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Metabolic alterations in adolescents with obstructive sleep apnea

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ABSTRACT

Importance: Obesity is one of the leading health concerns in developed and in developing countries. The risk of obstructive sleep apnea (OSA) is greatly increased by obesity. Obesity is known to be associated with the Metabolic Syndrome and cardiovascular disease in adults. This same association in children is not well defined. Understanding the relationship of obesity, OSA, and metabolic alterations in children would improve understanding of the risks of cardiovascular disease into adulthood.
Objective: To evaluate the association of OSA and metabolic outcomes, including lipid variables and insulin resistance, in obese adolescents.
Methods: Retrospective, case-control series at a tertiary care children's hospital. Obese adolescents aged 12–18 years who underwent overnight polysomnography (PSG) and routine laboratory testing for lipid levels, fasting glucose, and insulin from January 1, 2006 to December 31, 2012.
Results: A total of 42 patients with a mean age of 14.1 ± 1.9 years were analyzed. Nineteen (45.2%) were male. The mean body mass index (BMI) *z* score was 2.23 ± 0.86, and all patients were obese (BMI *z* score >95th percentile). Triglyceride, fasting blood glucose, insulin, and homeostasis model assessment-insulin resistance (HOMA-IR) levels were significantly higher in patients with OSA when compared to those with No-OSA ($p < 0.01$). There was incremental worsening of insulin and HOMA-IR with greater severity of OSA. The apnea–hypopnea index (AHI) was positively and significantly correlated with blood glucose and HOMA-IR ($p = 0.01$and $p < 0.001$, respectively). Multiple linear regression analysis showed that the AHI was a predictor of blood glucose ($p = 0.04$) and HOMA-IR ($p = 0.01$) independent of age, gender, total sleep time and BMI *z* score. Logistic regression analysis showed that elevated levels of blood glucose predicted severe OSA ($p = 0.02$) independent of gender and BMI *z* score. Elevation in HOMA-IR predicted severe OSA ($p = 0.004$).
Conclusion: OSA severity is associated with increased fasting insulin, blood glucose and HOMA-IR even after controlling for the age, and BMI *z* score in adolescents.

1. Introduction

Obesity in children and adolescents is a major health issue in the United States and in other countries. According to a recent report from the Center for Disease Control (CDC), childhood obesity has more than doubled in children and quadrupled in adolescents in the past 30 years [1]. In a population-based study of 5 to 17 year old children, 70% of obese youth had at least one risk factor for cardiovascular disease [2]. Obesity in children can cause early development of hypertension, cardiovascular disease, and hyperglycemia, which in later life develops into diabetes. Metabolic Syndrome is a cluster of increased blood pressure (BP), elevated triglyceride, cholesterol, low density lipoprotein, and glucose levels, and decreased high density lipoprotein levels. The prevalence of Metabolic Syndrome is 6.8% among overweight and 28.7% among obese adolescents [2,3]. Metabolic Syndrome, or the components of Metabolic Syndrome, increases the risk of developing atherosclerosis and cardiovascular disease, i.e. heart failure, stroke, and peripheral arterial disease.

Obstructive sleep apnea (OSA), a disorder of breathing during sleep, has been correlated to obesity. OSA is a common clinical

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condition characterized by intermittent and partial airway collapse, resulting in frequent episodes of apnea, hypopnea, and recurrent arousals from sleep [2–4]. The estimated prevalence of OSA is 2–3% in children [3]. This risk of OSA is greatly increased by obesity, with an estimated prevalence of 36% in obese children [5]. In adults, both the obesity and OSA are shown to be associated with cardiovascular disease, high cholesterol and high blood pressure. This association is less defined in children and adolescents. Some studies in children have shown OSA to independently increases insulin resistance [5,6], while other studies suggest that obesity is the variable increasing insulin resistance [7,8].

In this study, we hypothesize that OSA is linked with metabolic alternations, including lipid variables, fasting glucose and insulin levels, independent of BMI *z* score in adolescents. Alterations in metabolic variables and their association with individual components of OSA, including apnea–hypopnea index (AHI), oxygen saturation (SpO_2), and arousal index were studied. The relationship of metabolic variable laboratory test results and obesity were analyzed. Individual measures of the metabolic panel, particularly elevations in fasting glucose and insulin levels, were analyzed relative to OSA severity (19) to help better define the relationship between severity of OSA and metabolic abnormalities in adolescents.

2. Methods

2.1. Study population

The study was approved by the Institutional Review Board of Ann & Robert H. Lurie Children's Hospital of Chicago. This is a historical cohort study of consecutive patients, aged 12 to 18 years, having overnight polysomnography (PSG) at Ann & Robert H. Lurie Children's Hospital of Chicago between January 1, 2006 and December 31, 2012, who also had laboratory testing for the metabolic variables being analyzed within 3 months of their PSG. A total of 55 patients were identified. Patients were excluded from analysis if they had a history of Type I diabetes ($n = 3$), genetic abnormalities ($n = 3$), or used a continuous positive airway pressure device (CPAP) for OSA ($n = 2$). Other exclusions included those patients with craniofacial anomalies ($n = 1$), organ transplant recipients ($n = 2$), and multiple medical problems ($n = 2$). A total of 42 patients were available for the final analysis. The age, gender, laboratory data on metabolic variables, height, weight, and PSG findings were collected from the electronic medical records.

2.2. Definition and measurements

All laboratory analyses were conducted at the Ann & Robert H. Lurie Children's Hospital laboratory. The metabolic variables including fasting glucose, and insulin levels measured were attained after an overnight fast. Abnormal fasting glucose values were determined if a patient met the American Diabetes Association guidelines (fasting glucose $\geq$100 mg/dl) [9]. The homeostasis model assessment-insulin resistance (HOMA-IR) was used as an index of insulin resistance, and this was calculated using a standard equation (fasting insulin (μIU/mL) $\times$ fasting blood glucose (mmol/L)/22.5) [10]. Based on this score, insulin resistance was determined using the HOMA-IR cut-points described by Kurtoglu et al. (>2.67 for boy and >2.22 for girls) [11]. Height and weight were recorded for each patient. The BMI *z*-score was computed using Center for Disease Control (CDC) growth standards (www.cdc.gov/growthcharts) and online software (www.cdc.gov/epiinfo). Patients with a BMI *z* score above the 95th percentile were considered obese.

2.3. Polysomnography

A standard overnight PSG (Cadwell easy 3 versions 3.9.34, Kennewick, WA, USA) had been performed on all patients. The apneas and hypopneas were identified and scored according to the American Academy of Sleep Medicine (AASM) pediatric criteria as defined in the AASM Manual for Scoring of Sleep and Associated Events [12]. The apnea–hypopnea index (AHI) was defined as the total number of obstructive apneas and hypopneas per hour of sleep. Severity of OSA was classified as mild (AHI between 1 and 4.99 events per hour of sleep), moderate (AHI between 5 and 9.99 events per hour of sleep), severe (AHI $\geq$ 10 events per hour of sleep), and No-OSA (AHI $<$ 1 event per hour of sleep) [6,13].

2.4. Statistical analysis

Descriptive statistics were summarized using frequencies and percentages for categorical data, and mean and standard deviations for continuous data. To determine differences between groups of No-OSA, Mild-OSA, Moderate-OSA and Severe-OSA, both parametric and nonparametric tests were used. Chi^2 test of association was used for nominal data. *t*-Test and analysis of variance statistics were used for normally distributed data. Mann Whitney *U* and Kruskal Wallis statistics were used for non-normally distributed data. Outliers were identified and checked for accuracy. Scatter plots were used to graphically show correlations among PSG and metabolic variables. Multiple linear regression models were run to predict dependent variables for log transformed fasting insulin and log-transformed HOMA-IR. Predictors included age, gender, TST, BMI *z* score, and AHI. Multinomial logistic regression models were run to predict patients grouped into those with No-OSA, Mild-OSA, Moderate-OSA, and Severe-OSA. Results were considered significant with two-tailed test and $p < 0.05$. Statistical analysis was conducted using statistical product and service solution (SPSS) software version 20 (IBM SPSS Inc., Chicago, IL).

3. Results

A total 42 patients with a mean age of 14.1 $\pm$ 1.9 years were analyzed. Nineteen (45.2%) were male. The average BMI *z* score was 2.23 $\pm$ 0.86, and all patients were obese (BMI *z* score > 95th percentile). Eighteen patients (42.8%) had an AHI < 1/h (No-OSA), 7 patients (16.6%) had an AHI $\geq$ 1 $\leq$ 4.99/h (Mild-OSA), 5 (11.9%) had an AHI $\geq$ 5/h < 9.99/h (Moderate-OSA) and 12 (28.6%) had an AHI $\geq$ 10/h (Severe-OSA). There was no significant difference in age ($p = 0.44$), and BMI *z* score ($p = 0.16$) between the groups (Table 1). Patients with OSA had a significantly higher AHI and arousal index, and a lower average SpO_2 and SpO_2 Nadir, as expected. Stage 1 total sleep time (TST) was significantly higher in those with severe OSA ($p < 0.001$).

When comparing metabolic and PSG variables to OSA severity, there was no significant difference in HDL-C or LDL-C in those patients with No-OSA, and in those with all levels of OSA. Total cholesterol did not reach significance in the groups ($p = 0.05$) (Table 1). Triglyceride, blood glucose, fasting insulin, and HOMA-IR levels were significantly higher in patients with OSA compare to those with No-OSA. There was incremental worsening of insulin and HOMA-IR levels with greater severity of OSA: 3.9 $\pm$ 1.8 in those with No-OSA, 7.7 $\pm$ 2.1 in Mild-OSA, 8.2 $\pm$ 1.3 in Moderate, and 14.8 $\pm$ 5.3 in Severe-OSA. A similar trend was observed in insulin levels (Table 1).

Further correlation analysis suggested that the AHI was positively and significantly correlated with elevated blood glucose and HOMA-IR ($p = 0.01$ and $p < 0.001$, respectively) (Fig. 1A and B).