows a hypnogram of a night’s sleep divided in sleep stages for a patient with OSAS. As seen in many OSAS patients there is sleep fragmentation with repeated awakenings and decreased level of slow wave stage 3 and 4.

OSAS is part of the group of Sleep-Related Breathing-Disorders (SRBD), also called Sleep-Disordered Breathing (SDB). Apart from OSAS and OSA, SRBD also include habitual snoring without apneas. Further included in SRBD is the milder form of disturbed breathing known as Upper Airway Resistance Syndrome, in which the patient suffers from increased breathing effort without complete hypopneas, and from respiratory effort related arousals (RERA) with impaired sleep quality. Finally, SRBD also include the central apneas without breathing effort, as for example in patients with heart failure and Cheyne-Stokes Breathing. Figure 4 shows a central and an obstructive apnea with their differences in respiratory effort in the thoracic-abdominal muscles.

Figure 3. Hypnogram of a night’s sleep divided in sleep stages for a patient with OSAS. The level of slow wave (SW) sleep (= stage 3 and 4) is lower, and the number of awakenings are higher, compared to the normal sleep. Illustration from Principles and Practice of Sleep Medicine [1].
Figure 4. The relationship between airflow and respiratory effort demonstrated for an central and obstructive apnea. During a central apnea no ventilator effort is seen, while it continuous through an obstructive apnea. Illustration from Principles and Practice of Sleep Medicine [11].

Figure 5. Polysomnography recording of a patient with severe OSAS. The channels are chin EMG, EEG registrations as well as EOG and ECG in the top section, and in the bottom section are the pulse oximetry, respiratory movements and nasal airflow channels. The signals are time aligned as indicated with the vertical lines, but the top section represents about 30 seconds, and the bottom 5 minutes. The small rectangle indicates a respiratory arousal seen in the EEG channels, which was provoked by an obstructive apnea. Resumption of the nasal airflow can be noted directly after the arousal. Illustration from Principles and Practice of Sleep Medicine [16].

CHIN = chin electromyogram (EMG). C3-A2, C4-A1 and O2-A1 = electroencephalogram (EEG). ROC and LOC = electrooculogram (EOG). ECG = electrocardiogram. SaO$_2$ = oxyhemoglobin saturation. THOR and ABDO RES = thoracic and abdominal respiratory movement. Pulse = pulse rate. CPAP = continuous positive airway pressure pressure
OSAS is the fully developed disease with repetitive obstructive episodes of the pharynx, causing apneas with desaturations, increase of sympathetic activity and blood pressure during the end of apnea [12, 13]. The main disruptive patterns of sleep are the recurrent arousals which often follow the apneas. The arousals lead to activation of the opening muscles in the pharynx, in order to regenerate an open airway [14, 15]. Figure 5 presents a respiratory arousal in the PSG parameters in a patient with a long period of repetitive obstructive sleep apneas.

A nocturnal sleep investigation with a polysomnography (PSG) is the golden standard to quantify the respiratory disturbances. Different entities are used; the Apnea-Hypopnea-Index (AHI), the Apnea-Index (AI) and the Oxygen Desaturation Index (ODI). These entities calculate the numbers of nasal airflow limitations or desaturation events, respectively, per sleeping hour. In addition, the entity Respiratory Distress Index (RDI), including all events of AHI and RERA, is used.

Prevalence of OSAS

OSAS has a prevalence in adults of about 4 percent in males and 2 percent in females [17, 18]. OSA with AHI >5, without daytime symptoms, has been estimated to be around 17 to 26 percent in males and 9 to 28 percent in females in population studies [17, 19-21].

Around 60 to 90 percent of OSAS patients have obesity defined as a Body Mass Index (BMI kg/m\(^2\)) >28 [14]. There is a clear connection between the degree of obesity and the prevalence of OSA, shown in many studies. For example, the prevalence figures above can be compared to a population of 161 obese patients (57 men and 104 women) (mean BMI of 43.4 (range 30.0-67.3), for which 51.5 percent had a respiratory disturbance index (RDI) >10 [22]. Lopez et al have shown an increasing prevalence of OSA with increased severity of obesity; 71 percent for the severely obese group (BMI 35-39.9 kg/m\(^2\)), 74 percent for the morbidly obese group (BMI 40-49.9 kg/m\(^2\)), and 77 percent for the super obese group (BMI 50-59.9 kg/m\(^2\)). For those with a BMI >60 kg/m\(^2\), the prevalence of OSA rose to 95 percent. Furthermore, they found a total prevalence of OSA among their patients waiting for bariatric surgery of 78 percent (227 of 290), with the mean BMI of 52 kg/m\(^2\) (range 31-94 kg/m\(^2\)) [23].

Etiology of OSAS

The most important risk factors for developing OSA are narrow upper airways, male gender and obesity. Additional risk factors are alcohol, smoking and other causes of mucosal edema as well as muscle hypotonia, heredity and nasal congestion. There are studies indicating that SRBD is a progressive disease both in untreated [24], and surgically treated patients, independent of weight gain [25].

Thus, there are several factors adding to the collapse of the upper airways during inspiration and sleep, leading to a Bernoulli effect. Prevention, information and early treatment in a multifocal manner should be attempted to stop progression of SRBD.

Anatomy

OSA is characterized by narrowing at one or more sites along the upper airway; retropalatal, retroglossal, or hypopharyngeal obstruction. Factors such as macroglossia, adeno-tonsillar-hypertrophy, "curtain-like" soft palate and enlarged uvula can cause a narrowing of the upper airway during inspiration and sleep. Furthermore, craniofacial disorders such as mandibular and maxillar retro- or micrognathia, increase the prevalence of OSAS and abnormalities such as Down's, Treacher-Collins and Pierre-Robin syndromes, are overrepresented in patients with OSA [26, 27].

The apnea frequency is generally increased in supine position due to the reposition of the mandibula and tongue, and not only the frequency but also the severity of the apneas are found to increase [28]. Richard et al. showed that more than 50 percent of OSAS patients are position-dependent to such a degree that AHI in supine is at least two times higher than in other positions [29].

Gender

OSA is also more prevalent among males than in females; a 2- to 3-fold greater risk is often reported,
although less pronounced in elderly [30]. The reason for this gender difference is still unclear, but anatomical as well as hormonal factors are of importance. Male predisposition for pharyngeal collapse is suggested to be a result of increased length of the upper airway and increased size of the soft palate [31]. Differences in exogenous factors between gender are other possible factors, for example occupational, environmental and health risk factors (i.e., smoking and alcohol consumption) [32]. In terms of hormonal differences there are indications that the estrogen and progesterone have a protective role. Postmenopausal women without hormone replacement therapy (HRT) have been found to have a prevalence of sleep apnea that was significantly higher than the prevalence in premenopausal women with HRT (2.7 versus 0.6%, p = 0.02). However, when controlling for age and BMI this group difference was less significant [21]. These data indicate that menopause is a significant risk factor for sleep apnea in women and that HRT appears to be associated with reduced risk.

Obesity
The connection between excess weight and OSA has been in focus for a long time. In 1956 OSA was recognized as a disease of obesity and hypoventilation, named the Pickwickian Syndrome [33] after the Charles Dickens’ novel The Pickwick Papers from 1836. Dickens here described “Joe the fat boy” who was fat, heavy snoring, red faced and sleepy during the day. Since then, observations of patients diagnosed with OSA as well as findings from population studies have supported a strong and likely causal role of overweight in the field of OSA. Overweight is defined by evaluation of Body Mass Index (BMI) using the patient’s weight and height in the unit kg/m$^2$. BMI >25 kg/m$^2$ is the criteria for overweight and BMI >30 kg/m$^2$ for obesity. A majority of OSA patients are overweight [14]. It has been shown that OSAS patients have more fat in the lateral pharyngeal walls than non-OSAS patients with similar BMI [34-36]. Stepwise multiple regression analysis performed in a study by Resta et al., showed that neck circumference in men and BMI in women were the strongest predictors of OSA [22]. Young et al estimated the overall burden of SRBD that may be attributed to excess weight in the American population. They used the estimated age, sex, and BMI distributions among adults, age 30-69 years, and proposed that approximately 17 percent of adults have at least mild OSA (AHI >5). Out of these, as many as 41 percent were suggested to have OSA because of overweight (BMI >25 kg/m$^2$). Similarly, they estimated that approximately 5.7 percent of adults have at least moderate OSA (AHI >15) and that 58 percent of these would be caused by overweight [37].

Smoking, alcohol and reflux
Smoking is related to sleep apnea in a dose-response relationship. Compared with never smokers, current smokers were found to have a significantly greater risk of snoring (odds ratio, OR 2.29) and of moderate/severe SRBD (OR 4.44). Further, heavy smokers (>40 cigarettes per day) had a highly increased risk for moderate/severe SRBD (OR 40.47) [38]. In another survey habitual snoring was prevalent in 20 percent among never-smokers exposed to passive smoking daily at home compared to 13 percent among never-smokers without passive smoking [39]. The effect is probably mediated through an increased inflammation in the pharyngeal mucosa. Alcohol, the focus of PAPER I in this thesis, has several impacts related on OSA and is presented as a separate chapter below. Gastro-esophageal reflux is another reason for edema of the pharyngeal mucosa, and reflux is also common in OSAS patients [40]. Friedman et al treated OSAS patients who tested positive for gastroesophageal reflux with esomeprazole magnesium 40 mg once daily and found the apnea-hypopnea index to decrease significantly from mean 37.9 to 28.8 [41].

Pharyngeal neuromuscular impairment
There is evidence of generated nerve damage in the pharyngeal mucosa, probably caused by the vibration and tissue traction from snoring. The patient history often describes progressing symptoms from being snorer for many years before apneas become apparent. Snoring is a vibration of the soft tissue of the pharynx, and from occupational studies it has been shown that vibrations can cause local nerve lesions, for example sensory nerve damage in hands of the dentists [42, 43]. Besides the mechanical trauma associated with snoring and apneas, damages can be caused by the oxidative stress due to hypoxia and reoxygenation, and both these factors can be aggravated by a related inflammation. These
nerve lesions may result in a gradual collapse of the pharyngeal upper airway. The mechanism could be due to weakness or partial paresis of the dilating muscles or to impaired contracting reflexes. A reflex makes the pharynx dilate in response to a negative pressure or relatively cold air, and this reflex could be impaired due to decreased numbers of nerve fibers and abnormal muscles in the pharyngeal walls. There have been several studies indicating this [44-46]. The nerve damage could also explain that snorers have signs of dysphagia, which have been shown with videoradiography [47].

**Heredity**

There is support for a genetic predisposition of OSAS. Among 2,350 OSAS patients diagnosed in Iceland, the risk ratio for a first-degree relative of a patient with OSAS was 2.0 [48]. A recent Swedish study investigated family risks in siblings with a history of medically verified OSAS. The increased risk in adults (Standardized incidence ratio, SIR 3.3) could be caused by heredity or increased awareness of the symptoms [49]. Differences in facial anatomy and/or disposition to obesity are suggested as possible explanations for the familial aggregation [50].

**Nasal congestion**

Increased nasal resistance has been linked to snoring and OSA [51]. During sleep, nasal obstruction can provoke an increase in airflow resistance in the upper airways, promoting more negative intra-luminal pressure in the pharynx and predisposing to pharyngeal occlusion [52]. Despite the relationship between nasal obstruction and OSA, the therapeutic effect of improving nasal airway patency in OSA is unclear. OSAS patients with associated rhinitis have been shown to get a somewhat lowered AHI during treatment with intranasal corticosteroids [53]. Uncontrolled trials examining the impact of surgical correction of deviated nasal septum on OSAS severity have provided disappointing results [54]. Nasal surgery rarely treats obstructive sleep apnea effectively [55] but can improve CPAP compliance in selected patients [56].

**Symptoms of OSAS**

The most patognomone symptoms of OSAS are witnessed by the bed partner. The patient’s own complaints are often reactions from abnormal sleep, and do not differ much regardless sort of sleep disorder. The night- and daytime symptoms [14, 57] are presented in table 1.

<table>
<thead>
<tr>
<th>Night-time</th>
<th>Day-time</th>
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<tbody>
<tr>
<td>Snoring</td>
<td>Sleepiness</td>
</tr>
<tr>
<td>Witnessed apnea</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Choking</td>
<td>Morning headaches</td>
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<tr>
<td>Dyspnea</td>
<td>Poor concentration</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Decreased libido or impotence</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Personality change</td>
</tr>
<tr>
<td>Perspiration</td>
<td>Depression</td>
</tr>
<tr>
<td>Reflux</td>
<td>Decreased dexterity</td>
</tr>
</tbody>
</table>

Table 1. Symptoms of OSAS
Excessive daytime sleepiness is a cardinal symptom of OSAS, and could be explained by disrupted sleep architecture and intermittent hypoxemia. In the Wisconsin Sleep Cohort Study approximately 23 percent of women and 16 percent of men with AHI >5 reported sleepiness at least 2 days a week (described as excessive daytime sleepiness, awakening unrefreshed no matter how long they slept, and uncontrollable daytime sleepiness that interfered with daily living). This result was compared with the results from subjects without OSA, in which 10 percent of women and 3 percent of men reported sleepiness [17].

Daytime sleepiness can be evaluated in several ways. There are objective measurements such as multiple sleep latency test (MSLT), maintenance of wakefulness test (MWT) and the Osler test, as well as subjective ratings in questionnaires (Functional Outcomes of Sleep Questionnaire (FOSQ), Epworth Sleepiness Scale (ESS), Basic Nordic Sleep Questionnaire (BNSQ) etc). The most commonly used questionnaire is the Epworth Sleepiness Scale (ESS), which is also the one used in this thesis. Since its publication in 1991, the ESS has been used by several groups of investigators to measure daytime sleepiness in patients with known or suspected OSA [58]. The questionnaire includes 8 questions, each illustrating a daily situation, for which the respondents are asked to rate how likely they are to doze off. Ratings vary from "no risk of falling asleep" (0 points) to "high risk of falling asleep" (3 points). In spite of that the name includes "sleepiness" the creator claims that it measures "sleep propensity". The maximum sum in ESS is 24, and in most studies of OSAS patients a values above 10 are considered pathological [59]. ESS has also been used to track changes in daytime sleepiness during treatment of OSA [60]. However, there are indications that it suffers from variability problems. Nguyen et al. found that when the questionnaire was administered twice with a few months interval to a population evaluated for potential SRBD, as many as 23 percent had a difference of at least 5 points between the two ESS-ratings [61]. The ESS has been found to have a moderate correlation to mean sleep latency, as measured by the MSLT, for 44 patients who had been referred to a sleep disorders clinic [62, 63]. It should be noted that the ESS and the MSLT do not measure the same thing. The MSLT measures sleepiness by counting how many minutes it takes to fall asleep in a dark room at the time of testing. The ESS, however, is a questionnaire with recall bias, and attempts to reflect how sleepy the respondent has been at a variety of daily activities in the past weeks. Data from the Sleep Heart Health Study indicate that ESS ratings correlated positively to the AHI [64]. However, the worst apnoics had a mean ESS score of 9, in comparison with essentially normal subjects with a score of 7, that is, the patients scored only two points higher than normals. Bennett et al studied the relationship between health-related quality of life measured, as measured with the SF-36 questionnaire, and the ESS in 51 subjects, who had been referred to a sleep disorder clinic. They found that ESS correlated negatively with the energy/vitality dimension of the SF-36 (r = -0.47, p <0.001) [65].

Although the ESS-questionnaire has several weaknesses, its strengths are several: It reflects the patients’ subjective symptoms, is very well-known and established, is cheap and easy to distribute, and also validated in Swedish. ESS is therefore often used in clinical routine as a measurement of sleepiness.

OSAS patients often experience impaired ”sleep quality”, but the term has no strict definition. Sleep quality can be assessed subjectively as a rating of how undisturbed and restorative the sleep has been. Objectively it can be measured as a series of parameters from polysomnographic recordings, most often as sleep efficiency but also as arousal index. Furthermore, the subjective and objective measurements of sleep quality are not necessarily concordant. In the present thesis on OSAS patients we consider the arousal index and sleep efficiency important, since these parameters reflect the sleep fragmentation caused by the respiratory disturbances.

### Diagnosis of OSAS

#### Diagnostic criteria

The diagnostic criteria for OSAS are, according to the American Academy of Sleep Medicine [66], as follows:
A person must fulfill one of criteria A or B, as well as criterion C.

A. Excessive daytime sleepiness that is not better explained by other factors.

B. Two or more of the following that are not better explained by other factors:
- choking or gasping during sleep
- recurrent awakenings from sleep
- unrefreshing sleep
- daytime fatigue
- impaired concentration.

C. Overnight monitoring demonstrating five or more obstructive breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort related arousals.

The severity of the obstructive sleep apnea-hypopnea syndrome has two components: severity of daytime sleepiness and overnight monitoring. Concerning the laboratory sleep recording criteria the degree of OSA has the following criteria, according to the level of obstructive breathing events (RDI) [66]:
- Mild: 5 to 15
- Moderate: 15 to 30
- Severe: more than 30

**Diagnostic levels**
- Level I: Complete cardiorespiratory polysomnography (PSG) in sleep lab. Including a minimum of 7 channels with EEG, EOG, chin EMG, heart rate or ECG, respiratory flow, respiratory effort and oxygen saturation. In addition, until recently also continuous intrathoracic pressure monitoring with an esophageal catheter was included [67].
- Level II: Unattended PSG at home, used in PAPER III and IV.
- Level III: Polygraphy with a minimum of 4 channels, including respiratory flow or effort, heart rate or ECG and oxygen desaturation. This level is most frequently used in many parts of the world including Scandinavia, and used in PAPER I and II.
- Level IV: One or two channel sleep apnea screening devices such as Holter ECG, ambulatory blood pressure, portable oximetry, actigraphy or Watch-PAT etc.

Figures 6 and 7 show a polygraphy and a PSG respectively.

**Figure 6.** Schematic picture of a polygraphy with its registration of oro-nasal airflow, thoracic and abdominal respiratory efforts, pulse oximetry, pulse frequency, snoring, and body position.
Comorbidity of OSAS

Cardiovascular disease
There is considerable evidence available to support an independent association between OSAS and cardiovascular disease (CVD). The evidence is particularly strong for systemic hypertension and growing for ischemic heart disease, stroke, heart failure, atrial fibrillation and cardiac sudden death [68]. For example, in the Sleep Heart Health Study cohort there is indication of increased prevalence of CVD correlating to the degree of OSA. The multivariable-adjusted relative odds of prevalent CVD for the second, third, and fourth quartiles of the AHI (versus the first) were 0.98, 1.28, and 1.42, respectively [69]. The evaluation of OSAS as an independent risk factor for morbidity and mortality has to be done with adjustment for confounders. This is a challenge to the scientific researchers, and conflicting data are therefore found in the literature in many areas. The pathogenesis of cardiovascular disease in OSAS is likely to be multifactorial including all or some of the following factors: sympathetic nervous system overactivity, activation of inflammatory molecular pathways, endothelial dysfunction, abnormal coagulation and metabolic dysregulation, particularly involving insulin resistance and disordered lipid metabolism [68]. Here follows in more detail a presentation of the CVD entities: hypertension, coronary artery disease and stroke.

Hypertension
Data from the Wisconsin Sleep Cohort Study showed an association between hypertension and OSAS. The odds ratio for development of hypertension within 4 years was 2.9 among persons with AHI >15, compared to those with AHI = 0, when adjusting for age, sex, body mass index, neck and waist circumference, smoking and alcohol intake [70]. The Sleep Heart Health Study found a linear relationship between the severity of SRBD and prevalence of hypertension. Furthermore, the odds ratio for hypertension, comparing the highest category of AHI (>30 per hour) with the lowest category (<1.5 per hour), was 1.37 [71]. Hedner
et al. found the contribution of OSA to the hypertension risk to be sex dependent, higher in males than in females [72]. Grote et al. found the proportion of patients with uncontrolled hypertension to increase significantly with increased SRBD, at least for patients at <50 years of age [73]. Thus, SRBD should be excluded in patients with therapy resistant hypertension. CPAP is found to improve hypertension and also reduce sleepiness [15].

Coronary artery disease
The recurrent apneas during sleep in OSA patients cause episodes of desaturations, which are thought to predispose for coronary artery disease (CAD). Several studies on the area have shown an increased prevalence of OSA in patients with CAD. In a case-control study in which cases were randomly selected from men undergoing coronary angiography because of angina pectoris, a prevalence of ODI of 5 or more was found to be 39 percent, while the same proportion in controls were 22 percent (p=0.05). Controls were age-matched and selected from the population registry, and the significant association between sleep apnea with nocturnal hypoxemia and CAD remained, after adjustment for age, hypertension, body mass index, diabetes, and smoking [74]. In another case study of patients with nocturnal angina pectoris, OSA was found in 9 of 10 patients. Nocturnal angina diminished during treatment of sleep apnea with CPAP, and the number of nocturnal myocardial ischemic events, measured by computerized vector-cardiography, was reduced [75]. In middle-aged and elderly patients with coronary artery disease requiring intensive care, the occurrence of OSA was found to be 3.1 times more prevalent compared to matched controls [76]. In a longitudinal study, untreated SRBD significantly worsened the prognosis of patients with documented CAD. There was a 70 percent relative increase and a 10.7 percent absolute increase in the primary composite end point of death, cerebrovascular events, and myocardial infarction in patients with an ODI >5 [77]. Further, in patients with CAD and OSAS, Milleron et al. showed that the patients receiving CPAP or upper airway surgery had a better clinical course compared to those who refused treatment. An hazard ratio of 0.24 in favour for treatment was seen for risk of occurrence of the composite endpoint of cardiovascular death, acute coronary syndrome, hospitalization for heart failure, or need for coronary revascularisation [78].

Stroke
Several studies have shown a higher prevalence of stroke among snorers and apneics. Uncertainties of the role of OSAS in the pathogenesis of stroke can be due to the fact that SRBD can both precede and follow the stroke event [79]. Partinen et al. found a relative risk (RR) of 10.3 for stroke among snorers compared to non-snorers [80], Spriggs et al. reported an RR of 3.2 [81], and Neau et al. an RR of 3.4 [82]. Yaggi et al. found that OSAS retained a statistically significant association with stroke or death from any cause with a hazard ratio of 1.97 [83]. The Sleep Heart Health Study reported a small but significant increase in prevalence of stroke among OSA-patients, and higher in the upper OSA quartile compared to the lowest quartile [69]. With a cut-off limit of AHI >10, Mooe et al. reported an adjusted hazard risk of 2.98 for stroke [77]. Data from the Wisconsin Sleep Cohort showed that with an AHI >20 there was an odds ratio of 4.3 for the risk of stroke during a 4-year follow-up study [84]. In summary, there is indication for OSAS to be a risk factor for stroke, and for the OSAS-degree to be of importance, but the magnitude of the relationship is unclear.

Metabolic impairment
Dyslipidemia
Experimental studies have suggested a role of intermittent hypoxia in the pathogenesis of hyperlipidemia [85, 86]. Altered lipid metabolism and hepatic steatosis in OSAS have been found and it has been shown that total cholesterol tended to decrease after CPAP treatment [87]. Mean HDL increased after CPAP treatment and this change correlated with the decrease in AHI [88].

Glucose intolerance
OSA is considered to be a risk factor to develop glucose intolerance, insulin resistance as well as type-2 diabetes [89]. The prevalence of type-2 diabetes was found to be 30 percent, and impaired glucose tolerance 20 percent, among OSAS patients, which can be compared to 13.9 percent of both type-diabetes and impaired glucose tolerance among snorers [90]. In normal subjects,
induced hypoxia has been found to be an important contributor to glucose intolerance [91]. Ip et al. [92] reported that AHI as well as minimum oxygen saturation were associated with insulin resistance. Punjabi et al. [93] showed that SRBD was associated with insulin resistance in mildly obese healthy males from the general population. Data from the Sleep Heart Health Study and the Wisconsin Sleep Cohort found similar results in population cohorts [94, 95]. Moreover, an intervention study showed that treatment with CPAP rapidly restored insulin sensitivity, especially in non-obese patients [96].

Quality of life
Short Form Health Survey (SF-36), a questionnaire with eight different domains, is one of the most frequently used methods to evaluate quality of life [97]. The use of SF-36 has revealed that OSA patients have lower life quality compared to an age and gender matched control group [98]. Both the Wisconsin Sleep Cohort Study and the Sleep Heart Health Study have demonstrated associations between decrements on the eight SF-36 scales and degree of OSA [99, 100]. The authors Finn et al. found the magnitude of decrements on the SF-36, seen already in mild SRBD (AHI=5), to be comparable to other chronic conditions such as arthritis, angina, hypertension, diabetes, and back problems [99]. Also the PSG parameter "respiratory arousals" correlated significantly to several subscales of the SF-36, as found by Goncalves et al. [101].

Several studies on OSA populations and CPAP-intervention have shown improvements in some of the eight domains, often in the "role-physical" and the "vitality" domains [102]. For example, Pichel et al. showed that patients treated with CPAP for 6 months significantly improved in the vitality dimension, and after 18 months there were improvements in five SF-36 dimensions: physical functioning, role physical, social functioning, vitality, and in general health perception [103].

Traffic accidents
Due to sleepiness, OSAS patients have an increased risk for motor vehicle accidents. Because traffic safety is under governmental regulation, there is a legal aspect when driving skills are impaired. Estimates indicate that sleepiness causes over 20 percent of highway accidents in the UK [104], although sleepiness can be caused by many different reasons. Data have indicated a three- to seven-fold increased risk for OSAS patients compared to normal subjects [105, 106]. Haraldsson et al. found that drivers with heavy snoring, sleep disturbances, and daytime sleepiness had a higher risk than normal for car accidents. Especially the risk for single-car accidents was increased, and the risk returned to normal after surgery with uvulo-palato-pharyngoplasty (UPPP) [107].

Mortality
OSAS is associated with an increased mortality rate. Marshall et al. found that moderate-to-severe OSA was associated with greater risk of all-cause mortality, hazard ratio (HR) 6.24, compared to non-OSA (adjusted for age, gender, body mass index, mean arterial pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes, and medically diagnosed angina in those free from heart attack or stroke at baseline). On the other hand, mild OSA was not found to be an independent risk factor for higher mortality (HR=0.47) [108]. Marin et al. used multivariate analysis adjusted for potential confounders and showed that both long-term cardiovascular morbidity and mortality increased only in patients with untreated severe OSAS. The odds ratio was found to be 2.87 for fatal and 3.17 for non-fatal cardiovascular events compared with healthy participants during a mean of 10.1 years. Both simple snorers and OSAS patients, who had accepted CPAP treatment, showed morbidity and mortality values very similar to those obtained in the general population [109]. Similarly, Young et al. found in the Wisconsin Sleep Cohort sample that the all-cause mortality risk, adjusted for age, sex, BMI and other factors, significantly increased with SRBD severity. The adjusted HR for all-cause mortality with severe versus no SRBD was 3.0. After excluding persons who had used CPAP treatment, the adjusted HR for all-cause mortality with severe versus no SRBD was 3.8, and the adjusted HR for cardiovascular mortality in specific was 5.2 [110]. In a survey-study with prospective mortality collection, Lindberg et al. showed increased mortality in men below the age of 60 with both snoring and EDS. These men had an age-adjusted total death rate, which was 2.7 times higher than found in men with no snoring or EDS [111].
Treatment of OSAS

In general, OSAS needs to be treated in a multi-dimensional way including so called “conservative methods” in combination with a device or surgical intervention. There are three major alternatives in Sweden; the continuous positive airway pressure (CPAP), the mandible retaining device (MRD) and the surgical uvulo-palato-pharyngo-plasty (UPPP). There are also other types of surgery available, such as bi-maxillary surgery and tracheostomy, but they are seldom preferred by the patients, as well as emphasis in treating nasal congestion and gastro-oesophageal reflux. Included in the ”conservative treatment methods” are advices on sleep hygiene, reduction of alcohol, smoking and sedatives and for overweight subjects attempted weight reduction. Further, patients are advised to avoid sleeping in supine position, as it is in this position the pharyngeal airway is most obstructed. There are several devices to aid the patient with this, one example is ”The Positioner”, a soft vest attached to a board placed under the pillow, which makes it impossible for the patient to sleep on his back [112].

The three major treatment modalities CPAP, MRD and UPPP are presented in more detail below, followed by separate chapters on weight reduction as well as the influence of alcohol and benzodiazepines, since these are the main foci in this thesis.

Continuous Positive Airway Pressure (CPAP)

Nasal continuous positive airway pressure (CPAP) is the treatment of choice in OSAS [15]. It was described as a “pneumatic splint”, preventing upper airway collapse, by Sullivan et al in 1981 [113], and has since then been of steadily growing demand. There are several types of CPAP-devices with different levels of automation and ventilator invasiveness. The evidence is strong for CPAP to be highly effective in reducing the frequency of obstructive sleep apneas to normal values among patients with mild, moderate and severe obstructive sleep apnea. Much simplified, it is a question of finding the proper facial mask to fit tight without leakage and the right level of positive air pressure to resolve the obstructive events. In practice, this is not always easily done and unfortunately the compliance and long-term use may vary. In some studies the compliance has been very low [114-116] and therefore, there is still a demand for alternative treatments.

CPAP has been evaluated for impact on several different subjective and objective symptoms associated to OSAS. According to the Swedish Council on Technology Assessment in Health Care (SBU) [117] there is strong evidence that CPAP reduces daytime sleepiness regardless of the severity of the sleep apnea syndrome. In a meta-analysis of 18 different randomized studies, 712 patients were evaluated regarding changes in ESS after active CPAP treatment. Their mean ESS decreased from 12.4 to 8.1 during treatment, i.e., from abnormal to normal values for daytime sleepiness. The largest included study in this meta-analysis was Barnes et al.. They had a group of 114 sleep clinic patients with mild to moderate OSAS (AHI of 5-30) participating in a randomized controlled crossover trial of 3-month treatment with each of CPAP, MRD, and a placebo tablet. In detail they showed that among 89 patients treated with CPAP the mean ESS score was 9.2 compared to 10.2 in 90 patients receiving placebo tablets [118]. The study was randomized, but not blinded. Other studies try to blind their control group using sham-CPAP, but there is always a problem to actually succeed in blinding the study participants, as well as the CPAP therapists and doctors.

CPAP is found by Malhotra et al., to not only reduce sleepiness but also improve hypertension [15], at least in short-term [119]. Engelman et al. evaluated several parameters in patients with mild OSAS (AHI 5 to 15) treated with CPAP. Although the average CPAP-use was only 2.8 hours per night, CPAP improved subjective (ESS, p<0.01) but not objective (MWT, p>0.2) measurements of sleepiness, compared to oral placebo. Further, five subscales of the quality of life questionnaire SF-36 were improved (p<0.03) [60]. In another randomized trial, moderate to severe OSAS patients were evaluated. They were randomized to either receiving CPAP in addition to conservative weight reduction and sleep hygiene advises, or to only receive conservative treatment. The relief of sleepiness and other OSAS-related clinical symptoms, in combination with improvement in perceived health status, was found to be six times greater in the group receiving additional CPAP [120].
**Mandible Retaining Device (MRD)**

There are different models of oral appliances used for OSAS, models that either advances the tongue or the mandible during sleep. The later model, the Mandible Retaining Device (MRD) is in total dominance in Sweden. We use the name MRD, but the term Mandible Advancement Device is sometimes used in the literature. There are further many different models and materials of devices, and there are custom made as well as pre-fabricated where the patient is to adjust the device themselves, which often give insufficient result. The following text is only dealing with custom made MRD made by dentists and dental laboratories.

According to the American Academy of Sleep Medicines guidelines for OSA from 1995 the oral appliances are stated to be the first-line therapy in patients with simple snoring or mild OSA, and second-line for moderate and severe OSA, when other therapies have failed [121]. The increasing evidence for efficacy in randomized controlled trials nowadays gives support to expand the indication, at least to moderate OSAS. The Swedish Council on Technology Assessment in Health Care (SBU) [117] concluded that among a total of 250 patients in 6 randomized studies, treated with active MRD, the ESS decreased from a mean of 11.4 to 9.0, i.e., from abnormal to normal values for daytime sleepiness. Again, Barnes et al. is the largest included study, which showed an ESS value with a mean of 9.2 for the MRD compared to 10.2 for placebo. It can be noted that they found the exact same mean ESS for both the active treatment groups of CPAP and MRD. Barnes et al. have continuously showed that both MRD and CPAP improved the sleep parameters, but that CPAP had a greater effect. The quality of life and subjective symptoms improved to a similar degree with both treatments [118]. In comparison with a control device, the ESS in the MRD-treated was significantly lower with a mean of 7 compared to 9 for the controls in a study by Gotsopoulos [122]. Even though MRD can be recommended to patients, with not only mild, but also with moderate OSAS, a long-term follow up showed that patients with mild OSAS (AHI<15) were more likely to continue treatment than were patients with more severe OSAS [123].

The acceptance, adherence as well as treatment success of MRD have also their limitations, just as any OSAS treatment. For example, Marklund et al. reported that 19 of 33 consecutively treated patients experienced a short-term (mean 0.7 years) result with an AHI of <10 events per hour and a satisfactory reduction in snoring. Of the 19 patients, who continued the treatment until the long-term follow up (mean 5.2 years), the results did not differ from those at the short-term follow-up. The authors stressed that patients, who got their devices replaced or adjusted, experienced a better long-term effect compared to patients still using their original devices [124]. In Marklund’s study the 5.2-year-adherence was 19 out of 33, i.e. 58 percent. The Cochrane Review concludes that responders to both CPAP and MRD expressed a strong preference for the MRD. However, participants were more likely to withdraw on MRD than on CPAP therapy [119].

**Uvulo-Palato-Pharyngo-Plasty (UPPP)**

The same year as the nasal CPAP was introduced, 1981, Fujita described the surgical procedure of uvulo-palato-pharyngo-plasty (UPPP) [125]. The UPPP includes a tonsillectomy as well as a reduction of the soft palate and uvula. As for all surgical interventions there is a limited possibility to make blinded studies and therefore the evidence of effectiveness is restricted. The only RCT on UPPP compared to expectancy is a small study by Lojander et al. in which 18 patients were randomized to UPPP (and 5 of these had an additional mandibular osteotomy) and 14 to expectancy. They used a VAS-scale to evaluate excessive daytime sleepiness, and the results showed a statistically significant difference between the groups. The ODI changed significantly from 45 to 14 in the UPPP group, compared to 34 to 23 in the expectancy group, but the difference between the groups was insignificant [126].

There have been several studies indicating a long-term success rate of around 50 percent. Janson et al. showed, for example, that the 4 to 8 years follow-up success rate (defined as a 50% or more reduction in AHI and a postoperative AHI of 10 or less) was 48 percent (for 34 included patients, 25 participated in the follow-up and of these 12 were responders) [127]. Larsson et al. had a higher follow-up rate...
but similar results on success rate (defined as ODI reduced by at least 50 percent and a postoperative ODI of 20 or less). They showed that out of 50 patients, 30 were classified as success after six months, 19/49 after twenty-one months and 24/48 after four years. Obesity and severe degree of OSAS were found to be negative predictors [128]. Friedman et al. have found that their staging system based on palate position, tonsil size, and body mass index (BMI) predicted positive treatment effect, and showed a success rate (defined as RDI reduced by at least 50 percent and a postoperative RDI of 20 or less) of 80 percent for subjects with large tonsils and low tongue position compared to palate height. They recommended addition of a tongue-base reduction with the use of a radiofrequency technique, when their staging system indicates a large tongue [129, 130].

A study of 95 male OSAS patients, randomized between MRD and UPPP, indicated a lower success rate for UPPP [131, 132]. The success rate (defined as at least a 50 percent reduction in Apnea Index) for the MRD group was 95 percent, which was significantly higher than the 70 percent success rate for the UPPP group. A significantly higher proportion, 78 percent of the MRD group compared to 51 percent of the UPPP group, had an AHI of less than 10 after one year [131]. In the 4-year follow-up Walker-Engström et al. conclude that the MRD group showed significantly higher success rate regarding Apnea Index compared to the UPPP group, 81 compared to 53 percent, but that the effectiveness of the dental appliance was partly invalidated by the compliance of only 62 percent [132]. However, Weaver [133] applied an “intention to treat (ITT) analysis” on the data from Walker-Engström et al. above. The purpose was to include all the drop-outs in the MRD group, as treatment adherence is not an issue with surgical therapy. When evaluating the laboratory success rates (defined as at least a 50 percent reduction in Apnea Index) for MRD, it was found to be 54 percent compared to 49 percent for UPPP with the ITT analysis; no significant difference. Additionally, Weaver argued that the sleep registration values, obtained while patients wore the MRD during the sleep registration night, should be corrected for the actual usage in everyday life, in order to measure the full treatment effectiveness [133].

The mortality results among UPPP treated patients have been studied by Lysdahl et al., who found no increased mortality following UPPP in a 5- to 9-year follow-up of 400 consecutive, on average, non-obese snorers, 256 of whom had obstructive sleep apnea syndrome. The UPPP patients were compared to 744 control patients (median age, 43 years), who underwent nasal surgery during the same period and to a matched general control population. The authors conclude that their results might indicate a positive survival effect of surgery [134]. Different levels are reported for complications from the UPPP-surgery, involving the full spectrum from pharyngeal discomfort to mortality. A large study of complication rate was performed by Kezirian et al. from 2004. They investigated medical records retrospectively for 3130 patients who had undergone different surgical procedures for OSAS, mostly UPPP. They showed a 1.5 percent incidence of serious complications (in majority ventilator complications) and a perioperative mortality of 0.2 percent [135]. The authors recommended to not perform several surgical procedures simultaneously, as this increased the risks of serious complications.

Weight reduction as treatment of OSAS

The treatment of obese OSAS patients is a challenge since their compliance is insufficient and the disease is often life-long. The effects of weight reduction in obese OSAS patients have been in focus for a long time [136]. Previous studies have shown that a reduction in body weight reduces the frequency of apnea in the short term [137-139]. A reduction in upper airway collapsibility [140] and an increase in the size of the upper airway passage [141] are seen after weight reduction. The respiratory resistance from thoracic-abdominal fat is probably also reduced after weight reduction. The use of surgical intervention with different types of gastric banding is becoming increasingly common [142], with good results also on indices of sleep apnea [141, 143-145]. However, there is undoubtedly a considerable risk for complications and, according to some studies, even mortality [146]. Conservative weight reduction involves a much smaller risk as far as morbidity and mortality are concerned, but is not generally considered to be equally successful. An early study by Suratt et al. [147] showed reduced
respiratory disturbances after a very low-calorie diet in eight obese subjects in a non-randomized study as early as 1992. Another early low-calorie diet (LCD) study had shown approximately a halving of mean ODI levels together with improvements in blood pressure [148]. However, the LCD method had not been properly evaluated in this patient group at the time the present study was initiated. The effect of weight reduction on sleep quality was practically unknown. There was only one study on the subject by Noseda et al. [137]. The authors reported no improvements for the sleep quality parameters arousal index and awakening index. Improvement was found only for the parameter stage shift index. At the time for initiation of our study, the LCD method was the most commonly used weight-reducing method at the Obesity Unit, Karolinska University Hospital. Even nowadays, it is still a popular method of weight reduction [149]. LCD has been investigated for complications such as liver failure, but complications are found to be mild and transient [150, 151]. These findings lead us to the aim of the PAPER II, in which we first evaluated whether LCD was a feasible method of weight reduction in obese OSAS patients, and further on to PAPER III and IV, in which we evaluated the effects of weight reduction on sleep quality, as well as on metabolic status and quality of life.

Randomized controlled trials (RCT) of dietary weight reduction in obese OSAS patients are few and therefore needed [117, 152, 153]. Only four studies are found on Pubmed on this topic [154-157]. These studies all compare different types of dietary strategies, and comparisons are not made with the use of placebo or expectancy. The four randomized studies are summarized below:

1. A controlled trial of two forms of hypnotherapy (directed at stress reduction or energy intake reduction), verses dietary advice alone, in 60 obese OSA patients on CPAP. The results showed a statistically significant difference in favour of hypnotherapy with stress reduction, compared to the other two arms, at the follow up after 18 months. However, the authors conclude that the benefits were small and clinically insignificant [155].

2. An RCT study, in which OSAS patients were randomized to either a cognitive behavioral therapy to increase intake of vegetables and fruit, or to a control group with simple dietary advice given only at baseline [156]. The vegetable and fruit diet contributed to weight reduction of mean 3.0 kg compared to 0.9 in the control group. Further a small but significant difference in change of both systolic and diastolic blood pressure was seen, favoring the vegetable and fruit diet.

3. An RCT study of non-surgical interventions for OSAS patients. The patients were randomized among sleep hygiene, CPAP, and MRD with a 10 weeks follow-up. The problem of overweight was addressed, but there was no treatment-arm for weight reduction alone. Instead all included overweight patients were offered assistance for weight reduction [154]. Similarly to our findings presented in PAPERS II, III and IV, the authors found a linear relationship between the changes in AHI (without device) and body weight, and this relationship was further found to be independent of treatment group.

4. The RCT study with a design closest to our weight reduction studies is the study by Kajaste et al [157], in which the authors randomized between CPAP during 6 months or no CPAP as additive treatment to a weight reduction program with LCD. Their study did not indicate that CPAP improved the results of a weight reduction intervention, which is the same conclusion we draw in our non-randomized studies in PAPER III and IV.
ALCOHOL AND BENZODIAZEPINE USE

Alcohol

Definition of alcohol use
As an introduction, the spectrum of alcohol drinking needs to be defined. The so-called moderate drinkers are able to control their drinking and consume small amounts without adverse consequences. Population studies have suggested that mortality in such individuals (consuming one to three alcoholic drinks daily or 10–30 g ethanol/day) may be even smaller than the mortality in teetotallers (= total abstainers) [158, 159]. However, at higher alcohol levels the risk for adverse health effects rapidly increases [160]. The threshold for the concept heavy drinkers is not clearly defined, but epidemiological data have indicated that exceeding the level of approximately 300 g ethanol per week for men, or 200 g for women, cause a significant health risk. The method to detect alcohol over-consumption in PAPER I (CDT) has its cut-off limit approximately at this level [161]. Exceeding 5–7 drinks for men, or 3–5 drinks for women, on a single occasion is also found to be harmful. Clinically, heavy drinking should also be noticed and differentiated from alcohol abuse, when heavy drinking has resulted in social problems and adverse health consequences such as mental or physical complications. Alcoholism is the most severe stage of problems involving severe dependency, increased tolerance, and the occurrence of withdrawal symptoms after cessation of drinking.

Prevalence of alcohol use
There is a general opinion that about 10 percent of the Swedish population over-consume alcohol, i.e., are heavy drinkers, alcohol abusers or alcoholics. The choice of study population is always of great importance in prevalence studies, which definitely affects prevalence studies on alcohol use too. One important aspect is the fact that the prevalence at an emergency ward is expected to be higher than in a health survey in a community. In a questionnaire survey at a group of Swedish primary health care centers, the prevalence was found to be 13 percent for males and 5 percent for females [162]. In another questionnaire study, the heavy-drinking group was reported to be as high as 27 percent for males in an urban district population outside of Stockholm [163]. A large cross-sectional study with random sample drawn from the population in Finland (age 25 to 74 years), with a participation rate of over 70 percent, has been presented by Sillanaukee et al. In this population the CDT-test, as a marker of alcohol over-consumption, was positive in 13.2 percent of the men and 12.9 percent of the females [164]. There has been a rapid increase in total alcohol consumption per capita as well as in the problems created by excessive consumption in most Western countries [160, 165]. Overall, Room et al. estimate that 4 percent of the global burden of disease is attributable to alcohol, which globally accounts for about as much death and disability as tobacco and hypertension [160]. In a recent review, Niemelä estimates from current statistics that 20–30 percent of all hospital admissions and health care costs may be attributable to alcohol abuse [166].

Diagnosis of alcohol use
The methods to evaluate alcohol use can include both the use of questionnaires and laboratory markers. Some of the most used questionnaires are AUDIT and MAST. The limitation with questionnaires is naturally the self-reporting that is often controlled by self-denial and underestimation of the alcohol use. The most frequently used laboratory markers were earlier MCV, ASAT, ALAT, gamma-GT. These parameters are all suffering from rather low sensitivity and specificity. At the time for initiation of our study, in 1999, the Carbohydrate-deficient transferrin (CDT)-test was relatively new and unknown. In PAPER I we used CDT together with 5-hydroxytryptophol (5-HTOL) and urine-benzodiazepines to detect drug abuse. Nowadays CDT is available at clinical laboratories and a recommended method of screening for alcohol abuse. Actually, the CDT test is the only test for the identification of heavy alcohol use approved by the FDA [167]. CDT, carbohydrate-deficient-transferrin, is an iron transporting liver enzyme deficient of the terminal glucosaccharides. It reflects the alcohol use the last 14 days, and is elevated if consumed more than 60g alcohol/day, equivalent to 17 centiliters hard liquor or 65 centiliters of wine each day [161, 168]. The cut-off limit reflects the levels of alcohol over use called "heavy drinkers" or worse, see above.
There are conditions in which the CDT is falsely raised, however rare. They include severe hepatic failure, mainly primary biliary cirrhosis, and genetic variants of transferrin. CDT is considered less influenced by the alcohol induced liver damage in comparison with other screening methods such as for example ASAT, ALAT and gamma-GT. The CDT has an estimated specificity of 91-100 percent and a sensitivity of 81-94 percent according to the chemical laboratory. The CDT analysis was performed at the Laboratory Department of Karolinska University Hospital, Solna, and the result was presented in CDT-units per liter (U/l). The cut-off limit was set to >20 U/l. Nowadays more recent methods give the test results as a percentage of total transferrin (%CDT). The main advantage of this current approach is that it takes into account the natural variability in serum transferrin. This is especially important in women with a high prevalence of iron deficiency as well as in patients with liver diseases [169]. There are also different CDT measurement techniques, including Microcolumn anion-exchange chromatography, followed by an immunoassay for transferrin quantification, which is the method we used. Also high-performance liquid chromatography, capillary electrophoresis and isoelectric focusing methods are available nowadays [170].

5-hydroxytryptophol (5-HTOL) is another marker of alcohol use. It is a serotonin metabolite elevated between 6-20 hours after ethanol itself is metabolized from serum measured in urine [171]. There are conditions in which 5-HTOL is falsely raised as for example when consuming serotonin rich foods or using drugs that inhibit aldehyde dehydrogenase such as disulfiram (Antabus) [172, 173]. None of our included patients in PAPER I used these drugs according to their reports. The specificity for 5-HTOL is approximately 95 percent and the sensitivity is 87 percent [174]. The 5-HTOL analysis was performed at the Alcohol Laboratory at St Göran’s Hospital, Stockholm.

**Effects on sleep of alcohol use**

Alcohol has a variety of effects on sleep and there is also a reciprocal relationship between heavy alcohol consumption and sleep disturbances. Alcohol consumption may lead to sleep disturbances by affecting the neurochemistry (i.e., neurotoxicity). Additionally, sleep problems can lead to increased alcohol consumption for self-medication, and are also risk factors for developing alcohol abuse. Sleep disturbances may further persist even during recent and sustained abstinence in abstaining alcoholics, and are found to be a risk factor for relapse to drinking [175]. In sleep studies on abstinent alcoholics Brower has shown prolonged sleep latency and high percentage of REM sleep as well as short REM sleep latency, and also found these results to be associated with relapse into alcohol use [176].

The sleep disorder most often associated with alcohol use is probably insomnia, i.e., difficulties in initiating or maintaining sleep. In a household survey, the incidence of alcohol abuse was 2.4 times higher in adults who experienced persistent insomnia during the previous year compared to adults with no alcohol abuse [177]. Studies have also indicated a relationship between alcohol abuse and periodic limb movement (PLM), a rhythmic dorsiflexion of the foot with occasional flexions of the knee and hip. The PLM is often associated with EEG signs of arousals. An increased number of PLMs is found in abstinent alcoholic subjects compared to control subjects [178].

Apart from insomnia and PLM there are also evidence for a relationship between alcohol intake and OSA. Regular intake of alcohol and benzodiazepine can transform a snoring person into a patient with OSAS [179, 180] and increase the number and duration of apneas in OSAS patients [181, 182]. Alcohol and benzodiazepines depress the respiratory centre and their muscle-relaxant effect causes hypotonia of the pharyngeal dilator muscles [183, 184]. Alcohol also induces vasodilatation and swelling of the respiratory mucosa [182]. Apart from the acute effects of alcohol ingestion, it has been shown that long-term alcohol ingestion may be an important factor in the pathogenesis of OSA. In other words alcoholic patients may even during abstinence be more likely than control subjects to have SRBD [185, 186] OSA occurs more frequently in alcoholics than in non-alcoholics (Aldrich et al. 1999) [187]. On the other hand, previous studies, using questionnaires for evaluation of the alcohol consumption of OSAS patients, have found the consumption in such patients not to be higher than
in the normal population [188, 189]. The facts of reported over-consumption of alcohol in approximately 10 percent of the normal population, and the documented effects of alcohol on sleep and OSA, made us interested in evaluating the prevalence of alcohol over-consumption in our OSAS-population at the ENT-department, described in PAPER I. Theoretically, there was a possibility that we needed to focus a great deal more on alcohol abuse when dealing with our OSAS patients.

Benzodiazepine

There is an abuse of sedatives, such as benzodiazepines, in the western world. The effect of benzodiazepine on OSA has similarities to the effect of alcohol, including depression of the respiratory centre and the muscle-relaxant effect, which causes hypotonia of the pharyngeal dilator muscles [183, 184]. There is also a contra-indication to prescribe benzodiazepines to OSAS patients, according to FASS (The Swedish Medicines Compendium, published by The Swedish Association of the Pharmaceutical Industry). Since there is a covariation between alcohol and benzodiazepine use, in combination with the fact that they have similar effects on OSA, we screened for both addictives in PAPER I. We analyzed u-Benz, a measure of benzodiazepine metabolites in urine. The analysis method was the Online Screening® from Roche, which has an estimated specificity of 87 percent and a sensitivity of 86 percent [190]. The u-Benz analysis was performed at the Laboratory Department of Karolinska University Hospital, Huddinge.

2. AIMS

1. To investigate the prevalence of alcohol and benzodiazepine abuse in 98 OSAS patients, by using the blood test Carbohydrate Deficiency Transferrin (CDT), and urine tests of 5-hydroxytryptophol (HTOL) and benzodiazepines (u-Benz).

2. To investigate the effects of a weight reduction program with Low Calorie Diet (LCD) on weight and nocturnal respiration by using polygraphy in 20 obese OSAS patients with a randomized controlled pilot study.

3. To investigate the 6-month effects of a weight reduction program, with LCD and intensive behavioral modifying therapy in day-care, in 33 obese OSAS patients by using ambulant polysomnography, questionnaires and blood sampling. The outcomes were changes in weight, nocturnal respiratory parameters, sleep quality, daytime sleepiness and metabolic status. Further, to investigate whether results indicated differences among patients with use/no-use of OSAS-devices, and whether there were gender differences.

4. To investigate the long-term effects of a more sparse behavioral modifying therapy, which followed after the initial intensive therapy for the 33 patients in study 3. The patients were investigated with the same evaluation methods after two years, with the addition of a quality of life-questionnaire.
3. SUBJECTS AND METHODS

SUBJECTS

PAPER I
Ninety-eight consecutive male OSAS patients, of the age 20-69 years, were recruited from the ENT Clinic, Karolinska University Hospital, Huddinge and asked to participate in the study. Some patients were referred to the ENT Clinic by their general practitioners and others from the Clinic for Obesity because of loud snoring and excessive daytime somnolence. The hospital serves the whole general population in the southern half of Stockholm. Out of the 98 patients asked, 96 accepted participation in the study. We were unable to draw blood from one patient and one blood sample was lost. One patient was unable to give a urine sample.

PAPER II
The pilot study included 20 obese OSAS patients, recruited from the ENT Clinic at Karolinska University Hospital, Huddinge. Inclusion criteria were: adult men with BMI above 30, an ODI above 5 and daytime symptoms of OSAS. Some had failed other OSAS treatment (continuous positive airway pressure (CPAP) or a mandibular retaining device (MRD)). We excluded patients with insufficient knowledge of Swedish, which would prevent them from taking part in group therapy, and also patients with serious psychiatric diseases. The anthropometrics of the patients are listed in Table 2.

PAPER III and IV
Forty consecutive OSAS patients were recruited from the waiting list at the Obesity unit at the Karolinska University Hospital, Huddinge. In total, 33 accepted to participate in the study, 24 males and 9 females. They formed four consecutive therapy groups, during the years 2001-2003.

Inclusion criteria: men and women, 30-69 years old, with Body Mass Index (BMI) >30, and who fulfilled the criteria of OSAS, i.e., Apnea-Hypopnea-Index (AHI) >10 and/or Oxygen Desaturation Index of 4 % or more (ODI_4) >6, as well as with subjective symptoms of OSAS.

Exclusion criteria: low motivation for behavioural change, psychiatric disease or insufficient knowledge of the Swedish language that would prevent them from taking part in group therapy. In addition, the patients who changed their antihypertensive medication during the study were excluded from the blood pressure analysis.

Of the 33 included patients, 23 used OSAS-device: 19 had CPAP and 4 patients had MRD. All were well adapted to their devices since at least 3 months prior to study start. They continued with the same treatment throughout the whole study, with the exception for the sleep registration nights, during which they slept without their device. Of the 10 patients without other OSAS-device treatment, 5 had failed CPAP, 1 had failed MRD, and 4 were newly diagnosed with OSAS, and had chosen weight reduction as primary treatment. Anthropometric and respiratory data for the study population was age mean (range) 52 (31-68), BMI 40 (33-50), AHI 43 (6-93), ODI_4 42 (6-104) and ESS 9 (2-17).

Table 2. Patient characteristics at baseline for the two randomization groups in study 2, together with separate data for those completing the study and dropouts.

<table>
<thead>
<tr>
<th>Median (range)</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Completing</th>
<th>Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50 (35–69)</td>
<td>48 (28–57)</td>
<td>51 (35–69)</td>
<td>44 (28–55)</td>
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<tr>
<td>Weight (Kg)</td>
<td>120 (100–180)</td>
<td>106 (98–126)</td>
<td>107 (98–126)</td>
<td>116 (104–180)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>38 (33–54)</td>
<td>34 (30–36)</td>
<td>36 (30–40)</td>
<td>34 (30–54)</td>
</tr>
</tbody>
</table>

BMI = body mass index,
METHODS

PAPER I
Design: Prevalence study of OSAS patients.
Primary outcome: Percentage carbohydrate-deficient-transferrin (CDT) positive patients.
Secondary outcomes: Percentage 5-hydroxytryptophol (5-HTOL) and urine benzodiazepines (u-Benz) positive patients.
Dropouts: Defined as having no laboratory screening result.

Patients were asked to participate in a study during their visit at the ENT-clinic. Prior to the visit the patients had undergone a sleep recording and filled out a questionnaire regarding symptoms and were thereby diagnosed as fulfilling the criteria of OSAS (ODI₄ >5 and daytime sleepiness).
Without prior notice the patients were in the consultation situation asked if they were willing to participate in a study evaluating overuse of alcohol and benzodiazepine, and to give blood and urine sample directly after the consultation.
The methods to detect high alcohol use were the blood test CDT and the urine test 5-HTOL. The patients were also proposed to answer the question “Do you drink alcohol more than 3 times a week?” from a questionnaire. All patients who screened positive were offered help to decrease their intake of alcohol consumption and/or recommended to stop benzodiazepine use.

PAPER II
Design: Randomized prospective pilot study with a cross-over.
Primary outcome: Changes in Oxygen Desaturation Index (ODI₄).
Dropouts: Defined as having no ODI₄ scoring at follow-up.

Twenty patients examined for their OSAS diagnosis at the ENT-clinic were included in the weight reduction study. They were asked to participate by the physician during the consultation. A few weeks later they were randomized and by mail called to the Obesity unit at the hospital, a unit with long experience of conservative weight reduction programs. A nurse at the Obesity unit performed anthropometric data collection and the patients filled out a symptom-questionnaire. The patients were then referred to the Neurophysiology department for a baseline ambulant polygraphy. Thereafter, the randomized treatment group started with weight reduction, while the control group was asked to maintain their weight. The dietary treatment consisted of an 8-week low calorie diet (LCD), consisting of a protein drink (Nutrilett®) containing approximately 800 kcal daily, together with group meetings once a week with a specialized nurse for encouragement and support. During the first 7 weeks the patients were restricted to not eat anything else, but during the last week they gradually begun to eat balanced low-calorie meals. Individual follow-up visits were performed every second week, including physical check-ups and urine analysis for ketonuria, as a marker of dietary compliance.

After the first 8-week period of LCD or expectancy, the patients were investigated with a second ambulant polygraphy. Thereafter, a crossover took place and the control group was subjected to the LCD program with group meetings, and finally completed a third polygraphy. Figure 8 illustrated the flowchart of the study.

Figure 8. Flowchart of study 2.

OSAS = obstructive sleep apnea syndrome, Polygraphy = ambulant full-night polygraphy, LCD = low-calorie diet
PAPER III and IV
Design: Nonrandomized prospective intervention study.
Primary outcome: Changes in Apnea-Hypopnea Index (AHI).
Secondary outcome: Changes in arousal index (ArousInd).
Dropouts: Defined as having no AHI scoring at follow-up.

To be accepted for dietary treatment, a physician at the Obesity unit met each patient in a screening process, with the goal to evaluate motivation for behavioural change. After acceptance and study inclusion the 33 obese OSAS patients saw a physician and nurse at the Obesity unit for the baseline screening with anthropometric data collection, four electrode whole-body bioelectrical impedance analysis (BIA, see under BIA), and laboratory blood sampling (for example glycaemic control, lipids, liver-enzymes and urat). The patients filled out questionnaires regarding their symptoms, including the Epworth Sleepiness Scale (ESS) and the Short-Form Health Survey 36 (SF-36) (see below under ESS and SF-36 respectively). Thereafter followed sleep recordings with ambulant whole night polysomnography (PSG), which also included a sleep apnea recording (see below under "Sleep recordings"). Patients treated with CPAP or MRD slept without those devices during the nights of the investigation.

The weight reduction intervention started with an initial 8-week low calorie diet (LCD), with the same procedure as in Study II. After the LCD there was a time gap due to seasonal vacation of approximately 2 months, during which the patients were offered orlistat (Xenical®) or sibutramin (Reductil®) to maintain weight loss. Thereafter, a second period followed with day-care behavioural modifying group therapy. These meetings were led by specialists from different areas (nurse, dietician, physiotherapist, and physician) and their purpose was to increase each individual's ability and know-how in making behavioural changes. Nutritional education, cooking sessions and individualized physical activity programs were included to encourage long-term lifestyle behavioural changes. The therapy program had similarities to Cognitive Behavioural Therapy, but was even more focused directly on behavioural changes. During the first 3 months the group meetings were held once a week between 8 am until 3 pm. After the 6-month follow-up the meetings were shorter, two hours, and less frequent, once a month, until the 2-year follow-up.

Evaluations with ambulant polysomnography, questionnaires, laboratory samplings and anthropometries were performed after 6 months (Paper III) and at the study end after 2 years (Paper IV). A quality of life questionnaire (SF-36) was added to the 2-year follow-up. Figure 9 presents a flowchart of the whole study.

BIA Bioelectrical impedance analysis
A four electrode whole-body bioelectrical impedance analysis (BIA) was performed (Tanita TBF-300, Tanita Corp., Tokyo, Japan) measuring the total body fat percentage (Body fat %) and the fat mass in kilos (Body fat mass). A reduction of the weight was done with 0.5 kg to compensate for clothing. The measurement requires input on whether the subject is of athletic or standard body type, and the patients were all registered as standard.

Figure 9. Flow-scheme of study 3 and 4.
SLEEP RECORDINGS

PAPER I: Ninety-two of the patients were screened for OSAS with an ambulant nocturnal polygraphy and 6 with a daytime polysomnography at the hospital, including monitoring of respiration, body movements, body position, pulse oximetry and snoring levels.

PAPER II: An ambulatory full-night polygraphy was made in the patient’s home. It consisted of six channels (oronasal thermistor, mattress showing respiratory and body movements, pulse oximetry, pulse frequency, snoring and body position) (MicroDigitrapper, Synectics Medical, Stockholm, Sweden). The apnea-hypopnea index, measured by the thermistor, was not considered to be a consistently reliable measure of the airflow at this time and was therefore excluded. A blinded qualified neurophysiologist interpreted the recordings.

PAPER III and IV: A full night ambulatory polysomnography (PSG) was performed with a portable equipment (Biosaca, HIC AB, Gothenburg, Sweden) comprising 6 EEG channels, 2 EOG channels, ECG and submental EMG. The PSG data were transferred to Nervus EEG System (NicoletOne nEEG, Viasys Healthcare Inc., Madison, WI, USA) before analysis. Simultaneously with the PSG, the patient underwent an ambulant sleep apnea recording (Embletta, Medcare Flaga, Reykjavik, Iceland), comprising 7 channels (oronasal airflow, thoracic and abdominal respiratory efforts, pulse oximetry, pulse frequency, snoring, and body position). The sleep apnea recordings were analysed with Somnologica for Embletta software. The PSG and sleep apnea recording were time synchronized, and the sleep period and awakenings were derived from the PSG analysis. There are several possible reasons why an arousal is evoked such as respiratory disturbance, motor activity, external influences (light, noise) and central nervous system activity. When studies III and IV were initiated we did not have the technical means to record all these possibilities. A qualified neurophysiologist interpreted the recordings.

Definitions of sleep and respiratory parameters:

The PSG was scored manually in 30 seconds epochs according to Rechtschaffen and Kales’ criteria [191]. The following definitions were used:

- **Time in bed (TIB):** the total time of recording from lights out until lights on.
- **Sleep period time (SPT):** the time from the onset of sleep (three epochs stage 1, or first epoch stage 2) to the last awakening in the morning.
- **Total sleep time (TST):** SPT minus any time the subject was awake after the onset of sleep.
- **Total wake time (TWT):** the sum of time awake after the onset of sleep.
- **Sleep latency:** the period from lights out until the onset of sleep.
- **Sleep efficiency (SE):** the ratio TST to TIB, expressed as percentage.
- **Stage shift index (SSI):** the sum of all sleep stage shifts divided by SPT, expressed as a number per hour.
- **Rapid eye movement sleep (% REM sleep):** the proportion REM sleep out of TST, expressed in percentage.
- **Slow wave sleep (% Deep sleep):** the proportion slow wave sleep out of TST, expressed in percentage.
- **Arousal:** a 3-15 seconds long abrupt change in EEG frequency according to scoring rules recommended by ASDA [192].
- **Awakening:** one or more epochs scored as awake.
- **Arousal index (ArousalInd):** the number of arousals divided by the TST, expressed as a number per hour.
- **Awakening index:** the number of awakenings divided by the TST, expressed as a number per hour.
- **Apnea:** a more than 80% reduction of the airflow at the nose and mouth for at least 10 seconds, according to the Somnologica for Embletta software.
- **Hypopnea:** a reduction of the airflow of at least 30 percent, followed by a desaturation of at least 4 percent within 20 seconds.
- **Apnea-hypopnea index (AHI):** the sum of all apneas and hypopneas divided by TST, expressed as a number of events per hour.
- **Oxygen desaturation index (ODI):** the number of events when the pulse oximetry indicated a decline of oxygen saturation by at least four percentage steps from the patient’s individual baseline divided by TST, expressed as a number per hour.
STATISTICAL ANALYSIS

Non-parametric test methods were used; comparisons were made between unpaired groups with Mann-Whitney U (MWU) and Wilcoxon Sign Rank test (WSR) for paired groups. For correlations tests Spearman Rank Correlations (SRC) were used. P-values less than 0.05 were considered significant. In addition, in PAPER II, since the values were normally distributed, a parametric two-sample t test was added when analysing the difference between the groups in ODI improvement.

In the 2-year follow-up, PAPER IV, two different analysis methods were used, both a per protocol analysis (PP) of all the patients who fulfilled the program, and also a stricter intention to treat analysis (ITT). In the ITT-analysis missing values for dropouts were imputed by using their baseline values +/- 1. Hence, for dropouts we assumed a worsening between baseline and follow-up, a conservative imputation method to not favour a positive treatment effect.

All statistical analyses were made in R 2.5 and Statistica, and statistical models were chosen in collaboration with a professional statistician.

ETHICAL APPROVAL

All patients gave their informed consent and the studies were approved by the local ethics committee.

4. RESULTS AND COMMENTS

PAPER I

Results
Out of the 94 patients evaluated for CDT the screening was positive for 8 (8.5%) patients and 5-HTOL was positive in 6 of 95 (6.3%). Two patients screened positive for both CDT and 5-HTOL. The analyses for benzodiazepine metabolites were positive in 3 of 95 (3.2%) patients. See figure 10 for a distribution of the positive markers. There was no large difference in ODI values for the different subgroups. Only one patient admitted to use an excessive amount of alcohol in the local questionnaire, and of the 12 patients who screened positive for CDT or 5-HTOL none had admitted to this before the tests results became available. All patients screening positive for alcohol were offered therapy for their abuse, which none accepted.

Figure 10. Flowchart showing distribution of markers for alcohol and benzodiazepine consumption in male OSAS patients in study 1.
Comments
96 out of 98 patients accepted to participate, which is a major strength of this study. If assuming the two drop-outs were alcohol abusers, the prevalence according to CDT did not change much, from 8/94=8.5 to 10/94=10.6 percent. The prevalence rate of 5-HTOL was lower, probably due to the fact that it is elevated only up to 20 hours after the ethanol is metabolized, and the patients may avoid drinking alcohol the day before the visit to the physician.

None of the patients who screened positive admitted to have alcohol over-usage in our local questionnaire. This illustrates the difficulties in addressing these questions in a way that makes the patient willing to confess alcohol over-usage, both to herself and the physician. Further, the fact that no patient accepted help for their alcohol over-usage reflects the problem to motivate patients to make behavioral changes. Our study design, with the patients unaware of the study until just before the blood and urine samples were taken, did not give the patient a possibility to deliberately restrict the consumption prior to screening.

The main limitation of the study is the lack of a control group and there are few studies to compare with on alcohol prevalence in out-clinic settings like this. One study to compare with is a screening at the company routine health check-up in a blue-collar company in Sweden [193], in which the level of positive CDT-screening was found to be 8.9 percent, very similar to our finding of 8.5 percent. Another similar CDT prevalence study found a rate of 11 percent in a workplace in the transport sector [194], and in a population sample of 7650 adult Finns the prevalence was approximately 13 percent [164].

The general opinion is that around 10 percent of the Swedish population over-consumes alcohol, well in line with a questionnaire study from several primary health care centers’ findings of a prevalence of 13 percent in males and 5 percent in females [162]. Previous studies, using questionnaires to evaluate the alcohol consumption of OSAS patients, have not found the consumption in OSAS patients to be higher than in the normal population [188, 189].

We conclude that we did not find an increased rate of alcohol overconsumption in the OSAS population at our out-clinic ward, compared to the estimated consumption level in the general population. Further, a proposed question in the consultation situation at the ENT-department has little value in evaluating the alcohol use. Maybe a full questionnaire on alcohol usage such as for example AUDIT would increase the sensitivity. Moreover, it would be advisable to try increasing the self-reflection in the patients’ problems and limit the caregivers moralizing.

PAPER II

Results
Out of the 20 included obese OSAS patients, 11 completed the protocol. There were significant intra-individual changes (the difference from start to end for the individuals) in weight and ODI\textsubscript{4} in the treatment group (p<0.05, WSR test), which were not seen in the control group.

When comparing the intervention (n=6) and control (n=5) groups, a significant inter-individual difference (the difference in change between the intervention group and the control group) was seen in weight reduction (p<0.01, MWU test). A significant difference was also seen between the groups in ODI\textsubscript{4} improvement when using the two-sample t test (p=0.045), but when using MWU test there was only a tendency towards a significant difference in ODI\textsubscript{4} improvement (p=0.067), see Figure 11.

We also evaluated the results for the whole group (n=11) after the crossover, and its effects of the LCD diet. After the LCD, there was a significant positive correlation between the reduction in weight and ODI\textsubscript{4} (p=0.005, SRC test). The median reduction was 11 percent for weight (p<0.01 WSR) and 28 percent for ODI\textsubscript{4} (p<0.05 WSR). Out of 11 treated patients, 5 halved their nocturnal desaturations.

Eight patients did not show up for the baseline polygraphy and one did not start the LCD diet. The dropout analysis showed a rate of 9 out of 20 (45%), with minor non-significant differences: the dropout patients were slightly younger and slightly less obese.

Comments
In this randomized controlled pilot study, the obese OSAS males who were treated with our dietary program showed a significant reduction in weight and nocturnal desaturations compared to expectancy. There was also a significant positive
correlation between reduction in weight and nocturnal desaturations in the treated patients. There was a high dropout rate, making the results uncertain. However, the results indicate that weight reduction is an alternative treatment for OSAS, and that the LCD in a group program seems to be a feasible method.

To our knowledge, there is only one other randomized controlled study of obese OSAS patients involving dietary weight reduction, Smith et al. [138], who monitored 15 obese men and women for on average 5 months after dietary weight loss instructions, comparing them with 9 controls. They found a 9 percent weight loss and 47 percent apnea reduction in the intervention group, compared to a slight weight increase and an unchanged apnea frequency in the control group. Our results are in accordance with theirs. In another controlled study (non-randomized), Schwartz and coworkers [140] examined dietary weight loss in 13 obese patients compared to 13 age and weight-matched obese controls subjects (all men). Over an approximate 1.5-year period, the weight loss group dropped from a mean BMI of 42 to 35 kg/m$^2$ (17%) and the control group remained at a mean BMI of 38 kg/m$^2$. The weight loss group experienced a significant reduction in AHI, from 83 to 33 (60%), whereas the control group experienced no significant change in AHI.

The main weakness of our study is the high dropout rate (45%). The rate could probably have been reduced if we had better evaluated the patients’ motivation and if a physician at the Obesity unit had informed them of the dietary program. Further, we did not use a “run-in period” before the randomization, which could have decreased the drop-out rate. The dropouts did actually not quit during the weight reduction program, instead they were “no-shows”, who did not even start the diet. The randomization did unfortunately not give two equal groups; the controls were insignificantly less obese and had a lower number of nocturnal respiratory disturbances at the start than did the intervention group. In addition, the small number of patients is another obvious weakness, making it difficult to draw major conclusions from this pilot study.
Anyhow, the pilot RCT study encouraged us to continue weight reduction as a treatment for obese OSAS patients in collaboration with the Obesity unit. However, we considered the results not good enough to use weight reduction as the only treatment. It was also unpleasant and ethically doubtful to have these very sick people untreated in a control arm. We therefore chose to use weight-reduction as an additive treatment in patients with OSAS-devices (CPAP or MRD). In addition, we included patients who had failed CPAP and MRD in the forth-coming studies, which were not RCT.

**PAPER III and IV**

**Results**

Of the 33 included patients, 31 underwent the weight controls with a mean percentage weight reduction of 14 percent (18 kg) at 6 months. At 2 years, 23 were followed up with a mean weight reduction of 9 percent (11 kg) compared to study start. Thirty patients fulfilled the 6 months dietary program, and 27 (82%) had scoring on the primary outcome parameter AHI, with a mean reduction of 34 percent. At the 2 year follow up there were 23 who fulfilled the program and 22 (67%) patients who had scoring in AHI, with the mean AHI reduction of 22 percent.

In the *per protocol analysis* (WSR) after 6 months there were significant reductions in weight, daytime sleepiness and nocturnal respiratory disturbances (all p<0.001). There were also significant changes in four of nine PSG parameters with increased sleep efficiency and percentage deep sleep, as well as decreased arousal index and total wake time. In the metabolic status there were also significant improvements including fS-insulin, P-Cholesterol and blood pressure. The patients were evaluated extensively and the results of all evaluated parameters are shown in table 3. After 2 years there were still significant reductions in weight (p<0.001) and daytime sleepiness (p=0.003). The nocturnal respiratory disturbances measured with AHI showed only a tendency of improvement (p=0.054), but measured by ODI the reduction was statistically significant (p<0.001). There were still significant improvements in arousal index and stage shift index (both p<0.001), but not in the other PSG parameters. Of the metabolic status there were significantly improvements in insulin levels (p=0.014) and dyslipidemia (triglycerides p=0.042, LDL p=0.008).

The development during the intervention time of BMI is shown in figure 12, and the primary and secondary outcomes, changes in AHI and arousal index are shown in figure 13. There was a slight increase in weight and AHI after 2 years, compared to the results after 6 months. On the other hand, the arousal index was slightly reduced after 2 years, compared to after 6-months. Statistically the changes from 6 months to 2 years showed significant increases in the weight parameters, but only a trend for a significant increase of AHI (p=0.061). These results were the only statistically significant changes between 6 months and 2 years.

At 2 year an *intention to treat analysis* (WSR) was added to adjust for the dropouts. There were still significant reductions in weight (p=0.003), sleepiness (p=0.003), ODI (p=0.010) and improvement in sleep quality (arousal index p=0.019 and stage shift index p=0.003), but only one metabolic parameter was significantly improved; high-density lipoprotein (HDL p=0.037).

At the 2-year follow-up we also re-evaluated the questionnaire SF-36. In the per protocol analysis the domains “physical functioning” (p=0.031) and “vitality” (p=0.046) was significantly improved in the SF-36 questionnaire, but the differences did not remain significant in the intention to treat analysis.
Table 3. Descriptive and statistical results for changes in weight, respiratory, sleep and metabolic parameters after 6 months’ and 2 years weight reduction intervention (per protocol analysis (PP) and intention to treat analysis (ITT)) in study 3 and 4.

<table>
<thead>
<tr>
<th>Number at 6/24 months</th>
<th>Baseline Mean(SD)</th>
<th>6 months Mean(SD)</th>
<th>PP p-value</th>
<th>2 years Mean(SD)</th>
<th>PP p-value</th>
<th>ITT p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>31/23</td>
<td>122(19)</td>
<td>104(15)</td>
<td>&lt;0.001</td>
<td>110(15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31/23</td>
<td>40(5)</td>
<td>34(3)</td>
<td>&lt;0.001</td>
<td>35(3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body fat %</td>
<td>29/18</td>
<td>43(6)</td>
<td>35(7)</td>
<td>&lt;0.001</td>
<td>36(8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body fat mass (kg)</td>
<td>29/18</td>
<td>52(11)</td>
<td>36(9)</td>
<td>&lt;0.001</td>
<td>41(11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumf. (cm)</td>
<td>29/18</td>
<td>127(14)</td>
<td>114(11)</td>
<td>&lt;0.001</td>
<td>118(9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Waist Hip ratio</td>
<td>29/18</td>
<td>1.01(0.1)</td>
<td>0.99(0.1)</td>
<td>0.021</td>
<td>1.02(0.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>AHI</td>
<td>27/22</td>
<td>43(24)</td>
<td>26(20)</td>
<td>&lt;0.001</td>
<td>28(19)</td>
<td>0.0537</td>
</tr>
<tr>
<td>ODI</td>
<td>28/22</td>
<td>42(23)</td>
<td>24(19)</td>
<td>&lt;0.001</td>
<td>23(15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESS</td>
<td>30/22</td>
<td>9(4)</td>
<td>6(4)</td>
<td>&lt;0.001</td>
<td>5(3)</td>
<td>0.0029</td>
</tr>
<tr>
<td>Arousal Index</td>
<td>26/22</td>
<td>24(15)</td>
<td>15(12)</td>
<td>&lt;0.001</td>
<td>11(11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep sleep %</td>
<td>26/22</td>
<td>16(11)</td>
<td>24(8)</td>
<td>0.001</td>
<td>19(10)</td>
<td>n.s.</td>
</tr>
<tr>
<td>REM sleep %</td>
<td>26/22</td>
<td>14(7)</td>
<td>16(8)</td>
<td>n.s.</td>
<td>16(8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total Sleep time</td>
<td>26/22</td>
<td>357(67)</td>
<td>350(70)</td>
<td>n.s.</td>
<td>338(83)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total Wake time</td>
<td>26/22</td>
<td>60(42)</td>
<td>45(33)</td>
<td>0.028</td>
<td>55(29)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>26/22</td>
<td>78(10)</td>
<td>83(9)</td>
<td>0.018</td>
<td>79(12)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stage shift index</td>
<td>26/22</td>
<td>17(11)</td>
<td>22(17)</td>
<td>n.s.</td>
<td>11(10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Awakening Index</td>
<td>26/22</td>
<td>4(7)</td>
<td>5(6)</td>
<td>n.s.</td>
<td>5(9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>26/22</td>
<td>31(19)</td>
<td>23(18)</td>
<td>n.s.</td>
<td>24(17)</td>
<td>n.s.</td>
</tr>
<tr>
<td>fP-Glucose (mmol/L)</td>
<td>29/21</td>
<td>7.2(2.7)</td>
<td>6.5(2.1)</td>
<td>0.004</td>
<td>7.0(3.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>B-HbA1C (%)</td>
<td>29/21</td>
<td>5.7(1.3)</td>
<td>5.3(1.0)</td>
<td>0.006</td>
<td>5.6(1.7)</td>
<td>0.059</td>
</tr>
<tr>
<td>fS-Insulin (pmol/L)</td>
<td>29/21</td>
<td>147(78)</td>
<td>76(32)</td>
<td>&lt;0.001</td>
<td>90(52)</td>
<td>0.014</td>
</tr>
<tr>
<td>P-Cholesterol (mmol/L)</td>
<td>29/21</td>
<td>5.3(1.1)</td>
<td>5.1(1.1)</td>
<td>0.022</td>
<td>4.9(1.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>P-Triglycerides (mmol/L)</td>
<td>29/21</td>
<td>1.8(0.8)</td>
<td>1.6(1.2)</td>
<td>n.s.</td>
<td>1.6(0.7)</td>
<td>0.042</td>
</tr>
<tr>
<td>P-HDL (mmol/L)</td>
<td>29/21</td>
<td>1.2(0.3)</td>
<td>1.4(0.4)</td>
<td>&lt;0.001</td>
<td>1.4(0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-LDL (mmol/L)</td>
<td>29/21</td>
<td>3.4(1.0)</td>
<td>3.0(1.0)</td>
<td>&lt;0.001</td>
<td>2.7(1.1)</td>
<td>0.0083</td>
</tr>
<tr>
<td>P-ASAT (ukat/L)</td>
<td>29/21</td>
<td>0.5(0.3)</td>
<td>0.4(0.1)</td>
<td>&lt;0.001</td>
<td>0.5(0.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>P-ALAT (ukat/L)</td>
<td>29/21</td>
<td>0.7(0.4)</td>
<td>0.4(0.2)</td>
<td>&lt;0.001</td>
<td>0.6(0.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>P-ALP (ukat/L)</td>
<td>29/15</td>
<td>3.1(0.9)</td>
<td>2.9(0.7)</td>
<td>0.050</td>
<td>2.9(1.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>P-gammaGT (ukat/L)</td>
<td>29/21</td>
<td>0.9(0.8)</td>
<td>0.6(0.3)</td>
<td>&lt;0.001</td>
<td>0.7(0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-Urat (umol/L)</td>
<td>29/21</td>
<td>400(69)</td>
<td>371(83)</td>
<td>0.005</td>
<td>418(86)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Syst BP (mmHg)</td>
<td>25/13</td>
<td>144(19)</td>
<td>133(16)</td>
<td>0.007</td>
<td>129(10)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diast BP (mmHg)</td>
<td>25/13</td>
<td>89(14)</td>
<td>82(10)</td>
<td>0.033</td>
<td>81(6)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Kg= kilogram (2.2 pounds), BMI= Body Mass Index, Body fat %= Percentage body fat, Waist circumf.= Waist circumference, AHI= Apnoea Hypopnoea Index, ODI= Oxygen Desaturation Index, ESS= Epworth Sleepiness Scale, Deep sleep %= Percentage Slow Wave Sleep, REM sleep %= Percentage REM sleep, fP-Glucose= fasting plasma glucose level, HbA1C= glycosylated hemoglobin A1c, HDL= high-density lipoprotein, LDL= low-density lipoprotein, ASAT= aspartate aminotransferase, ALAT= alanine aminotransferase, ALP= alkaline phosphatase, gammaGT= gamma-glutamyl transpeptidase, Syst BP= systolic blood pressure, Diast BP= diastolic blood pressure, SF-36= Short Form 36, PF= Physical Functioning, RP= Role-Physical, BP= Bodily Pain, GH= General Health, VT= Vitality, SF= Social Functioning, RE= Role Emotional, MH= Mental Health, PP= per protocol analysis, ITT= intention to treat analysis, mean(SD)= mean value together with standard deviation, WSR= Wilcoxon Sign Rank test, n.s.= non significant
**Figure 12.** Box-plots showing Body Mass Index (BMI) at baseline (bl) and after 3, 6, 12 and 24 months (3m, 6m, 12m, and 24m) weight reduction program (per protocol analysis, \(***= p<0.001\), Wilcoxon Sign Rank test) in study 3 and 4.

**Figure 13.** Box-plots showing Apnea-hypopnea index (AHI) and Arousal Index (ArousInd) at baseline (bl), after 6 months (6m) and 2 years (2y) weight reduction program (per protocol analysis, \(***= p<0.001\), n.s. = non significant, Wilcoxon Sign Rank test) in study 3 and 4.
The statistical analyses revealed no significant differences between the patients treated with devices (CPAP or MRD, n=23) and those without device (n=10), for changes in the following seven parameters: percentage weight reduction, kilos, BMI, AHI, ODI, arousal index and ESS (MWU p>0.05). The same seven parameters were evaluated for gender differences, and there were no significant differences between the 24 men and the 9 women, with one exception at the 6-month results: Data showed that the women lost less weight in kilograms compared to the men at 6-month, but there were no significant differences in percentage weight reduction or BMI reduction, and at 2-year there were no significant differences.

There was a significant positive correlation between reduction in BMI and AHI both at 6-month and 2-year. The 2-year scatter plot is shown in figure 14, r=0.498 (p<0.05, SRC). There were no correlation between AHI and ESS or arousal index.

In baseline data there was a significant correlation between the percentage body fat and baseline AHI, r=0.41 (p<0.05). In addition, there was a significant negative correlation between age and baseline sleep efficiency, r=-0.45, as well as between age and baseline total sleep time, r=-0.45 (both p<0.05). There were no further significant correlations between metabolic and sleep apnea parameters.

Five different treatment success levels at 6-month and 2-year (per protocol and intention to treat analyses) are presented in table 4.

**Figure 14.** Scatter plot illustrating the correlation between improvement in AHI and BMI reduction after the 2-year weight reduction intervention, (Spearman correlation (r) 0.498, p=0.019) in study 4.

Delta AHI = changes in Apnea Hypopnea Index, Delta BMI = changes in Body Mass Index (kg/m²)
Table 4. Different criteria of success were used for the results after the 6-month and 2-year weight reduction program, analysed with per protocol and intention to treat analysis in study 3 and 4.

<table>
<thead>
<tr>
<th>Success criteria</th>
<th>Per protocol</th>
<th>2 years</th>
<th>Intention to treat</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of weight &gt;10%</td>
<td>24/30 (80%)</td>
<td>7/23 (30%)</td>
<td>24/33 (73%)</td>
<td>7/33 (21%)</td>
</tr>
<tr>
<td>Reduction of AHI &gt;50% and AHI &lt;20</td>
<td>9/27 (33%)</td>
<td>5/22 (23%)</td>
<td>9/33 (27%)</td>
<td>5/33 (15%)</td>
</tr>
<tr>
<td>Reduction of ArousIn &gt;50% and ArousIn &lt;12</td>
<td>8/27 (30%)</td>
<td>11/22 (50%)</td>
<td>8/33 (24%)</td>
<td>11/33 (33%)</td>
</tr>
<tr>
<td>Reduction of ODI4 &gt;50% and ODI4 &lt;20</td>
<td>10/22 (45%)</td>
<td>8/22 (36%)</td>
<td>10/33 (30%)</td>
<td>8/33 (24%)</td>
</tr>
<tr>
<td>Reduction of ESS &gt;50% and ESS &lt;8</td>
<td>8/30 (27%)</td>
<td>9/22 (41%)</td>
<td>8/33 (24%)</td>
<td>9/33 (27%)</td>
</tr>
</tbody>
</table>

AHI= Apnea Hypopnea Index, ArousIn= Arousal Index, ODI4= Oxygen Desaturation Index, ESS= Epworth Sleepiness Scale

The LCD treatment was well tolerated by all participants and there were no medical complications, i.e., no renal or other side effects.

Dropout analysis on the baseline data showed that the patients with missing AHI values displayed only minor non-significant differences in terms of mean and range values for anthropometrics, nocturnal respiration and daytime sleepiness data.

Comments

In our 2-year weight reduction program, performed in groups of obese OSAS patients, the AHI and quality of life measurements were significantly improved in the per protocol analysis, but not in the intention to treat analysis. However, there were significant improvements in both statistical analyses concerning the degree of obesity, ODI, arousal index, as well as daytime sleepiness. 70 percent of the patients completed the 2-year program. The dropout rate was much lower than in PAPER II, which could be explained by our increased effort to select better motivated patients.

In our opinion, the weight reduction program is a valuable and reasonably successful intervention for motivated obese OSAS patients in comparison with the success rates and compliance of other OSAS treatments. The success rate of our dietary program varies depending on criteria. In a previous study, it was shown that 10 percent reduction of weight had a positive influence on hypertension, glucose metabolism and dyslipidemias [195] which is in agreement with our results. With this criterion, 73 percent were successfully treated after 6 months but only 21 percent after 2 years in the intention to treat analysis. This finding could be compared to an LCD & day-care study by Pekkarinen et al. [196], which showed a 32 percent success rate after 2 years among healthy obese patients, and by Kajaste et al. which showed 42 percent among obese OSAS patients [157]. With the same 10 percent weight reduction criteria, Anderson et al. had in a per protocol analysis a 30 percent success rate after 3 years [197], but they only evaluated 76 of initial 426 patients. The authors did not make an intention to treat analysis, which would have shown an estimated success rate of 5 percent. Our success rate after 2 years for improved nocturnal respiration varied in the intention to treat analysis from 15 percent (AHI) to 24 percent (ODI4), see table 4. The success rate for arousal index was somewhat higher; 33 percent. Kajaste et al. showed a success rate on ODI4 after 2 years of approximately 33 percent [157].

Altogether, we conclude that approximately one of four patients was successfully treated for their OSAS by our weight reduction program at the 2-year follow-up. The OSAS patients, who did reduce weight but not fulfilled the weight success criteria in a strict sense, were likely to benefit from the program in terms of the reduced CPAP-pressure and/or improved compliance of CPAP or MRD, although such results were not measured. We have not performed a cost-benefit calculation for our weight reduction program, and such analysis would be of future interest.

The dietary intervention is to be compared to the surgical method of weight reduction in OSAS patients. The use of surgical intervention with different types of gastric banding is becoming increasingly common [142], showing good results also on indices of sleep apnea [141, 143-145]. However, there is undoubtedly a considerable risk
of complications and, according to some studies, even mortality with such an aggressive treatment [146]. Conservative weight reduction involves fewer and lower risks, but is generally not considered to be equally successful. Our study-results agree on that it is difficult to achieve a long-term weight reduction. Further, the external validity of our study is probably low, partly because only patients with high motivation were included, but also because the Obesity unit is a specialized, government-funded clinic, with an extensive experience of dietary weight reduction and behavioural modifying therapy. There is definitely a place for both dietary and surgical methods, as the dietary interventions are often insufficient for severely obese patients or for patients with low motivation. On the other hand, not all patients are suitable for surgical interventions considering the associated risks. However, the optimal program for conservative weight reduction will probably still be debated far in the future.

The use of SF-36 has earlier revealed that OSA patients have lower quality of life compared to an age- and gender matched control group [98]. The questionnaire has been used in several studies on OSA populations and CPAP-intervention, which have shown improvements in some of the eight domains, often the “role-physical” and the “vitality” domains [102]. Also in the obese patients, the SF-36 has shown impaired quality of life, with a correlation between increased degree of obesity and decreased quality of life [198]. In addition, dietary weight-loss methods have shown improvements in several domains including vitality and physical functioning [199, 200]. Our intervention in obese OSAS patients showed improvements in two of the domains of the SF-36, the “physical functioning” and “vitality” in the per protocol analysis, results that are well in line with previous findings.

The fact that we included different patient groups, both with and without MRD/CPAP-device, gave us an opportunity to evaluate whether this difference had any influence on the weight reduction and other parameters. One could assume that patients with devices would have more energy to focus on the weight reduction program and therefore succeed better than those without. In the present study this could not be shown. There were no major differences in the baseline data for the subgroups with device compared to without, and they also responded similarly to the dietary intervention. This result agrees with data from Kajaste et al [157], who reported no significant differences in weight loss between a randomized group given CPAP treatment in addition to weight reduction, and a group treated only with weight reduction. There have been stipulations that CPAP alone would induce weight reduction by for example increased physical activity and/or increased responsiveness to the appetite down-regulatory hormone leptin [201]. However, this was not shown in a retrospective study, in which subjects, who adhered to prescribed CPAP treatment for OSAS, did not lose more weight after one year compared to control subjects, who were either untreated or did not adhere to prescribed CPAP treatment. On the contrary, the CPAP group was associated with weight gain, especially in the females [201].
5. GENERAL DISCUSSION

Alcohol consumption is increasing in most Western countries [160, 165] with an associated health risk. We still don’t have a perfect method for evaluating overconsumption, but CDT is considered to be the best available parameter [167]. There are also difficulties in finding efficient ways of assisting the patient to cut down on drinking. None of the patients in PAPER I, who were offered help for their abuse, accepted the offer. Since also sleep problems are increasing and the fact that many use alcohol as self-medication for sleeping problems adds to the problem. In the specific field of OSAS, there is a good reason to believe that alcohol over-usage also reduces compliance to any OSAS treatment and is therefore important to evaluate. Until now this has in general not been in focus when dealing with patients suffering from sleep disturbances including SRBD. The result from PAPER I revealed no increased prevalence of alcohol over-usage among OSAS patients, but the proportion of approximately 10 percent is still a considerable risk factor. At our clinic we still have the same question in our questionnaire today, as the patients were asked in the study: “Do you drink alcohol more than 3 times a week?” As seen from the results of our study this question does not provide much information of the actual alcohol usage.

Alcohol is also attributing to the daily calorie intake, and patients with heavy drinking habits often gain weight, and may develop obesity. This contrasts to alcoholics, who usually are underweight due to a loss of normal eating habits, and food intake is often neglected in long periods.

In PAPER II, III and IV we found that obese OSAS patients were successful to reduce weight with our program and experienced effects on several different parameters. The reason for the improved nocturnal respiration, sleep quality, daytime sleepiness and metabolic status after weight reduction is not fully understood, and is probably multi-factorial. The obese OSAS patients are in a vicious circle, and weight reduction is an important treatment with several possible mechanisms to improve their general health and sleep. Figure 15 is trying to illustrate this complexity in a picture, and here follows six conceivable mechanisms:

1. Fat reduction may increase the lumen of the upper airways [202], thereby reducing the obstructive apneas and sleep fragmentation.
2. OSAS patients have hormonal and inflammatory imbalances; i.e., they have decreased levels of growth hormone [203], increased levels of cortisol [204], tumour necrosis factor alfa (TNF-alfa) and interleukin 6 (IL-6) [205], and these factors are shown to be influenced by impaired sleep quality [206, 207]. There is also a reversed relationship as these factors can cause sleep disturbances, i.e., elevated evening cortisol secretion may promote sleep fragmentation [208, 209], and raised levels of both IL-6 and cortisol together cause poor sleep [210]. Our sleep recordings in PAPER III and IV indicated that the sleep fragmentation and sleep quality were improved after weight reduction.
3. Obesity itself influences the inflammatory status. TNF-alfa and IL-6 correlate positively to Body Mass Index [211], and adipose tissue is shown to produce at least IL-6 [212]. By reducing fat, this may be a pathway to improved sleep quality.
4. The metabolic syndrome (central obesity, hypertension, impaired glucose tolerance, dyslipidemia) was present in 82 percent of our patients at baseline in PAPER III, and OSAS patients are known to often suffer from the metabolic syndrome [213, 214]. The metabolic syndrome itself may impair sleep quality, as it also affects the hormonal and inflammatory balance [205]. We found that the parameters of the syndrome were all improved after weight reduction, at least at the 6-month follow-up in PAPER III.
5. Impaired sleep, daytime sleepiness and sleep deprivation can increase the degree of OSA. As an example of this, a daytime PSG registration after sleep-deprivation has shown higher apnea index compared to a nocturnal registration [215].
6. Impaired sleep has been shown to cause obesity by imbalance of the appetite regulating hormones leptin and ghrelin [216, 217], thus keeping the patient trapped in this vicious circle.
Almost all over the world an epidemic of obesity has been proclaimed! The population is growing both in numbers and in kilos and the degree of overweight and obesity is increasing every year. The International Obesity Task Force estimates suggested in 2004 that at least 1.1 billion adults are overweight (BMI >25), including 312 million who are obese (BMI >30). When adding the new Asian BMI criteria of overweight at the lower cut-off level of 23.0 kg/m², the number was even higher, approximately 1.7 billion people. The prevalence of obesity has at least doubled in less than two decades [218]. Overweight prevention and reduction is attempted by medical services all over the world with little result. According to The Official Statistics of Sweden (Statistiska Centralbyrån, www.sbc.se) the proportion of overweight in the Swedish population, 16-84 years of age, is 43.5 percent (35.8 percent among women and 50.7 among men). These figures are the latest available on their web page and originate from 2005, and can be compared with the earliest available from 1981 when the proportion of overweight was 30.7 percent. Obesity was set to overtake smoking as the main preventable cause of illness and premature death already in 2005 according to Mokdad et al. and Popkin et al [219, 220]. They describe excess body weight to be the sixth most important risk factor contributing to the overall burden of disease worldwide. Further, with increasing degree of obesity the OSAS prevalence is known to increase too, and medical service needs to be prepared for the consequences. The obesity and thereby OSAS complexity is huge!
6. CONCLUSIONS

1. The prevalence of heavy alcohol drinkers in OSAS patients was found to be approximately 10 percent, which is comparable to other questionnaire studies as well as with CDT studies of the normal population. The prevalence of benzodiazepine abuse was low. There was no correlation between the responding to a question of alcohol abuse and test results. We consider the abuse issue to be important in OSAS patients, and a laboratory screening is advised to increase accuracy.

2. The dietary intervention of LCD in obese OSAS patients showed significant reductions in weight and nocturnal respiratory disturbances compared to the control group. In addition, the more the patients lost weight the more they improved their nocturnal respiration. However, a high dropout rate of 45 percent makes the results uncertain. The dropout rate also illustrates the difficulties to motivate this patient group to undergo an ambitious weight reduction program.

3. The six-month results, after a dietary program of LCD and intensive behavioral modifying day-care on obese OSAS patients, showed significant reductions in weight, respiratory and sleep parameters as well as daytime sleepiness and metabolic status (blood pressure, blood glucose levels and lipidemia). There were no differences in results between patients with OSAS-devices compared to those without, nor were there any gender differences.

4. The two-year results, after the sparser behavioural modifying day-care on obese OSAS patients, showed deterioration from the six-month follow-up. However, there were still significant improvements between baseline and two years of weight, daytime sleepiness and some of the sleep and nocturnal respiratory parameters. There were indication of improvement in the quality of life, in the SF-36 subscales vitality and physical functioning. We conclude that dietary intervention on obese OSAS patients is to be attempted in well motivated patients as a supplement to other OSAS-treatments.

7. FUTURE PERSPECTIVE

It would be of future interest to evaluate the CDT-marker in all patients who have failed OSAS treatment. We are actually enrolling patients for a RCT surgical intervention with UPPP at our clinic. The patients are mostly failures of CPAP and MRD and we screen them for alcohol over-usage with CDT. Until October 2008, 18 patients are included; one had a positive CDT test. All patients who screen positive will receive careful information about the connection between OSAS severity and alcohol abuse, and if accepting, they are referred to an abuse clinic for aversion treatment. In the future, we would also like to improve our handling of patients with suspected abuse.

In the field of OSAS and obesity there are still questions to be answered. In our opinion, the most tempting study to perform would be a RCT study with weight reduction compared to expectancy of a large number of OSAS patients. The evaluations should include subjective measurements (daytime sleepiness, sleep questionnaires and quality of life) as well as objective measurements (AHIs, ODI, arousal index, vigilance tests, MSLT, BMI, neck and waist circumferences). The primary outcome should be carefully chosen to achieve high internal validity. There have been discussions that the often used AHI is a surrogate measurement. On the other hand, AHI has been shown to correlate to morbidity and mortality in recent studies of high quality [108, 110]. A subjective measurement as primary outcome is an alternative, but they all have limitations in validity. Cardiovascular event would probably be the preferable choice, if ethical aspects, time, size of study population and economy had no restrictions. Our hypothesis would be that weight reduction is effective as treatment of obese OSAS patients. However, high motivation and effort from both study objects and investigators are needed, since it is difficult to make behavioral modifications. The issue of which weight reduction method is the most successful, efficient and cost-effective for obese OSAS patients is another difficult question that needs further evaluation. Until more is known within this field we consider it important to inform the patient of the different weight reduction alternatives, dietary or surgically, and to involve the patient in the decision.
Obstruktivt sömnapnésyndrom (OSAS) är en folksjukdom som uppskattningsvis 2 till 4 procent av den vuxna populationen lider av. OSAS karaktäriseras av återkommande andningsuppehåll under sömn, på grund av att svalgets väggar sugs ihop vid inandning. De vanligaste besvären av OSAS är dagtrötthet och snarkning. OSAS medför stort lidande för drabbade personer och omfattande kostnader för samhället.

Orsakerna till att man drabbas av OSAS är flera, men övervikt är den vanligaste faktorn. Statistiska Centralbyrån uppskattar att 43 procent av Sveriges vuxna befolkning är överviktiga. Andningen under sömn påverkas dessutom av nästäppa, trånga förhållanden i svalget, sovställning (ryggläge är sämst), rökning samt alkohol. Tidigare studier av alkoholkonsumtion bland Sveriges vuxna befolkning har visat att runt 10 procent dricker ohälsosamt mycket alkohol.

Denna avhandling utvärderar två separata aspekter av OSAS, dels andelen OSAS-patienter som överkonsumerar alkohol, dels hur viktreduktion fungerar som behandling av OSAS.

I DELARBETE I värderade vi alkoholöverkonsumtion hos 98 OSAS-patienter på vår öronnäs-halsmottagning, både med blod- och urinprov, samt genom enkätfrågor. Vi använde oss bland annat av det nya blodprovet CDT som visar hur mycket alkohol patienten druckit de senaste två veckorna. Hos våra patienter var andelen med förhöjt CDT prov 8,5 procent, alltså ungefär på samma nivå som hos normalbefolkningen i Sverige. Ingen av dem som hade prover med påvisad överkonsumtion av alkohol hade uppgivit detta i enkäten, och ingen var heller villig att delta i rehabilitering för sin överkonsumtion. Vi hade ett mycket litet bortfall, vilket innebär att våra resultat bedöms vara tillförlitliga.


I DELARBETE III och IV fortsatte utvärderingen av viktreduktion med låg-kalori-diet. Vi följde både dagtrötthet, andningsuppehåll, sömnkvalitet, kroppssammansättning samt livskvalitet för att få en helhetsbild av hur viktreduktion fungerar, vilket inte är gjort tidigare. Vi införde nu ett förlängt program för viktreduktion med tillägg av gruppterapi för att förbättra kost och motion under totalt två års tid. OSAS-patienterna fick alla aktiv dietbehandling, tillåts att samtidigt ha OSAS-behandling med näsmask (CPAP) eller tandskena (MRD), och både kvinnor och män deltog. 30 av initialt 33 patienter följdes upp efter sex månader, och 23 vid två år. Resultaten vid sexmånadersuppföljningen var mer uttalade än vid tvåårsuppföljningen, till exempel var medelviktnedgången vid sex månader 18 kg jämfört med 11 kg efter två år. Efter två år sågs dock fortfarande signifikanta förbättringar av vikt, blodfetter, sockerbalans, andningsuppehåll och mikrouppvaknanden. Resultaten skiljde sig inte åt mellan kvinnor och män, inte heller mellan de som hade eller inte hade CPAP/MAD. Till skillnad från andra studier fann vi goda skäl till att behandla motiverade obesa OSAS-patienter med viktreduktion som komplement till annan OSAS-behandling.
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Weight reduction and alcohol abuse in sleep apnea patients

10. REFERENCES


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