Obstructive sleep apnea in obese adolescents referred for bariatric surgery

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Original Article

Obstructive sleep apnea in obese adolescents referred for bariatric surgery: association with metabolic and cardiovascular variables

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ABSTRACT

Background: obstructive sleep apnea syndrome (OSA) is a well-described disease entity in adults, with a higher prevalence in severely obese individuals, while at the same time associated with several comorbidities independently of BMI. Literature regarding OSA in severely obese adolescents is qualitatively and quantitatively limited, possibly resulting in suboptimal diagnosis and treatment.
Methods: polysomnographic, demographic, anthropometric, and comorbidity-related data were prospectively collected in 56 adolescents with morbid obesity refractory to conservative treatment who presented for surgical therapy. Differences between adolescents with no/mild (apnea–hypopnea index (AHI) 0–4.9) and moderate/severe OSA (AHI $\geq$ 5.0) were evaluated using independent-samples t, chi-square or Fisher's exact tests. Multivariable linear regression analysis was performed to evaluate the association of several variables with AHI, corrected for BMI z-score.
Results: of the 53 included subjects, 48 (90.6%) showed some degree of sleep disordered breathing and 20 (37.7%) had moderate/severe OSA. Patients with moderate/severe OSA had on average a higher neck circumference (42.4 versus 40.1 cm, $p = 0.008$), higher BMI z-score (3.7 versus 3.4, $p = 0.003$), higher plasma triglyceride level (2.2 versus 1.5 mmol/L, $p = 0.012$), and lower IGF (29.6 versus 40.2 mmol/L, $p = 0.010$) than those with no/mild OSA. BMI z-score and plasma triglyceride levels were independently related to AHI.
Conclusions: OSA is highly prevalent amongst morbidly obese adolescents and is strongly associated with BMI z-score. Elevated plasma triglyceride levels are associated with AHI, independent of BMI z-score.

1. Introduction

Obesity forms a global public health issue since its prevalence has increased dramatically over the past few decades, both in adult and pediatric populations [1–4]. In 2013, the combined prevalence of pediatric overweight (sex- and age-adjusted BMI $\geq$25–30 kg/m^2) and obesity (sex- and age-adjusted BMI $\geq$30 kg/m^2) in developed countries was 23.8% and 22.6% for boys and girls, respectively [5]. A large number of conditions have been associated with obesity, such as type 2 diabetes, cardiovascular disease, and obstructive sleep apnea (OSA) [6].

OSA, defined in adults as an apnea–hypopnea index (AHI) $\geq$5 with specific symptoms, has been extensively studied and its reported prevalence varies between 5 and 38% in the general adult population [7,8]. By contrast, OSA prevalence can increase to over 75% in subgroups of severely obese patients undergoing bariatric

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surgery [9]. This high prevalence is alarming as a vast body of evidence suggests an association of OSA, independent of BMI, with dyslipidemia, type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), hypertension, and other endocrine deregulation (eg elevated insulin like growth factor (IGF)) [10–16]. For screening purposes, several adult prediction models for OSA have been formulated, which include basic demographic and anthropometric measures, providing sensitivities ranging from 76 to 96% and specificities from 13 to 54% [17–19].

There is a relatively limited number of studies in obese children and adolescents with sleep disordered breathing which address associated metabolic and cardiovascular variables and many of these are retrospective with a heterogeneous study population with regard to pubertal status [20]. A retrospective chart review of morbidly obese adolescents who had undergone bariatric surgery by Koeck et al. showed OSA (defined as obstructive AHI $\geq$ 5) in 21 out of 49 adolescents (42.9%) [21]. They found that patients with OSA had a higher BMI, were more frequently male and more frequently hypertensive. A relatively limited number of retrospectively collected clinical variables were used to assess correlations with OSA and these correlations were not corrected for BMI or BMI z-score. Kalra et al. retrospectively reported OSA prevalence (defined as AHI $\geq$ 5) of all morbidly obese adolescents who received Roux en Y gastric bypass during a specified timeframe, yielding 34 subjects with an OSA prevalence of 55% [22]. Kalra et al. did not evaluate clinical correlates of OSA with comorbidities. Watson et al. retrospectively evaluated 96 obese patients aged 12–16 years and found an independent positive association between AHI and fasting insulin, HOMA-IR and triglyceride levels [23]. Other studies have found associations between pediatric obesity and an adverse metabolic profile, but these studies also evaluated non-morbidly obese individuals and included an even broader age range [24,25].

The main purpose of the current study was to assess the prevalence of OSA in severely obese adolescents and correlations between OSA and an extensive number of potentially relevant clinical variables, including demographic, anthropometric and comorbid factors. Thus, we aim to shed a light on the burden of OSA in this population and evaluate its predictors.

2. Methods

This study was conducted as part of a prospective study in adolescents eligible for bariatric surgery (BASIC trial, NCT01172899) [26]. The study population consists of morbidly obese adolescents who all had been treated before with extensive combined lifestyle interventions for at least twelve months without effect. The current study was based on the baseline measurements of this trial before interventions took place.

2.1. Participants

All patients included in the BASIC trial who received a baseline polysomnographic evaluation of sufficient quality were used for this baseline analysis. Detailed information regarding the BASIC trial study design, in- and exclusion criteria, and randomization process were published previously. In summary, inclusion criteria were: age 14–16 years; sex- and age-adjusted BMI $\geq$40 kg/m^2 (or $\geq$35 kg/m^2 combined with presence of obesity-associated comorbidity); participation in combined lifestyle interventions during at least 12 months without expected weight loss (defined as 5% total body weight loss). Girls were excluded if they were premenarchal, boys if their bone age was <15 years.

All participants were subjected to standardized comprehensive baseline measurements and investigations in order to confirm physical fitness for possible surgery and absence of (subclinical) conditions causing obesity.

2.2. Measurements

All measurements within one patient were carried out during a single visit. Body height and weight were measured using a stadiometer and digital scale respectively, with patients dressed in underwear. A tape measure was used for standardized measurement of body circumferences at neck level, abdominal level and hip level. BMI was calculated as [body weight]/[body height*body height] in kg/m^2, BMI z-scores were calculated using Cole's LMS method [27]. Daytime blood pressure was measured while the patient was resting, during a period of 60–90 min with intervals of 3 min between measurements, using the Mobil-O-Graph® NG (I.E.M. GmbH, Stolberg, Germany). Prehypertension and hypertension were defined according to the fourth report from the National High Blood Pressure Education Program, blood pressure z-scores were calculated according to the method described in that same report [28].

Video-assisted 12 channel polysomnography (PSG) (Brain RT, OSG, Rumst, Belgium) was performed at the pediatrics department of Maastricht University Medical Center. The following parameters were assessed: electrocardiography, oxygen saturation (pulse oximeter), nasal airflow (nasal pressure transducer system and nasal end-tidal pCO2 measurement), chest and abdominal motion (inductive plethysmographic belts), EEG, EOG and EMG (submental muscles and anterior tibialis muscles), digital video (infrared camera synchronized with the polysomnography data), snoring sounds and body position. The scoring of sleep stages and respiratory related events were performed by a single specialized analyst (CvdG) using the American Academy of Sleep Medicine (AASM) 2012 updated guidance for scoring pediatric respiratory events [29].

OSA was defined as mild (AHI 1–4.9/h), moderate (AHI $\geq$ 5.0–9.9/h), or severe (AHI $\geq$ 10/h), following the guideline of the American Academy of Pediatrics [30]. Since OSA is often defined as an AHI $\geq$5.0 in comparable studies on adolescents, patients were grouped as either no/mild OSA (AHI 0–4.9/h) or moderate/severe OSA (AHI $\geq$ 5.0/h) [21,22]. Snoring was assessed with the use of a questionnaire. If they answered 'sometimes' or 'always', this was considered as snoring.

With a fasting laboratory evaluation serum glucose, insulin, cholesterol, triglycerides, free fatty acids, glycated hemoglobin (HbA1C), alanine transaminase (ALT), aspartate aminotransferase (AST), cortisol, insulin-like growth factor (IGF), and c-reactive protein (CRP) were assessed.

2.3. Statistical analysis

Numerical data are presented as mean ± standard deviation or median [range] where appropriate. Categorical data are presented as number (percentage). Demographic and clinical variables were compared between patients with no or mild OSA and patients with moderate to severe OSA, using an independent-samples t-test for numerical variables and chi-square or Fisher's exact test for categorical variables. Multivariable linear regression analysis was used to evaluate the association between several relevant demographic, anthropometric and comorbid endpoints and AHI. Due to sample size, these variables were assessed separately with correction for BMI z-score, as this is a known variable related to AHI. All assumptions were checked using plots (scatterplots for linearity, Q–Q-plots and histograms for normality, residual plots for homoscedasticity), where Cook's distance was used to detect influential outliers. In case normality was violated, a log or square root transformation was considered to achieve normality. For comparison, a similar

Table 1
Patient characteristics of total group and according to no/mild OSA and moderate/severe OSA. Data are described as 'mean ± SD' or 'number of patients (%)'. *Fischer's exact test applied.

Baseline parameter	Total (n = 53)	Group 1: no/mild OSA (n = 33)	Group 2: moderate/severe OSA (n = 20)	*p*-value
Gender female	42 (79.2%)	26 (78.8%)	16 (80.0%)	1.000*
Age – yr	15.7 ± 1.0	15.4 ± 1.0	16.1 ± 1.0	**0.032**
Smoking – n	11 (20.8%)	6 (18.0%)	5 (25.0%)	0.728*
Snoring positive – n	25 (47.2%)	15 (45.5%)	10 (50.0%)	0.531
Weight – kg	128.9 ± 19.5	123.5 ± 14.3	137.9 ± 23.7	**0.008**
Length – cm	171.0 ± 0.1	170.7 ± 7.8	171.1 ± 10.2	0.856
BMI – kg/m^2	44.1 ± 5.2	42.4 ± 4.3	46.9 ± 5.5	**0.002**
BMI z-score	3.5 ± 0.3	3.4 ± 0.3	3.7 ± 0.3	**0.003**
Neck circumference – cm	41.0 ± 3.1	40.1 ± 2.9	42.4 ± 3.0	**0.008**
Abdominal circumference – cm	128.2 ± 12.5	125.9 ± 10.2	131.9 ± 15.0	0.090
Hip circumference – cm	130.3 ± 10.3	128.1 ± 8.7	133.8 ± 11.9	0.054
Waist–hip ratio	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.335

Bold *p*-values denote statistical significance.

multivariable linear regression was performed with a direct marker of oxygenation, namely the 3% oxygen desaturation index (ODI-3%).

IBM SPSS Statistics for Windows (version 24.0; Armonk, NY, USA) was used for the aforementioned statistical analysis. Two-sided p-value ≤ 0.05 was considered statistically significant.

3. Results

Of the 60 adolescents included in the BASIC trial, 56 subjects received a polysomnographic evaluation. The four last subjects did not receive a polysomnographic evaluation, due to unforeseen practical circumstances not related to the study. One subject was excluded from analysis due to a newly diagnosed prolactinoma. Furthermore, poor registration quality was observed in two polysomnographies due to device malfunction, which were therefore excluded from analysis.

The baseline characteristics of the remaining 53 adolescents are presented in Tables 1 and 2. None of the adolescents had a prior diagnosis of OSA or received treatment for OSA. The majority (79.2%) was female, the mean age was 15.7 ± 1.0 years, and the mean BMI was 44.1 ± 5.2 kg/m^2. Forty-eight patients (90.6%) had some degree of sleep disordered breathing (AHI ≥ 1.0) and 20 (37.7%) had moderate/severe OSA (AHI ≥ 5.0). The median AHI was 3.7 (range 0.0–26.0).

In comparison to subjects with no or mild OSA, adolescents with moderate/severe OSA were on average older (16.1 ± 1.0 versus 15.7 ± 1.0 years, $p = 0.032$), more overweighed (137.9 ± 23.7 versus 123.5 ± 14.3 kg, $p = 0.008$), and had a higher BMI (46.9 ± 5.5 versus 42.4 ± 4.3 kg/m^2, $p = 0.002$) and BMI z-score (3.7 ± 0.3 versus 3.4 ± 0.3, $p = 0.003$). Moreover, adolescents with moderate/severe OSA had larger neck circumferences (42.4 ± 3.0 versus 40.1 ± 2.9 cm, $p = 0.008$). Snoring percentages were similar in the groups with no/mild OSA and moderate/severe OSA (45.5% versus 50.0%, p = 0.531).

A comparison of several endpoints of comorbidity between patients with no/mild OSA and moderate/severe OSA is presented in Table 3. In the latter group, plasma triglyceride levels were higher (2.2 ± 1.0 versus 1.5 ± 0.7 mmol/L, $p = 0.012$), whereas IGF levels were lower (29.6 ± 8.7 versus 40.2 ± 15.8 nmol/L, $p = 0.010$). No statistically significant differences were observed in glycemic, vascular and hepatic endpoints.

The results of multivariable linear regression analysis of the association between several clinical variables and AHI, correcting for BMI z-score is shown in Table 4. BMI z-score was significantly related to AHI (unstandardized β = 6.685, *95% CI* = 1.701–11.669). Additionally, higher plasma triglyceride levels (unstandardized β = 1.655 mmol/L, *95% CI* = 0.071–3.239) were associated with a higher AHI, independently of BMI z-score. Since AHI was slightly skewed to the right, a sensitivity analysis using square-root transformed AHI as the dependent variable was performed, revealing no differences in statistically significant outcomes to the original analysis. Multivariable linear regression with ODI-3% showed that ODI-3% predicted triglyceride levels with comparable strength (unstandardized β = 0.057, 95% CI = 0.013–0.101).

4. Discussion

This is the first prospective study that systematically evaluates clinical correlates of OSA in severely obese adolescents. The main unique feature of our study population is the narrow age range, which represents adolescents in their late puberty and thus contributes to the internal validity of our findings. Moreover, our population specifically concerns those morbidly obese adolescents who were referred for bariatric surgery and consists mostly of females. In addition to polysomnography, we have prospectively collected extensive data of a wide range of comorbidities. Among the 53 analyzed severely obese adolescents, sleep disordered breathing was seen in 48 (90.6%), of whom 20 (37.7%) suffered from moderate/severe OSA. We found that elevated plasma triglyceride levels is independently associated with higher AHI.

Comparable studies in severely obese adolescents are limited to retrospective studies including patients with a wide BMI and age range, as detailed in the introduction [21–24]. Koeck et al., to a lesser extent and partially via retrospective chart review of adolescent bariatric surgery patients who had undergone PSG, compared characteristics of severely obese adolescents with no/mild and moderate/severe OSA. They reported a prevalence of moderate/severe OSA of 42.9%, which is equivalent to our study

Table 2
Polysomnographic variables in this population. Where applicable, data are described as 'mean (±SD)', 'median [range], or 'number of patients (%)'.

Variable	Total sample (n = 53)
Level of sleep disordered breathing – n	
No OSA (AHI < 1)	5 (9.4%)
Mild OSA (AHI 1.0–4.9)	28 (52.8%)
Moderate OSA (AHI 5.0–9.9)	10 (18.9%)
Severe OSA (AHI ≥ 10.0)	10 (18.9%)
AHI	3.7 [0.0–26.0]
Average O_2 dip (%)	3.0 ± 0.5
Maximum O_2 dip (%)	6.4 ± 2.7
Lowest O_2-sat. (%)	89.4 ± 3.5
Wake O_2-sat. (%)	96.7 ± 0.8
Time O_2-Sat. under 90% (min.)	1.3 ± 6.3
ODI > 3% per h	6.5 ± 5.9

Table 3
Comparison between no/mild OSA and moderate/severe OSA with regard to dyslipidemia, insulin resistance, cardiovascular disease risk, NAFLD risk, and other variables. Data described as mean ± SD.

Variable	Total sample ± n = 53	Group 1: no/mild OSA ± n = 33	Group 2: moderate/severe OSA ± n = 20	*p*-value
Triglycerides – mmol/L	1.8 ± 0.9	1.5 ± 0.7	2.2 ± 1.0	**0.012**
Free fatty acids – mmol/L	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.435
Total cholesterol – mmol/L	4.6 ± 0.8	4.6 ± 0.8	4.8 ± 0.9	0.315
HDL – mmol/L	1.1 ± 0.4	1.1 ± 0.3	1.0 ± 0.4	0.298
LDL – mmol/L	2.8 ± 0.8	2.7 ± 0.9	2.9 ± 0.8	0.552
TC/HDL-ratio	4.6 ± 1.6	4.4 ± 1.7	5.0 ± 1.6	0.192
HbA1cRel – %	5.6 ± 1.3	5.6 ± 1.6	5.5 ± 0.4	0.917
Fasting glucose – mmol/L	5.4 ± 1.8	5.5 ± 2.2	5.4 ± 0.6	0.780
Fasting insulin – pmol/L	211.0 ± 118.3	208.7 ± 123.1	215.7 ± 113.4	0.859
HOMA-IR	7.4 ± 4.9	7.3 ± 5.2	7.5 ± 4.6	0.860
RR systolic – mmHg	121.8 ± 10.6	121.7 ± 10.5	122.0 ± 11.2	0.915
Z-score RR systolic	0.8 ± 1.1	0.8 ± 1.0	1.0 ± 1.3	0.468
RR diastolic – mmHg	69.7 ± 8.8	70.1 ± 9.0	68.9 ± 8.5	0.656
Z-score RR diastolic	0.5 ± 0.9	0.4 ± 0.8	0.6 ± 1.1	0.471
ALAT – U/L	31.2 ± 16.0	28.5 ± 12.7	35.7 ± 19.9	0.167
ASAT – U/L	25.4 ± 9.4	23.7 ± 6.7	28.2 ± 12.4	0.153
CRP – mg/L	6.8 ± 6.8	5.9 ± 7.0	8.4 ± 6.4	0.233
Cortisol – nmol/L	340.3 ± 156.3	322.5 ± 129.1	370.3 ± 194.0	0.295
IGF – nmol/L	36.1 ± 14.4	40.2 ± 15.8	29.6 ± 8.7	**0.010**

Bold *p*-values denote statistical significance.

[21]. This suggests that OSA is highly prevalent amongst severely obese adolescents and raises the suspicion that OSA is underdiagnosed and/or undertreated in this population, as is also likely the case amongst severely obese adults [31]. Possible contributing factors to under recognition of OSA are lack of symptoms or awareness of symptoms, suboptimal screening tools and an expensive and time-consuming diagnostic tool in the form of polysomnography.

Importantly, we found that the typical adult predictors of OSA, such as neck circumference and blood pressure, did not independently predict AHI in our population. Moreover, although self-reported snoring was common in our population (47.2%), there was no significant difference in the prevalence of self-reported snoring between those with no/mild OSA and moderate/severe OSA. This is consistent with the literature, which reports a weak relationship between self-reported snoring and AHI [32]. Based on our findings, a statistically significant association existed between AHI and BMI z-score. In addition, higher plasma triglyceride levels were associated with a higher AHI and a higher ODI-3%, independently of BMI z-score. This positive association between plasma triglyceride levels and AHI and ODI-3% is concordant with recent evidence that suggests that OSA independently predicts adverse lipid profiles in adults [33–36]. Drager et al. showed that the fractional clearance rate of plasma triglycerides is lower in adults with OSA, compared to controls, and that 3 month treatment with continuous positive airway pressure (CPAP) resulted in a five-fold increase in fractional triglyceride clearance rate [35]. These findings suggest that early recognition and proactive treatment of OSA results in better metabolic outcomes.

Table 4
Results of multivariable linear regression analysis for the predictive value of several variables regarding AHI, correcting for BMI z-score. *Variable not corrected.

Variable	Unstandardized β	*95%-CI*
BMI z-score*	6.685	**1.701–11.669**
BMI (kg/m^2)*	0.399	**0.128–0.669**
Neck circumference (cm)	0.087	−0.477 to 0.651
Abdominal circumference (cm)	−0.049	−0.218 to 0.120
Hip circumference (cm)	0.006	−0.197 to 0.209
Waist–hip ratio	−4.533	−22.641 to 13.575
Triglycerides (mmol/L)	1.655	**0.071–3.239**
Free fatty acids (mmol/L)	3.430	−2.634 to 9.495
Total cholesterol (mmol/L)	1.109	−0.592 to 2.811
HDL (mmol/L)	−0.700	−5.022 to 3.622
LDL (mmol/L)	0.544	−1.192 to 2.279
TC/HDL-ratio	0.326	−0.580 to 1.232
HbA1cRel (%)	−0.159	−1.305 to 0.987
Fasting glucose (mmol/L)	−0.164	−0.987 to 0.660
Fasting insulin (pmol/L)	0.002	−0.011 to 0.014
HOMA-IR	0.008	−0.291 to 0.306
RR systolic (mmHg)	−0.033	−0.175 to 0.108
Z-score RR systolic	0.158	−1.190 to 1.506
RR diastolic (mmHg)	0.008	−0.160 to 0.176
Z-score RR diastolic	0.603	−0.987 to 2.192
ALAT (U/L)	−0.001	−0.099 to 0.096
ASAT (U/L)	−0.006	−0.169 to 0.157
CRP (mg/L)	−0.033	−0.255 to 0.189
Cortisol (nmol/L)	0.002	−0.007 to 0.012
IGF (nmol/L)	−0.090	−0.194 to 0.014

Bold 95%-CIs denote statistical significance.

OSA, if left untreated, is independently associated with several comorbidities and thus early recognition is crucial [10–16]. These findings in this study may help in clinical decision making to detect OSA in severely obese adolescents: since (severe) obesity becomes more common, assessing every obese child for OSA would be challenging when the limited resources and infrastructure are taken into account. Approximately 40% of the severely obese adolescents suffer from moderate/severe OSA, and therefore severe obesity on its own seems to provide suboptimal guidance in the decision whether to assess possible OSA by resource-intensive polysomnography (as gold-standard diagnostic tool) or not. Routine laboratory testing, eg plasma triglycerides levels may be used as an additional measure to justify polysomnography to diagnose OSA in morbidly obese adolescents. Larger studies need to be performed to further evaluate these associations.

Contrasting to the study by Koeck et al., where 80% of the male and 33.3% of the female morbidly obese adolescents had moderate/severe OSA, in our study this was the case for 30.0% of the male and 42.5% of the female subjects, respectively. In the adult population, a higher prevalence of OSA has been reported in men [37]. Our contrasting findings imply that the gender differences found in adolescent literature may be due to chance. Further studies are necessary to elucidate the role of gender predisposition to OSA in adolescent populations.

There are a number of limitations to this study. Though a relatively large sample was used compared to other studies, the sample size may have limited the statistical power to prove some

of our findings. Moreover, the small proportion of male inclusions made it impossible to reliably determine gender specific differences in implications and predictors of OSA. In addition, our analysis did not take into consideration the presence of anatomical factors which influence the risk of OSA, such as tonsil, uvula and tongue size.

5. Conclusion

Our data show that OSA is highly prevalent among severely obese adolescents and is significantly associated with BMI z-score. Elevated plasma triglyceride levels were also associated with OSA, independent of BMI z-score. We advise high clinical suspicion of OSA and low threshold utilization of polysomnographic studies in this population, especially when these associated factors are present. Further research should evaluate the influence of weight loss intervention on the prevalence of OSA in this population, as well as the influence of OSA on success of weight loss intervention.

Conflict of interest

All authors declare that they have no conflict of interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.02.026.

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