Lifestyle Intervention with Weight Reduction
First-line Treatment in Mild Obstructive Sleep Apnea

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***Rationale*: Obesity is the most important risk factor for obstructive sleep apnea (OSA). However, although included in clinical guidelines, no randomized controlled studies have been performed on the effects of weight reduction on mild OSA.**

***Objectives*: The aim of this prospective, randomized controlled parallel-group 1-year follow-up study was to determine whether a very low calorie diet (VLCD) with supervised lifestyle counseling could be an effective treatment for adults with mild OSA.**

***Methods*: Seventy-two consecutive overweight patients (body mass index, 28–40) with mild OSA were recruited. The intervention group (n = 35) completed the VLCD program with supervised lifestyle modification, and the control group (n = 37) received routine lifestyle counseling. The apnea–hypopnea index (AHI) was the main objectively measured outcome variable. Change in symptoms and the 15D-Quality of Life tool were used as subjective measurements.**

***Measurements and Main Results*: The lifestyle intervention was found to effectively reduce body weight (-10.7 ± 6.5 kg; body mass index, -3.5 ± 2.1 [mean $\pm$ SD]). There was a statistically significant difference in the mean change in AHI between the study groups ($P = 0.017$). The adjusted odds ratio for having mild OSA was markedly lowered (odds ratio, 0.24 [95% confidence interval, 0.08–0.72]; $P = 0.011$) in the intervention group. All common symptoms related to OSA, and some features of 15D-Quality of Life improved after the lifestyle intervention. Changes in AHI were strongly associated with changes in weight and waist circumference.**

***Conclusions*: VLCD combined with active lifestyle counseling resulting in marked weight reduction is a feasible and effective treatment for the majority of patients with mild OSA, and the achieved beneficial outcomes are maintained at 1-year follow-up.**

Keywords: obstructive sleep apnea; obesity; lifestyle intervention; weight loss

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Obesity is the most important risk factor for obstructive sleep apnea (OSA), and both obesity and OSA are increasing public health burdens. However, although included in clinical guidelines, no randomized controlled studies have been carried out on the effects of weight reduction on mild OSA.

What This Study Adds to the Field

This study indicates that lifestyle intervention with early weight reduction is a feasible, low-cost, and curative treatment for the vast majority of patients with mild OSA. The treatment also results in an improvement of other obesity-related risk factors for cardiovascular diseases.

Obstructive sleep apnea (OSA) is one of the most common sleep disturbances, and it has been estimated that one of five adults experiences at least some degree of sleep-related breathing disturbance (1). OSA affects mostly the middle-aged work force, and exerts a negative impact on public health by increasing both morbidity and mortality (2–4). OSA has been found to have an independent association with hypertension, cardiovascular disease, stroke, type 2 diabetes, metabolic syndrome, and an overall deterioration of an individual's quality of life and working capacity (5–10). Even mild OSA is a risk factor for increased cardiovascular morbidity, although the risk is more frequently associated with more severe degrees of obstructive sleep apnea (11). On the other hand, originally mild OSA can progress to moderate or severe OSA (12). Obesity is considered the most important risk factor for OSA (13, 14), and it is, as such, a contributory factor to many diseases including diabetes, cardiovascular diseases, and metabolic syndrome (6–8, 15). It has been estimated that in the United States 32% of all adults have body mass index (BMI) greater than 30 (16). In Europe, the trends are all in the same direction, for example, in Finland one of five adults has a BMI greater than 30 (17). In view of the prevalence of mild OSA, and the beneficial effects of even marginal weight loss on both the severity of OSA and the likelihood of developing OSA, lifestyle intervention including weight reduction represents a viable option for the treatment of patients with mild OSA (18, 19). However, although this recommendation is included in the clinical guidelines, there is a lack of well-executed studies on the effect of

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weight reduction and lifestyle intervention on OSA. Accordingly, we report here the results of the first randomized study on the effects of an intensive lifestyle intervention with an initial weight reduction program in the most prevalent subgroup of patients with OSA, that is, overweight patients with mild OSA. Our 1-year follow-up study had two main objectives. First, we wanted to determine if a supervised weight reduction with very low calorie diet (VLCD) including individualized dietary counseling could represent an effective treatment for patients with mild OSA. Second, our aim was to find out whether weight reduction as a part of a lifestyle intervention results in permanent improvement in patients with mild OSA.

METHODS

Design Overview

Our study was a randomized, clinical 1-year follow-up trial with two groups in patients with mild OSA. The patients in the intervention group received a 1-year lifestyle intervention including an initial weight reduction program with a 12-week VLCD. For the control group, a single general dietary and exercise counseling session was implemented. Our hypothesis was that a successful weight reduction with lifestyle intervention would result in an improvement of mild OSA, and morbidities related to OSA. The participants were examined once immediately after the VLCD with nocturnal cardiorespiratory monitoring and quality of life (QoL) questionnaire to determine whether the treatment modality had been effective. The main end point of the study at 1 year consisted of clinical examination, nocturnal cardiorespiratory monitoring, symptom questionnaires, and biochemical measurements. This study was conducted in collaboration with Kuopio University Hospital (Kuopio, Finland), University of Kuopio (Kuopio, Finland), National Public Health Institute (Helsinki, Finland), and Skogby Sleep Research Center (Skogby, Finland). The patients were given oral and written information about the trial protocol and they provided written consent. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo (Kuopio, Finland).

Participants

The study was conducted at a single center, Kuopio University Hospital. The study subjects were consecutively recruited from among patients referred from primary health care centers of the District of Northern Savo to the outpatient clinics of otorhinolaryngology and respiratory medicine of Kuopio University Hospital because of a clinical suspicion of sleep-disordered breathing. The recruitment was planned to last for 2 years, and it started in October 2004 (October 20, 2004) and ended in December 2006 (December 1, 2006). Patients were assigned to undergo nocturnal cardiorespiratory monitoring. Their weight and height were checked, and their upper airway signs were evaluated. The inclusion criteria were as follows: (*1*) working age, 18–65 years; (*2*) BMI, 28–40 kg/m^2; and (*3*) apnea–hypopnea index (AHI), 5–15 events/hour. We also agreed to exclude patients undergoing active treatment of OSA of any kind, as well as pregnant women and those with chronic kidney, thyroid, or liver disease. It is worth noting that of the 544 patients excluded, 326 patients (60%) may be considered simple snorers, that is, they presented snoring as a symptom only, and had AHIs less than 5 in sleep recordings. However, according to the current Finnish clinical guidelines for treating patients presenting symptoms of sleep-disordered breathing, these patients were referred from local primary health care centers, and examined at Kuopio University Hospital. Of all the patients presenting a clinical suspicion of OSA (n = 301), the overweight patients with mild OSA represented a significant (28%) subgroup. The study flowchart is presented in Figure 1. After the visit to the study physicians and the confirmation that the patients fulfilled the inclusion criteria, the subjects were allocated randomly to two study groups by a study nurse according to a previously generated randomization plan. A block randomization with a block size of 16 was used. The study nurse did not take part in the intervention part of the study, nor did the study nutritionist see the patients before the first group session for the intervention group. No stratification was used in the allocation of the participants into the two groups. The primary outcome measure was the change of AHI. The secondary outcome measures were changes in QoL, symptoms related to OSA, and cardiorespiratory, glucose, and insulin metabolism parameters.

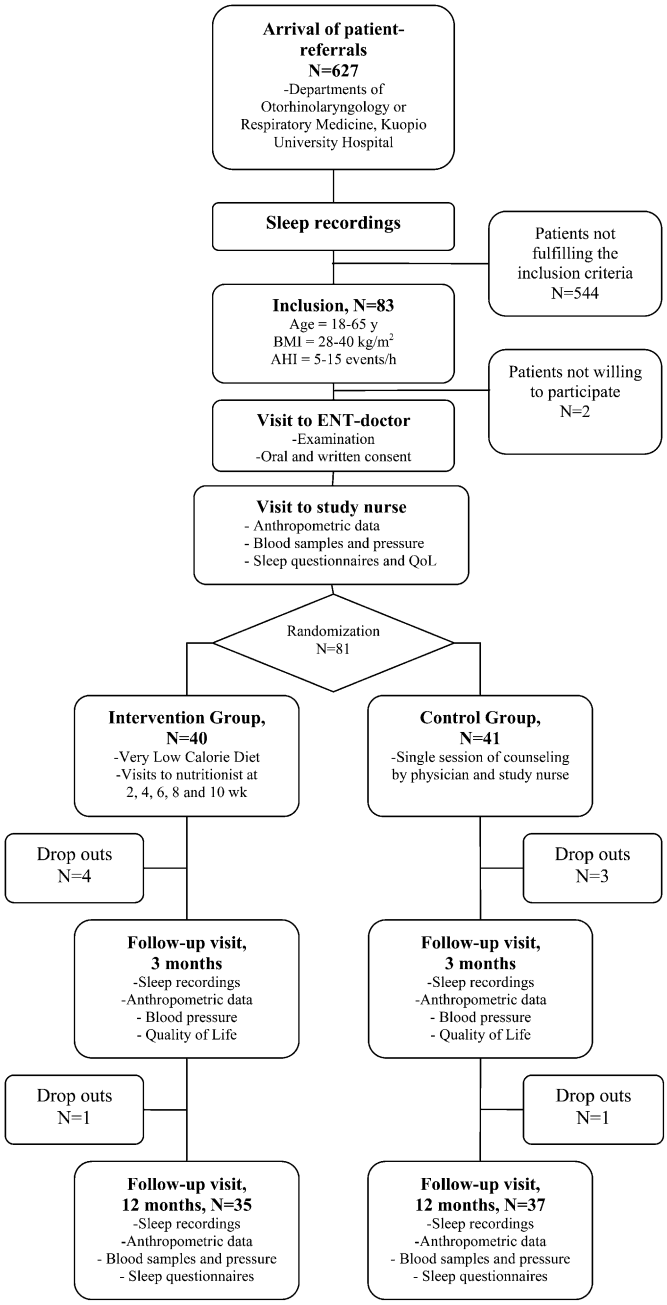

Figure 1. Study flowchart. AHI = apnea–hypopnea index (the number of apnea–hypopnea events with at least a 4% oxygen desaturation per hour); BMI = body mass index; ENT = ear, nose, and throat; QoL = quality of life = 15D (21, 22). Sleep questionnaires included (*1*) Snore Outcomes Survey, (*2*) Epworth Sleepiness Scale, and (*3*) information about witnessed apneas. Of the 544 excluded patients, 326 (60%) may be considered simple snorers, that is, presented snoring as symptom only, and had an AHI less than 5 in sleep recordings.

Intervention

At the beginning of the trial, the patients were informed about the general health risks associated with OSA and obesity (including, i.e., information about harmful lifestyle factors, such as smoking and

alcohol drinking). Study subjects were asked to keep a 3-day food diary at baseline to estimate their nutrient intake. After screening, the intervention group participants were provided with a group-based VLCD of 600–800 kcal/day (Nutrilett [Nycomed Pharma, Oslo, Norway], Modifast [Novartis, Basel, Switzerland], Nutrifast [Leiras, Helsinki, Finland], or Naturdiet [Vitamex, Norrköping, Sweden]) for 12 weeks. At the beginning of the intervention, previous attempts to lose weight were discussed and an individual goal for weight loss was set. During the VLCD period, follow-up visits were arranged every second week and the sessions were supervised by the nutritionist. Compliance with the program and supervision for any possible adverse events were monitored by individual interviews at each visit by the nutritionist. The weight was measured at every visit and the patients were asked about the lifestyle changes he or she had made. The nutritionist provided face-to-face counseling individually tailored to each patient in the intervention group and also in the group sessions. Each session lasted 60–90 minutes. In addition to VLCD products, the patients were allowed to have calorie-free drinks and vegetables in accordance with our outpatient clinic's weight reduction program. The clinical nutritionist provided dietary and lifestyle counseling at each visit, with the emphasis placed on diet, exercise, and modification of lifestyle in general, specifically focusing on eating behavior. After the VLCD program, the patients were advised to reduce fat to no more than 30% of total energy by increasing their intake of fruits, vegetables, poultry, fish, and lean meat, and by limiting dairy fats, fatty meat, sweets, pastries, and desserts. The subjects were recommended to increase their overall level of daily physical activity, and endurance exercise (such as walking, skiing, jogging, or swimming) was also recommended. After the VLCD, a physiotherapist supervised two of the group meetings, which focused on circuit-type resistance exercise to improve functional capacity. However, none of the patients had ongoing weight loss procedures, were enrolled into formal exercise programs, or were provided with personal trainers. The lifestyle intervention lasted for 1 year, and consisted of 14 visits with the study nutritionist. During the intervention period, the rate of participation in these sessions varied from 70 to 80%. The subjects in the control group were given general oral and written information about diet and exercise at baseline, at the 3-month visit, and at the 1-year visit by the study nurse and physician, but no specific individualized programs were offered to them. No individual or specific instructions were given regarding sleeping positions to any of the study patients.

Procedures and Measurements

Nocturnal cardiorespiratory monitoring by Embletta (Embla, Broomfield, CO) at home was conducted in accordance with accepted guidelines for diagnosing OSA (20). The recordings were manually evaluated by a blinded, trained physician. Apnea was defined as a cessation (more than 90%) of airflow of more than 10 seconds with oxygen desaturation for more than 4%. Hypopnea was defined as a reduction (more than 30%) of airflow of more than 10 seconds with oxygen desaturation for more than 4%. The apnea–hypopnea index was defined as the number of apneas and hypopneas per hour, and mild OSA was defined as an AHI of 5–15 events/hour (20). Other parameters were assessed, for example, arterial oxygen saturation, time and percentage with arterial oxygen saturation below 90%, and heart rate. The sleep recordings were conducted at baseline, at the 3-month visit, and at the 1-year visit. The OSA was considered objectively cured when the AHI was less than 5 events/hour.

BMI was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured on the right arm with the subject in a sitting position, and was determined three times, after 10 minutes of rest, using a standard sphygmomanometer. The mean value of the measurements was used as the result. At the study site, a trained nurse measured height, weight, waist circumference, and blood pressure at baseline, at the 3-month visit, and at the 1-year visit.

To measure changes in subjective well-being in a comprehensive manner, the patient's QoL was estimated with the validated generic 15D tool (21, 22). Patients completed the self-administered 15D questionnaires at baseline and at the 3-month visit. The index scores of 15D range from zero to one, with one representing perfect health and zero death. The average changes in the 15D index score and in the individual dimensions of 15D were estimated by subtracting the baseline values from those taken at the 3-month visit. The Minimum Important Difference (MID) for the before–after measurements is 0.030 (21). In a previous study based on the results of a population survey, the age- and sex-matched 15D QoL value of a healthy Finnish population has been reported to be 0.904 (23).

The sleep questionnaires used in our study have been previously validated and used to screen for the intensity of snoring (Snore Outcomes Survey) and daytime sleepiness (Epworth Sleepiness Scale) (24, 25). In the sleep questionnaires, the respondents were also asked whether their bedfellows had noticed breathing pauses during their sleep and subsequently these were classified as "witnessed apneas." The questionnaires were filled out by the patients both at baseline and at the 1-year visit.

All the biochemical measurements were performed both at baseline and at the 1-year visit in the clinical chemistry laboratory of Kuopio University Hospital after a 12-hour fasting period. Serum cholesterol, high-density lipoprotein, triglycerides, and glucose were determined from fresh serum samples, using an automated analyzer system (Konelab 60 analyzer; Thermo Fisher Scientific, Waltham, MA) and serum insulin was measured with a fluoroimmunoassay system (Wallac; PerkinElmer, Waltham, MA).

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

Statistical Analysis

Mean values and standard deviations are used to describe the baseline characteristics of the two treatment groups. Fisher's exact test or *t* test was used to assess equality between the treatment groups. Changes in sleep recordings and anthropometric measures during the follow-up were calculated by subtracting the baseline measurement from the 1-year follow-up measurement, and the mean difference in change between the treatment groups was calculated. The statistical significance of differences in changes between the groups was assessed with *t* tests, and additionally by analysis of covariance. In the analysis of covariance models, baseline differences in age, sex, BMI, and the baseline level of respective variable were accounted for by including these variables as explanatory variables in the model. Age and BMI were included in the models as continuous variables, and sex as dichotomous variable. Recovery from OSA was analyzed with a logistic regression model, adjusting for baseline differences in age, sex, BMI, and AHI between the groups. The differences in risk are reported as odds ratios with 95% confidence intervals. All comparisons between the treatment groups were based on the intention-to-treat principle, and all analyses were based on the 72 subjects who completed the 1-year follow-up. The study sample size was set to achieve 90% power at a 5% significance level to detect 25% lower prevalence of mild OSA at follow-up in the intervention group as compared with the control group. This calculation was done under the assumption that there would be no improvement in mild OSA in the control group. Analyses were done with the statistics package Stata (Stata statistical software, release 9.2, 2005; StataCorp LP, College Station, TX).

RESULTS

A total of 81 patients were randomized into the study. The demographics of the patients at baseline are shown in Table 1 and Table 2. In spite of the randomization, weight (mean, 101.2 kg [minimum, 74.6; maximum, 124] vs. 92.3 kg [minimum, 75.2; maximum, 118]), BMI (33.4 [minimum, 28.7; maximum, 38] vs. 31.4 [minimum, 28.1; maximum, 39.2]), and waist circumference (112.5 cm [minimum, 96; maximum, 130] vs. 105.3 [minimum, 85; maximum, 132]) were significantly higher in the intervention group compared with the control group. There were no differences between the two treatment groups in the other relevant

TABLE 1. PATIENT DEMOGRAPHICS AT BASELINE

	Control Group	Intervention Group	*P* Value*
Study sample, randomized, n	41	40	
Complete 1-yr follow-up, n (dropout %)	37 (10)	35 (13)	1.00
Sex, male/female, n	27/10	26/9	0.56
Age, yr	50.9 (8.6)	51.8 (9.0)	0.66
Weight, kg	92.3 (11.3)	101.2 (11.9)	0.002
BMI, kg/m^2	31.4 (2.7)	33.4 (2.8)	0.004
Waist circumference, cm	105.3 (8.3)	112.5 (8.7)	<0.001
Plasma glucose, fasting, mmol/L	6.1 (1.6)	6.3 (2.5)	0.62
Serum insulin, mU/L	10.9 (4.7)	13.5 (7.0)	0.08
Serum HDL cholesterol, mmol/L	1.11 (0.37)	1.02 (0.23)	0.23
Serum triglycerides, mmol/L	1.59 (0.92)	1.74 (1.17)	0.54
Systolic blood pressure, mm Hg	130.0 (12.8)	131.2 (10.2)	0.66
Diastolic blood pressure, mm Hg	80.7 (7.8)	81.8 (8.9)	0.57
SOS	51.2 (12.3)	54.8 (11.9)	0.215
ESS	9.9 (4.8)	10.1 (5.0)	0.85
Witnessed apneas, n (%)	28† (88)	31† (100)	0.11
Smoking, n (%)	8 (22)	7 (20)	1.00
Menopause, n (%)	8 (22)	8 (22)	1.00
Substantial consumption of alcohol, n (%)	6 (18)	4 (13)	0.74
Antihypertensive medication, n (%)	15 (41)	18 (51)	0.48
Diabetes medication, n (%)	3 (8)	4 (11)	0.71
Cholesterol medication, n (%)	18 (49)	12 (34)	0.24

Definition of abbreviations: BMI = body mass index; ESS = Epworth Sleepiness Scale; HDL = high-density lipoprotein; SOS = Snore Outcomes Survey.

Data represent mean values with standard deviation (SD) or frequency (%).

* Fisher's exact test or *t* test for equivalence between groups.

† For witnessed apneas n = 63; data missing from 9 patients.

baseline characteristics. Nine patients dropped out from the study, five from the intervention group and four from the control group. Seven patients dropped out from the study before the 3-month visit; four from the intervention group and three from the control group. In the intervention group, most (four of five) of the dropouts occurred within the first 5 weeks after the start of the intervention. The reasons for dropouts included a dislike of the VLCD products in two cases, work-related schedule problems in six cases, and a death not related to OSA in one case. Thus, although the overall dropout rate was low, there was no difference in compliance between groups and most of the patients who dropped out had reasons not related to the treatment. Therefore it is unlikely that nonparticipation would result in any major bias in the results. There were no crossovers to VLCD diets during the trial period, and the study participants did not receive any cointervention or concomitant therapy other than that included in the study design.

TABLE 2. FINDINGS FOR CARDIORESPIRATORY VARIABLES AT BASELINE

	Control Group	Intervention Group	*P* Value*
Sleep recording time, min	447.6 (72.2)	397.8 (81.1)	0.024
AHI (total)	9.3 (3.0)	10.0 (3.0)	0.35
Apnea indices separately per hour	2.9 (2.6)	2.5 (2.2)	0.58
Hypopnea indices separately per hour	6.3 (2.8)	7.5 (2.9)	0.09
AHI (supine)	21.3 (17.3)	20.1 (14.1)	0.76
Percentage of supine recording	32.3 (26.3)	39.5 (23.4)	0.34
AHI (positions other than supine)	5.5 (4.3)	5.6 (3.7)	0.92
Mean Sa_{O2}	94.3 (1.4)	93.8 (1.5)	0.20
Time with mean Sa_{O2} below 90%, s	7.3 (16.0)	11.5 (20.5)	0.37
Percentage of time with Sa_{O2} below 90%	1.7 (3.6)	2.8 (5.2)	0.32
Heart rate, beats/min	58.4 (7.5)	59.7 (7.4)	0.67

Definition of abbreviations: AHI = apnea–hypopnea index (the number of apnea–hypopnea events with at least a 4% oxygen desaturation per hour); Sa_{O2} = arterial oxygen saturation.

Data represent mean values with standard deviation (SD).

* *t* test for equivalence between groups.

Anthropometric Characteristics Data

The mean change in weight during the follow-up was −10.7 kg (10.6% of the initial weight) in the intervention group, and −2.4 kg (2.6% of the initial weight) in the control group ($P < 0.001$). The prevalence of obesity (BMI > 30) in the study groups at baseline was 89% in the intervention group and 60% in the control group, and at the 1-year visit 46 and 49%, respectively. A marked difference was found in all anthropometric measurements between the study groups at the 1-year visit, although in most recordings there was also some decrease noted in the control group (Table 3).

Sleep Recordings

At the 3-month visit, the mean total AHI of all the patients in each group was 5.3 events/hour in the intervention group (n = 36), and 8.1 events/hour in the control group (n = 38) ($P = 0.036$). According to AHI, 22 of 36 patients (61%) in the intervention group, and in 12 of 38 patients (32%) in the control group, were objectively cured ($P = 0.019$, Fisher's exact test). The change was found to be maintained at the 1-year follow-up. At the 1-year visit, there was a statistically significant difference in the mean total AHI and in the mean change in total AHI during the follow-up between the study groups. The mean total AHI for all the patients was 6.0 events/hour for the intervention group (n = 35), and 9.6 events/hour for the control group (n = 37) ($P = 0.043$). The baseline BMI did not have an effect on the effectiveness of the treatment (*P* value for the BMI treatment interaction was 0.818 when analyzing the change in AHI total) (Table 3). Moreover, according to AHI, mild OSA had been objectively cured in 22 of 35 patients (63%) in the intervention group, and in 13 of 37 patients (35%) in the control group ($P = 0.033$, Fisher's exact test). Taking into account the baseline differences in age, sex, BMI and AHI between the groups, the adjusted odds ratio for having mild OSA at 1 year was 0.24 (95% confidence interval, 0.08–0.72; $P = 0.011$) in the intervention group as compared with the control group.

Significant improvement was detected in mean oxygen saturation in the intervention group compared with the control group at 1 year. Moreover, patients belonging to the intervention group spent a significantly less percentage of time with arterial oxygen saturation below 90% during their sleep compared with patients in the control group (Table 3).

Quality of Life

At baseline, the average QoL in the total sample was 0.848, with no significant difference between the groups ($P = 0.891$). Therefore, compared with the previous population reference, in the present study OSA was associated with a significant 0.056 loss in QoL at baseline. Between the baseline and 3-month visits, the intervention and control groups had experienced, on average, 0.041 and 0.022 increases in overall QoL score ($P = 0.167$), respectively. The intervention group gained more than the 15D MID of QoL (i.e., ⩾0.030). Statistically significant differences in the dimensional changes between the groups were observed in sleeping ($P = 0.016$) and elimination ($P = 0.017$). Changes in breathing, vitality, and sexuality also favored the intervention ($P = 0.371$, $P = 0.073$, and $P = 0.184$, respectively).

Sleep Questionnaires

At the 1-year visit, the change in the Snore Outcomes Survey was significant in the intervention group (19.0) compared with

TABLE 3. CHANGES IN CARDIORESPIRATORY RECORDINGS, BODY WEIGHT, BODY MASS INDEX, AND WAIST CIRCUMFERENCE AFTER 12-MONTH INTERVENTION

	Control Group	Intervention Group	*P* Value*	*P* adj†
Patients with follow-up data, n	37	35		
AHI (total)	0.3 (8.0)	−4.0 (5.6)	0.011	0.017
Number of cured patients,‡ n (%)	13 (35)	22 (63)	0.033	0.019
Apnea indices separately per hour	1.3 (5.1)	−0.9 (2.4)	0.029	0.005
Hypopnea indices separately per hour	−0.9 (4.3)	−3.5 (4.1)	0.013	0.053
AHI (supine)	−5.9 (23.9)	−6.5 (13.0)	0.90	0.29
AHI (positions other than supine)	1.4 (9.3)	−1.8 (8.5)	0.24	0.015
Percentage of supine recording	−1.4 (28.9)	−0.4 (21.2)	0.89	0.85
Mean Sa_{O2}	−0.3 (1.3)	0.8 (1.2)	<0.001	0.002
Time with mean Sa_{O2} below 90%, s	2.5 (21.0)	−4.8 (12.8)	0.126	0.068
Percentage of time with Sa_{O2} below 90%	1.8 (6.3)	−1.7 (4.1)	0.016	0.042
Heart rate, beats/min	1.1 (5.0)	−2.8 (5.8)	0.081	0.075
Weight, kg	−2.4 (5.6)	−10.7 (6.5)	<0.001	<0.001
BMI, kg/m^2	−0.8 (2.0)	−3.5 (2.1)	<0.001	<0.001
Waist circumference, cm	−3.0 (6.0)	−11.6 (6.6)	<0.001	<0.001
Plasma glucose, fasting, mmol/L	−0.4 (1.4)	−0.6 (2.3)	0.52	0.30
Plasma insulin, mU/L	−1.2 (3.4)	−5.9 (7.0)	<0.001	0.004
Serum HDL cholesterol, mmol/L	0.05 (0.22)	0.14 (0.22)	0.085	0.103
Serum triglycerides, mmol/L	−0.06 (0.65)	−0.48 (1.13)	0.054	0.027
Systolic blood pressure, mm Hg	−1.1 (19.6)	−1.7 (14.7)	0.88	0.47
Diastolic blood pressure, mm Hg	−0.4 (12.6)	−1.9 (10.6)	0.62	0.87
SOS	11.8 (12.6)	19.0 (14.2)	0.025	0.001
ESS	−2.1 (2.9)	−3.1 (4.0)	0.25	0.31
Witnessed apneas, n (%)	33 (97)	23 (74)	0.011	<0.001

Data represent mean changes with standard deviation (SD).
* *P* value: Fisher's exact test or *t* test for equal change between groups.
† *P* adj: Test for equal change between groups, adjusted for age, sex, BMI, and baseline level of respective variable.
‡ *Cured* is defined as an apnea–hypopnea index less than 5 events/hour.

control subjects (11.8) ($P = 0.001$). In the Epworth Sleepiness Scale, there was a major decrease in both the intervention group (−3.1) and the control group (−2.1) at the 1-year visit; however, the difference was not significant between the groups. There was a significant improvement in "witnessed apneas" in the intervention group (totally vanished in 26% of the patients) compared with the control group (3%) ($P < 0.001$) (Table 3).

Association between OSA and Weight Reduction

Changes in AHI during the 12-month follow-up were strongly associated with changes in weight and waist circumference (Figure 2). In the combined study population, a weight reduction of 5 kg from the initial body weight was associated with a reduction in AHI of 2.0 units (95% confidence interval, 1.1–3.0). Changes in AHI were −7, −4, 0, and 3 in the weight change categories less than −15 kg, −15 to −5 kg, −5 to 0 kg, and greater than 0 kg, respectively. Mild OSA was objectively cured in 7 of 8 patients (88%) in the weight change group less than −15 kg as compared with 16 of 26 (62%), 11 of 29 (38%), and only 1 of 9 (11%) in the weight change groups −15 to −5 kg, −5 to 0 kg, and greater than 0 kg, respectively. Further, a reduction of 5 cm in waist circumference was associated with a reduction in AHI of 2.5 units (95% confidence interval, 1.5–3.5).

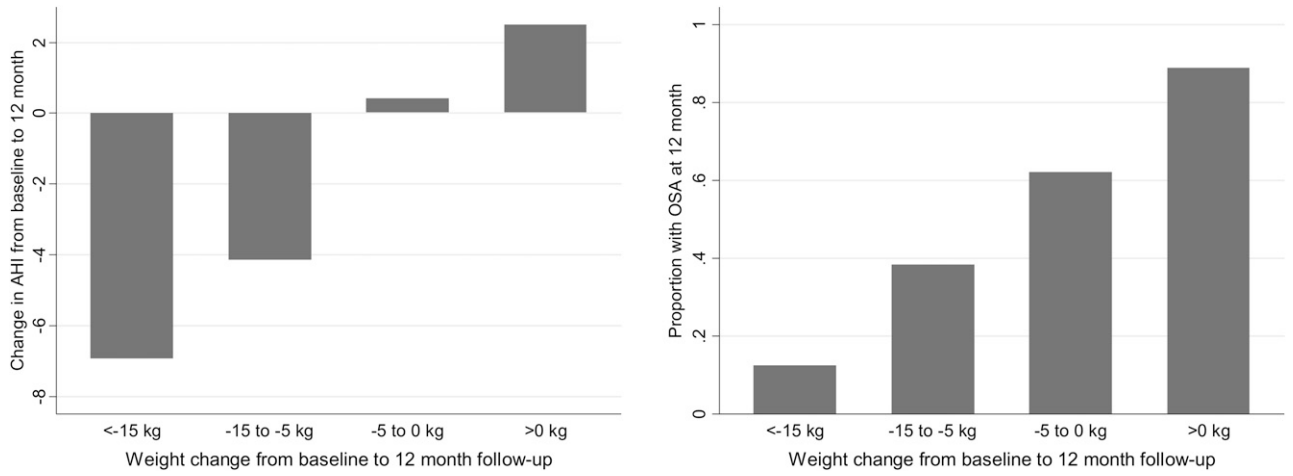

Figure 2. Changes in apnea–hypopnea index (AHI) in relation to changes in body weight (*left*), and the proportion of patients (expressed as a percentage) with OSA (AHI > 5) (*right*) in relation to the following weight change categories: less than −15 kg, −15 to −5 kg, −5 to 0 kg, and more than 0 kg.

Biochemical Measurements and Blood Pressure

A significant decrease in serum insulin concentration was found in the intervention group compared with the control group. The reduction in insulin concentration and AHI did not exhibit a significant correlation ($r = 0.15$, $P = 0.26$). However, in the combined study population, changes in insulin were -9, -5, and -1 in the weight change categories less than -15 kg, -15 to -5 kg, and greater than -5 kg, respectively ($P < 0.001$ for adjusted test of trend). In the intervention group, two of four patients with oral diabetes medication were able to discontinue the medication, whereas in the control group two patients had started to take oral diabetes medication and a total of five were being treated with drugs at the 1-year follow-up. With respect to antihypertensive medication, 5 of 18 patients in the intervention group were able to terminate the medication compared with 2 of 15 in the control group. With respect to the cholesterol medication, 6 of 12 patients in the intervention group were able to discontinue the drug treatment compared with 3 of 18 in the control group.

Adverse Events

Other than the two patients who dropped out from the study because of a dislike of the products, no other adverse events attributable to the weight reduction program were recorded. No abnormalities in clinical variables requiring further action were observed during the follow-up period.

DISCUSSION

We have shown that intensive lifestyle counseling with an initial weight reduction program can be an effective treatment modality in the majority of patients with mild OSA, and that the persistence of the achieved outcome is excellent over a 1-year period. In the intervention group, a 40% reduction in AHI was achieved from baseline, and two of every three patients had an AHI less than 5 at follow-up. In the control group, two of every three patients still had an AHI of 5 or more, and the mean AHI did not change from baseline at rerecording. These results indicate that even a simple counseling session about lifestyle can result in some weight loss. However, to achieve a better outcome, an aggressive weight reduction program supplemented by supervised counseling may be needed. We used a VLCD program that is known to result in marked weight reduction within a relatively short period of time. The mean reduction within 1 year was 11 kg, demonstrating also that the patients were highly motivated to apply this treatment modality.

The importance and the effectiveness of weight loss in treating OSA have been evaluated in earlier studies. The majority of the weight reduction and sleep apnea studies have evaluated the effects of low and very low calorie diet programs in moderately overweight patients with OSA or the effects of bariatric surgery on weight and concurrent obstructive sleep apnea in severely obese patients (18, 19, 26–30). Although the effect of weight reduction on obstructive sleep apnea has been found encouraging in most studies, the studies thus far have lacked control groups, randomized design, or sufficient sample sizes to provide evidence for the clinical practice guidelines on the benefits of weight loss on OSA (31). Moreover, many studies have been conducted with small subgroups, severely obese patients with usually severe or at least a highly heterogeneous degree of OSA. All these factors have led to conclusions that weight loss may reduce the severity of OSA, but is not a curative treatment in most patients. In our opinion it was logical to target a weight reduction program with lifestyle counseling to the early phases of the disease (i.e., mild OSA), which in the case of OSA also accounts for the vast majority of patients. Indeed, in patients with mild OSA weight reduction resulted in a significant relieve of partial and complete obstructions by reducing both hypopnea, and especially apnea indices. At this stage it is most likely that the organ systems still have the capacity to recover from the adverse effects of the disease or at least, the progression of the disease may be prevented. Furthermore, the homogeneity of the study population makes drawing the conclusion more justified. An early intervention has been shown effective as a means of prevention of type 2 diabetes in the Finnish Diabetes Prevention Study (32).

Patients with even mild OSA state that the disease is clearly detrimental to their health and have significant symptoms related to their disease. When patient subjective well-being was measured using the 15D for QoL tool comprehensive overall score, nearly twice the increase was achieved in the intervention group compared with the control group. The QoL losses related to OSA in the present study (-0.056) seem to equate to that encountered in depressive disorder (-0.060) and in Parkinson's disease (-0.070) (23). The intensity of snoring was found to be remarkable, which, if nothing else, is most disturbing for the bedfellow. Half of the patients reported significant sleepiness (Epworth Sleepiness Scale $\geqslant 10$). Almost all the patients experienced breathing pauses during their sleep as reported by their partners. The lifestyle intervention was found to effectively reduce all these common symptoms related to OSA, and therefore to improve quality of life for the patients and their bedfellow.

Obesity increases the risk for OSA, but, on the other hand, OSA may predispose the individual to weight gain (15). It has been suggested that obesity leads to narrowing of the upper airway structure (33), alteration in function (such as collapsibility) (29), reduced chest wall compliance, disturbances in the relationship between respiratory drive and load compensation (13, 26), and reductions in functional residual capacity and hypoxemia (34). Sleep fragmentation, on the other hand, is associated with decreased leptin levels, increased ghrelin levels, and therefore with an increase in hunger and appetite (35).

The standard for diagnosing OSA has been based on in-laboratory polysomnography. Polysomnography has been found to be accurate, and with a low failure rate for diagnosing sleep disorders other than OSA; however, it is expensive and technically demanding. The rapidly increasing number of patients with OSA has led to the development of reliable methods other than in-laboratory recording to confirm the diagnosis of OSA. Clinical guidelines for the use of portable monitors, such as those used in the present study, have been introduced (36). The guidelines recommend that a routine use of portable sleep-recording devices may be accepted for diagnosing and monitoring the response to non–continuous positive airway pressure (CPAP) treatments for OSA with some limitations (20, 36). Portable monitoring may be used as an alternative to polysomnography for the diagnosis of OSA only in conjunction with comprehensive sleep evaluation, and in patients with well-defined symptoms related to OSA. The scoring criteria used should be consistent with the current standards of the American Academy of Sleep Medicine (Westchester, IL) (20).

The current "gold standard" of OSA treatment is CPAP (37). In mild OSA, compliance with CPAP is frequently far from optimal, and moreover it is not a curative treatment for OSA. Nonetheless, this treatment may help to control the symptoms, but it does need to be used every night on a regular basis (38). Upper airway surgery is rarely effective in the treatment of OSA, but after a careful selection of patients, including a meticulous evaluation of the region of airway collapse, it can be taken into consideration (39). Mandibular advancement devices have been found to be

beneficial in some patients (40). On occasion, lateral positioning therapy may also be an option for the treatment of mild to moderate OSA (41). Also, regular exercise training has been reported to serve as an important adjunct to the OSA treatment strategy (42).

The patients belonging to our control group also received general counseling on lifestyles and they displayed some improvement in weight and OSA. Therefore, the difference between the groups might have been even greater if the control group had consisted of untreated patients. Although randomized at baseline, the intervention group was heavier than the control group. It is unfortunate that a stratified randomization design was not used for the BMI at baseline. However, we adjusted the main results for the initial BMI, and as expected this further emphasized the difference between the intervention and control groups. Furthermore, the greater the change in body weight or waist circumference, the greater was the improvement in OSA. In the present study the data from 3- and 12-month measurements were consistent, strongly favoring the weight reduction group. The intervention was conducted by a clinical nutritionist who was particularly familiar with the VLCDs and had marked experience in the treatment of severe obesity. Therefore, the findings may not be directly generalizable to routine practice without an appropriate caveat, and although these data are encouraging, they need to be replicated in a larger study. It would also be tempting to conduct a study with a similar design on patients with more severe OSA, who are using CPAP treatment. The outcome criteria have varied substantially in previous studies that have evaluated the effects of different treatment modalities in patients with OSA. Therefore, it has been proposed that objective cure rates based on the AHI not exceeding 5 or 10 should be used (43). In the present study, the results were based on sleep recordings from a single night. In routine practice, repeated recordings are extremely demanding, and the findings of single-night recordings have been found to be reliable in most patients (44).

The present report represents the long-term maintenance of the achieved change of lifestyles, which is crucial for the successful outcome of OSA. This is emphasized by our findings that, in conjunction with the improvement in AHI, significant improvements were also found in symptoms related to OSA, insulin resistance, lipids, and cardiorespiratory variables, such as arterial oxygen saturation, in patients belonging to the intervention group. The overall effect of weight loss on blood pressure in patients with mild OSA was minor. However, in the intervention group a notable number of patients were able to discontinue drug treatment for hypertension, and the same was true with diabetes and hypercholesterolemia. The total number of dropouts was a mere nine patients (11%). In fact, seven of nine patients dropped out before the 3-month visit. This is considerably less than the dropout rates found with other treatment modalities, such as CPAP or mandibular advancement devices (37, 39). Earlier studies have demonstrated that weight gain and weight loss do impact the degree of obstructive sleep apnea. Weight gain increases the possibility for the development of OSA in previously healthy people, and accelerates the progression of OSA in patients with earlier diagnosed disease, particularly in patients who are overweight (1, 26). Moreover, the Wisconsin Sleep Cohort Study, and the Sleep Heart Health Study observed that it is more difficult to improve sleep apnea by weight reduction than to develop worse sleep apnea by weight gain (26, 45). Therefore, it is important to note from our results that even simple general counseling is worthwhile and may prevent worsening of the disease.

It is commonly claimed that lifestyle change may not be sufficient when treating patients with OSA, and that the change is difficult to achieve, and even more difficult to maintain. Our results show that these arguments may not be justified. It has been presented that the coexistence of OSA, obesity, insulin resistance, hypertension, and dyslipidemia could have an even more widespread impact on cardiovascular and metabolic sequelae than these conditions could on their own (15, 46, 47). Whenever people attending medical clinics complain of habitual snoring, witnessed apneas, or excessive daytime sleepiness, the clinician should consider the possibility of OSA, particularly in the case of an overweight patient. In addition, the association between type 2 diabetes, hypertension, and OSA should be kept in mind. For all these conditions, weight reduction should be the first-line treatment when they are linked to excess weight.

CONCLUSION

A more aggressive treatment of obesity in patients with OSA is well founded. Lifestyle intervention with an early VLCD is a feasible, low-cost, and curative treatment for the vast majority of patients with mild OSA, and it can be implemented in a primary care setting after diagnosis of OSA. Weight reduction also results in an improvement of obesity-related risk factors for cardiovascular diseases.

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