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Clinical predictors of residual sleep apnea after weight loss therapy in obese adolescents

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Short title: Predictors of residual sleep apnea after weight loss

Abstract

Background: Sleep-disordered breathing (SDB) is prevalent in childhood obesity. Adenotonsillectomy in this setting is associated with low success rates. Weight loss seems to be more effective in treating obese subjects with SDB. This study aimed to investigate clinical factors that could predict residual SDB after weight loss.

Methods: Obese subjects between 10 and 19 years were recruited while entering an in-patient weight loss treatment program. All subjects underwent anthropometry and a sleep screening using a portable device at baseline and after 4-6 months of therapy. Sleep and ISAAC questionnaires were completed at baseline.

Results: 339 patients were included. Median age was 15.4 years (10.1-19.1). BMI z-score at baseline was 2.75 ± 0.42 , and 35% of subjects were boys. SDB was present in 32%. After a mean decrease in BMI z-score of 32%, residual SDB was found in 20% of subjects with SDB at baseline. Subjects with more severe SDB ($OR = 1.18$; $CI = 1.01 - 1.34$; $p=0.02$) and respiratory allergies ($OR = 7.85$; $CI = 1.20 - 51.39$; $p = 0.03$) were at higher risk of developing residual SDB, unlike age, gender and anthropometric variables.

Conclusions: Weight loss had a high success rate of 80% for treating SDB. More severe SDB and the presence of respiratory allergies at baseline were associated with a higher risk of residual SDB after weight loss.

Introduction

Childhood obesity is one of the most serious public health challenges of the 21th century. The prevalence is increasing globally at an alarming rate. Obstructive sleep-disordered breathing (SDB) is a well-known pulmonary complication of obesity both in adults and children. It includes primary snoring, upper airway resistance syndrome and obstructive sleep apnea (OSA). OSA is the most severe entity in the spectrum of SDB, and is characterized by intermittent cycles of upper airway collapse associated with hypoxia and arousal during sleep.

The prevalence of SDB in the general pediatric population is about 2-3%¹, and adenotonsillar hypertrophy is considered as the major cause of SDB in children. Adenotonsillectomy is therefore considered the first line treatment for SDB in the general pediatric population. However, the prevalence of SDB in obese children is much higher and has been reported to be between 13-59%². SDB in overweight and obese children is distinguished by a different underlying phenotype compared to normal-weight children, since adenotonsillar hypertrophy is not always the main contributor to the development of SDB in childhood obesity. Other factors that could be responsible are: fat infiltration of the upper airway structures, fat deposits in the neck region, and pulmonary function abnormalities³⁻⁵. Adenotonsillectomy, the first-line treatment for SDB in the general pediatric population, is therefore only successful in less than 50% of obese children and adolescents^{2,6}. Furthermore, a high recurrence rate is observed in obese subjects often associated with postoperative weight gain⁷. Moreover, a large multicenter study has shown that 88% of obese children have persisting sleep apnea after adenotonsillectomy^{8,9}. For these reasons, our research group suggested weight loss as the first line treatment for obese children with OSA. Meanwhile, our studies showed that weight loss was more effective than adenotonsillectomy in treating obese children with OSA^{10,11}, and weight loss has been proven to have beneficial effects on metabolic dysregulation and cardiovascular risk factors¹².

In two previous studies by our group, weight loss had a success rate of 62 and 71%, which means that 29-38% of patients had residual SDB even though they experienced significant weight loss^{10,11}. These

results indicate that adiposity is not the only underlying factor in the pathophysiology of OSA in obese children. There were indications that local upper airway factors were responsible for residual SDB as a higher degree of tonsillar hypertrophy was observed in the obese children and adolescents with residual SDB group in one of the studies¹⁰. The aim of this follow-up study was to identify possible clinical predictors of residual sleep apnea after weight loss in a larger sample of morbidly obese children and adolescents. The identification of these predictors would make it possible to develop more effective individually-tailored treatments in the future, such as combination therapies (e.g. weight loss and pharmacological treatment or weight loss and adenotonsillectomy).

Material and methods

Study population and study design

Obese children were consecutively recruited while entering an in-patient weight loss treatment program at the rehabilitation center “Het Zeepreventorium” at De Haan (Belgium). The weight reduction program was a multi-component treatment with moderate dietary restrictions (1400-1600 kcal/day), increased physical activity (minimum of 10 hours/week), psychological individual and group support and medical supervision. No anti-obesity drugs were prescribed. Exclusion criteria were neuromuscular or known endocrine disease, genetic or craniofacial syndromes, acute illness, uncontrolled chronic disease or the use of anti-inflammatory drugs at the moment of the study.

All patients were asked to complete 2 visits: a baseline visit at the moment of admission in the weight loss program, and a second visit 4 to 6 months after weight loss treatment.

Anthropometry

Height, weight, waist circumference and waist-to-hip ratio (WHR) were measured using standardized techniques by skilled personnel. BMI was calculated as weight in kilograms over height in m^2 and was further analyzed as z-scores, using the Flemish growth study as a reference population¹³. Overweight and obesity were defined according to the International Obesity Task Force criteria¹⁴.

This was repeated after 4 to 6 months and the relative decrease in BMI z-score was determined.

Questionnaires

All patients completed a sleep questionnaire¹⁵ and the ISAAC questionnaire (ISAAC; International Study of Asthma and Allergies in Childhood)¹⁶ at baseline.

Reflux was diagnosed by means of clinical history and the paediatric sleep questionnaire. Allergy was defined as the presence of previously doctor diagnosed respiratory allergy.

Tonsillar hypertrophy

The degree of tonsillar hypertrophy was clinically assessed by using the Brodsky score for tonsillar hypertrophy, which ranges from a value of 0 to 4¹⁷. Tonsillar hypertrophy was defined by a Brodsky score of 3+ or 4+.

Sleep assessment

Sleep assessment was performed using a portable device (ApneaLink™, ResMed, Switzerland)^{18, 19} at baseline and after 4 to 6 months of therapy when SDB was observed during the first investigation. Respiratory airflow was measured by a nasal pressure cannula (detecting -10 hPa to +10 hPa) and oxygen saturation and pulse rate were obtained by using a pulse oximeter and a pulse sensor (sampling rate of 1 Hz). Tracings were all manually reviewed and measurements associated with poor pulse tracing or aberrant respiratory signals were excluded from the analysis. The sleep study was repeated in case less than 4 hours of good quality signal were obtained.

Since ApneaLink™ is a screening device it is not possible to make the difference between obstructive and central events, or to recognize arousals. Therefore, SDB was diagnosed in the presence of an ODI ≥ 2 .

Statistical analysis

All statistical analyses were performed using SPSS 23.0 (SPSS, Chigaco, Illinois, USA). Normality was tested by the Kolmogorov-Smirnov test and bar graph. Normally distributed data are presented as mean \pm standard deviation. Skewed data are reported as median (minimum - maximum). Patients were distributed in groups based on their ODI. Groups were compared using χ^2 , independent sample t-test or Mann Witney U-test. Correlations were calculated using Pearson's or Spearman's correlation analysis as appropriate. The analysis of SDB predictors was performed using binary logistic regression modelling by means of the backward stepwise entry method. For all analyses, $p \leq 0.05$ was considered

statistically significant. A ROC analysis was performed to determine possible cut-off values for diagnosis of residual SDB at baseline.

Results

Baseline assessment

A total of 339 obese patients were included. Age ranged from 10.1 to 19.1 years with a median of 15.4 years, and 35% of the subjects (N=118) were boys. Mean BMI z-score at the start of treatment was 2.75 ± 0.42 . Mean interval between baseline and follow-up visit was 5.2 ± 0.5 months. The mean absolute decrease in BMI z-score was 0.86 ± 0.46 , which corresponds with a relative decrease in BMI z-score of $32 \pm 14\%$.

SDB was diagnosed in 108 patients. Characteristics of both groups are presented in Table 1. Adolescents with and without SDB were comparable regarding age and most features of the sleep and ISAAC questionnaire. A significant difference between groups was seen for gender, BMI z-score, WHR, reflux and all sleep variables.

Follow-up study

Of the 108 patients with SDB at the baseline visit, 79 participated in the follow-up study. This means a dropout rate of 27%. Main reasons for discontinuation were early termination of the treatment program, refusal of a second sleep study or technical problems with the sleep screening. Adolescents that dropped out of the study were similar regarding all baseline characteristics and sleep parameters. Figure 1 represents a flow diagram indicating the elimination process down to the 79 patients who participated in the follow-up visit.

Only 16 of the 79 subjects with SDB at baseline showed residual sleep apnea after weight loss treatment. This corresponds to a treatment success rate of 80%. Further analysis was performed to detect baseline characteristics that could predict this presence of residual SDB. These baseline

characteristics are summarized with the corresponding p-values in Table 2. Subjects with residual SDB had more severe disease at baseline as reflected by a higher baseline ODI ($p=0.002$), a significantly higher baseline AHI ($p=0.05$) and a significantly lower mean SaO₂ ($p=0.009$) and SaO₂ nadir ($p=0.002$). Furthermore, adolescents with sleep apnea after weight loss reported at baseline more often respiratory allergies ($p=0.03$).

The items of the sleep and ISAAC questionnaire (tonsillar hypertrophy, rhinitis, asthma, allergies and smoking) together with age, BMI z-score and ODI at baseline were also analyzed as predictors for residual SDB in a binary logistic regression model. Table 3 represents the final model of predictors. The presence of a respiratory allergy, as well as the severity of SDB at baseline, as reflected by ODI, was associated with a higher risk for residual OSA. Other covariates did not prove to be significant predictors in the regression analysis.

To identify the range of severity of SDB associated with the risk of residual SDB after weight loss, we categorized the ODI in 3 groups: no SDB (ODI <2), mild SDB (ODI between 2 and 5), moderate-to-severe SDB (ODI >5). This categorical variable was then added in our final binary logistic regression model. Table 4 represents the model of predictors with the ODI as a categorical variable.

A ROC-curve was made to determine a possible cut-off value for ODI above which the risk for developing residual OSA was significant. An ODI of 4.03 had a sensitivity of 63% and a specificity of 77% for determining the risk of residual OSA. An ODI of 2.92 had a sensitivity of 81% but only a specificity of 51%. Our AUC was 0.725, which is a moderate result.

Delta's (Δ) were established for ODI and AHI by calculating the difference between the baseline and the follow-up values. Δ ODI and Δ AHI were not correlated with patient-related factors such as gender, age, BMI z-score, WHR or with absolute and relative degree of weight loss. Patients with asthma had a higher Δ AHI ($p=0.04$), while patients who smoked had a higher Δ ODI ($p=0.03$). The other items of the sleep and ISAAC questionnaire did not show any relationship with the Δ -values.

Discussion

In this study of 339 obese adolescents, more severe sleep apnea at baseline as well as the presence of respiratory allergies were associated with residual sleep apnea after weight loss therapy.

The prevalence rate of SDB in this clinical sample of obese adolescents reached 31.9%, which corresponds with previous findings²⁰. After an average decrease in BMI z-score of 32%, SDB was successfully treated in 80% of the subjects. This is in occurrence with our previous reports^{10, 11}, that weight loss has a much higher treatment success rate in obese children with SDB compared to adenotonsillectomy. A recent review by Boudewyns et al. described that only 12% of obese children had a normalized sleep study after adenotonsillectomy²¹. Our results show that weight loss is a better first-line alternative for treating SDB in an obese adolescent patient. Systematic studies of the effect of weight loss on the severity of SDB in children are scarce. However, Kalra et al. studied 34 morbidly obese adolescents who underwent bariatric surgery²². Prior to surgery, 55% of the subjects were diagnosed with OSA. After surgical weight loss only one subject had sleep apnea. In another study by Alqahtani et al., 226 obese children underwent bariatric surgery. At baseline 43% of the children were diagnosed with OSA, and after 6 months of surgical weight loss OSA persisted in 18% of the patients²³. In contrast, our study focused on a weight loss treatment program that uses moderate diet, increased physical activity and psychological support, without pharmacological intervention. Even though an in-patient weight loss program is difficult to extrapolate to the general obesity clinic, this report stresses the need for the development of intensive weight loss management programs in ambulatory setting not only for the treatment of SDB in obese children, but also to tackle other obesity-related comorbidities.

Although treatment was successful in 80% of the patients, residual sleep apnea was still observed in an important proportion of the subjects. This means that adiposity is not the only underlying factor in the pathophysiology of SDB in obese children. In this study, individuals with residual SDB after weight

loss had more severe SDB at baseline and reported more often a history of respiratory allergies. Other factors such as gender, age and anthropometry were not associated with treatment failure. Children with moderate-to-severe SDB (defined as an ODI above 5) had 7.6% more risk of developing residual sleep apnea compared to patients with only mild SDB (defined as an ODI between 2 and 5). In a previous study we found that children with residual sleep apnea had a higher degree of tonsillar hypertrophy¹⁰. However, we couldn't confirm this finding in this study, suggesting that tonsillar hypertrophy is not the discriminative factor that can hamper treatment success by weight loss in obese children with SDB. Even though we expanded the population of children with residual SDB compared to the study by Van Hoorenbeeck et al.,¹⁰ it is possible that our study was still underpowered to detect a significant association between tonsillar hypertrophy and residual sleep apnea. Respiratory allergies are associated with airway inflammation, and studies have shown a link between SDB and airway inflammation^{24, 25}. It is possible that airway inflammation is involved in the presence of residual sleep apnea after weight loss, and this should be explored in future studies. In view of this, future research could focus on the combination of weight loss and pharmacological treatment. For example, a study in adults showed that corticosteroid treatment had significant improvement on OSA symptoms in allergic subjects²⁶.

An important limitation of this study is the rather short follow-up period of 6 months, as it is known that in obesity management long-term follow-up is highly recommendable. Because of the interval of 4 - 6 months between the baseline and the follow-up visit we were not able to identify a dose-response effect of the degree of weight loss on the recorded sleep parameters, which might be interesting to look into in future studies. A second limitation of the study is the use of a portable device instead of the gold standard PSG, since a full PSG is not available in the rehabilitation center. We did not perform full PSG and were therefore not able to assess the impact on sleep architecture. Because the portable device is not able to identify arousals, the number of hypopneas could have been underestimated. Since ApneaLink is a screening device we were unable to differentiate between obstructive and central

respiratory events. We chose to use an ODI ≥ 2 as a diagnostic threshold for SDB based on previous literature²⁰ and because two validation studies have shown a good correlation between the ODI measured by the ApneaLink device and the AHI measured during full polysomnography^{18, 27}. Furthermore, the recent ERS statement on the diagnosis and management of obstructive SDB in children stated that an ODI >2 predicts an AHI >1 ²⁸. A third limitation is that we did not do an assessment for enlarged adenoids in our population, since only the tonsillar hypertrophy was scored by means of the Brodsky score.

Furthermore we are aware that a drop-out rate of 27% is quite high, but this is a drawback in most of the obesity research and clinics. As mentioned before, conventional treatment of obesity, also in children and adolescents, is highly prone to compliance and motivation issues and therefore high long-term follow-up rates are very difficult to achieve. Unfortunately, the drop-out rate reported in this study is a reflection of reality in obesity treatment programs.

In conclusion, this study reports a high success rate of 80% for treating SDB in obese adolescents with conventional weight loss management strategies. More severe SDB at baseline and respiratory allergies are possible clinical predictors for residual sleep apnea after weight loss treatment in obese adolescents. Future studies should further investigate the link with respiratory allergies and a possible role for airway inflammation in the presence of residual sleep apnea after weight loss, and explore the options for a combination therapy with pharmacological treatment.

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Figure legend

Figure 1; online: Flow chart of the elimination process from the initial target population down to 79 participants.