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Sleep-disordered breathing in obese adolescents is associated with visceral adiposity and markers of insulin resistance

TAMARA S. HANNON[1,2], **SOJUNG LEE**[1], **SANGEETA CHAKRAVORTY**[3], **YAN LIN**[4], and **SILVA A. ARSLANIAN**[1,2]

[1]Division of Weight Management and Wellness, Department of Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, PA

[2]Division of Pediatric Endocrinology, Metabolism, and Diabetes Mellitus, Department of Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, PA

[3]Division of Pulmonary Medicine, Allergy, and Immunology, Department of Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, PA

[4]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

Abstract

Sleep-disordered breathing is associated with obesity, insulin resistance, and the metabolic syndrome in adults. Similar data in children is limited and conflicting. This pilot study examined the relationships between sleep-disordered breathing, visceral adiposity, and cardiometabolic risk factors in obese adolescents. Twenty obese (body mass index ≥95th percentile), otherwise healthy adolescents (age 14.9 ± 2 years) underwent polysomnogram studies, fasting lipid profile and oral glucose tolerance tests, and measures of body composition (dual-energy X-ray absorptiometry) and visceral adiposity (abdominal computed tomography). The severity of sleep-disordered breathing (as measured by apnea-hypopnea index) was positively associated with visceral adipose tissue (r=0.73, p<0.001) but not with other measures of body composition. After controlling for body mass index, the severity of sleep-disordered breathing was positively associated with markers of insulin resistance (homeostasis model assessment and fasting insulin). Further study to allow for critical assessment of the relationships between sleep-disordered breathing and cardiometabolic risk factors in obese youth remains necessary.

Keywords

Sleep apnea; insulin resistance; central adiposity; abdominal obesity

Introduction

Sleep-disordered breathing (SDB) has been linked with obesity and the metabolic syndrome in children (1,2). However, pediatric studies examining the association between SDB and measures of insulin resistance are limited and conflicting. Some have shown a positive relationship between SDB and fasting insulin levels (3–5), while others show no association

Correspondence: Tamara S. Hannon, Children's Hospital of Pittsburgh, 3705 5th Avenue, 4A, Room 424, Pittsburgh, PA 15213, USA. Fax: 1 412 692 7805. tamara.hannon@chp.edu.

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between SDB and markers of insulin resistance among normal weight (6) and obese children (7,8). This was a pilot study to begin to evaluate the hypothesis that SDB is associated with markers of insulin resistance and cardiometabolic disease in obese adolescents. Specific aims included determining the associations between SDB, as measured by the apnea-hypopnea index (AHI), during polysomnography and 1) measures of insulin sensitivity from oral glucose tolerance testing, and 2) cardiometabolic risk factors (visceral adiposity, fasting lipid profile, blood pressure).

Methods

This prospective study was approved by the University of Pittsburgh Institutional Review Board and performed in the Pediatric Clinical and Translational Research Center at the Children's Hospital of Pittsburgh. Twenty patients referred to the Weight Management and Wellness Center at the Children's Hospital of Pittsburgh for evaluation of obesity who met study criteria were recruited for participation. Eligibility criteria were: 12–18-year-old male or female adolescents (Tanner stage (III–V) of any race with BMI ≥95th percentile. Exclusion criteria were tonsil grade >1+; smoking; chronic diseases or medications interfering with sleep or glucose regulation; and syndromic obesity. The study included 12 males (5 black, 6 white, 1 mixed-race) and 8 females (3 black and 5 white).

A 2-hour oral glucose tolerance test (OGTT; 1.75 g/kg, maximum 75 g) was performed. Plasma glucose was measured by the glucose oxidase method. Plasma insulin was determined by multiplexed immunoassay (Millipore) and the Luminex-200 system (Luminex Corporation). Fasting lipid profile was measured using the standards of the Centers of Disease Control and Prevention. Measures of insulin sensitivity were calculated: homeostasis model assessment-insulin resistance (HOMA-IR) to express basal insulin resistance (9), and whole body insulin sensitivity index (WBISI), which is an estimate of euglycemic clamp-derived insulin sensitivity (9). Insulin secretion was expressed as the ratio of the incremental response of insulin to glucose at 15 and 30 minutes during the OGTT, which has been shown to correlate with first phase insulin secretion during hyperglycemic clamps (10).

Body composition was measured by dual-energy X-ray absorptiometry (DXA) in 17 of the 20 participants. In the remaining three, DXA was not performed due to the participant's weight exceeding the limits for the equipment. Abdominal adiposity (subcutaneous adipose tissue [SAT] and visceral adipose tissue [VAT]) was assessed with a 10 mm single axial computed tomography (CT) scan of the abdomen at the level of L4–5 vertebrae.

Overnight polysomnogram was performed under the direction of the Pediatric Sleep Program. Polysomnogram data were recorded using Sensormedics Somnostar Pro version 7.2 software. Respiratory variables included chest and abdominal wall movements, oral/nasal airflow, and oxyhemoglobin saturation (SaO_2). The AHI (total number of central and obstructive apneas+hypopneas/hour of sleep) was calculated from digitized data (11). Sleep efficiency refers to the percentage of the total recording time spent asleep.

Spearman's correlation coefficients were calculated to quantify the association between the AHI and outcome variables. In addition, partial correlation analysis was conducted after controlling for BMI to quantify the association between the AHI and outcome variables. Variables that were not normally distributed were log transformed for partial correlation analysis. Two-sided t-tests were used to compare continuous variables between individuals with AHI ≥1.5 and those with AHI <1.5. Previous pediatric studies show that healthy children and adolescents have AHI <1.5 (12–14). Mann Whitney U-tests were utilized for

non-normally distributed outcomes. Data are expressed as the mean ± Standard error of the mean (SEM).

Results

All but one of the participants had >6 hours of data recorded during polysomnography. Total sleep time was 423 ± 37 (standard deviation, SD) minutes (range 354–484 minutes). Nine of the participants had normal breathing during sleep (AHI <1.5), 7 had mild SDB (AHI ≥1.5-<5), and 4 had severe SDB (AHI ≥10). Characteristics of the participants according to AHI are shown in Table I. Participants with AHI<1.5 and those with AHI ≥1.5 did not differ with regard to age (14.8 ± 0.6 vs. 14.9 ± 0.7 years, P=0.94) and had similar BMIs (38.4 ± 2.2 vs. 42.1 ± 3.4 kg/m^2, P=0.57). Fasting glucose, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol and blood pressure were not significantly different between the groups. Participants with AHI ≥1.5 tended to have greater insulin secretion and evidence of more insulin resistance; although the group differences did not reach statistical significance. Participants with AHI ≥1.5 had significantly more VAT, while SAT and percent body fat did not differ between the groups.

AHI was positively associated with VAT (Figure 1) but not with BMI (r=0.24, p=0.31) or SAT (r=0.19, p=0.43). AHI was positively associated with measures of insulin resistance (fasting insulin and HOMA-IR) and negatively associated with insulin sensitivity (WBISI), after controlling for BMI (Table II).

Discussion

Results of this study indicate that the presence of SDB (AHI ≥1.5) is associated with significantly greater visceral adiposity in obese adolescents. The severity of SDB (as measured by AHI) was associated with 1) amount of visceral fat, and 2) markers of insulin resistance after controlling for BMI among obese adolescents. These findings support our hypothesis that SDB is associated with insulin resistance and may increase risk for cardiometabolic disease in obese adolescents.

Visceral adiposity is associated with the metabolic syndrome (15), and is recognized as a predictor of insulin resistance among obese adolescents (16). Few pediatric studies have addressed the association of SDB and the metabolic syndrome, and no previous pediatric study has explicitly measured visceral adiposity in relationship to SDB. SDB was not significantly associated with other measures of body composition. Three participants did not have DXA scans, which may have falsely decreased the mean body fat in the group with AHI ≥1 and should be further examined.

Other pediatric studies support a relationship between the metabolic syndrome and the severity of SDB. In a population-based study, adolescents with AHI ≥5 had 6.5 times increased odds of having the metabolic syndrome (2). After adjustment for BMI, SDB was associated with increased blood pressure, LDL, and fasting insulin levels (2). during PSG has been In clinic-based studies, SaO_2 shown to be predictive of the metabolic syndrome (1), and waist circumference has been positively associated with central sleep apnea (17). Studies evaluating markers of insulin resistance in youth with SDB have conflicting results. Studies in mixed populations of pre-pubertal and pubertal children with snoring (3), and children undergoing evaluation of obesity (4,5) have shown SDB to be associated with fasting insulin and HOMA-IR. Other studies have found no association between SDB and markers of insulin resistance in populations of normal weight (6) and obese children (7,8).

Because of the relative infancy of this area of study in pediatrics, this pilot study and former studies have been small and the field will benefit from larger, hypothesis-driven studies.

Previous studies have not addressed puberty as a modulator of insulin sensitivity; and in studies where both lean and obese children are included, obesity is likely to be the strongest predictor of insulin resistance. In this study, minority race participants were equally distributed among the study population with regard to AHI (5 had AHI <1.5 and 4 had AHI >1.5), but future studies may focus on racial and gender differences. Finally, our study was limited by the use of serum markers of insulin resistance, rather than *in vivo* methods of measuring insulin sensitivity and secretion. Sensitive measures of insulin sensitivity and secretion are likely to be required to adequately evaluate the association between insulin resistance and SDB.

In conclusion, visceral adiposity is linked with SDB and markers of insulin resistance in obese adolescents. The non-abating epidemic of childhood obesity is expected to lead to an increased prevalence of insulin-resistance related co-morbid conditions in children and young adults. Thus, further assessment of the relationships between the severity of SDB, insulin resistance, and cardiometabolic risk factors in obese youth remains crucial. Early recognition and treatment of SDB in obese children may improve conditions associated with insulin resistance, which is of great clinical importance.

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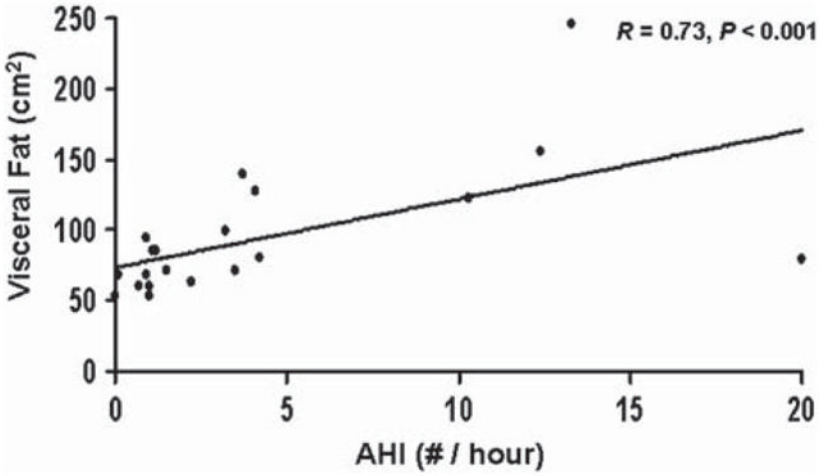

Figure 1.
The association between the apnea-hypopnea index (AHI) and visceral adipose tissue (VAT).

Table I

Physical, sleep, and metabolic characteristics of study participants according to apnea-hypopnea index (AHI).

	AHI <1.5 (N=9)	AHI ≥1.5 (N=11)	*P*
Nadir SaO_2 (%) during polysomnogram *	92.3±0.5	84.5±1.7	0.001
Mean SaO_2 (%) during polysomnogram *	97.0±0.3	94.6±0.8	0.05
Fasting insulin * (pmol/L)	132.0±14.4	186.0±28.2	0.18
Fasting glucose/insulin ratio	4.5±0.5	3.4±0.4	0.09
HOMA-IR *	4.9±0.6	6.8±1.0	0.10
WBISI	1.9±0.2	1.6±0.1	0.16
$\Delta Insulin_{15}/\Delta Glucose_{15}$ (pmol/L per mmol/L)	426.6±51.8	590.8±72.4	0.09
$\Delta Insulin_{30}/\Delta Glucose_{30}$ (pmol/L per mmol/L)	355.3±57.2	529.2±62.6	0.06
Visceral adipose tissue (cm^2) *	69.7±5.1	114.1±16.2	0.01
Subcutaneous adipose tissue (cm^2)	586.9±64.6	629.1±60.3 (N=10)	0.64
Percent body fat (%)	44.3±1.9 (N=8)	45.5±1.8 (N=9)	0.66

HOMA-IR: Homeostasis model assessment-insulin resistance; WBISI: Whole body insulin sensitivity index.

* Mann Whitney U-test for non-parametric data utilized to compare means.

Table II

Partial correlations of AHI with VAT and measures of insulin sensitivity after controlling for BMI.

	Log (VAT)	Log (Fasting insulin)	Log (HOMA-IR)	WBISI
Log (AHI)	0.67***	0.483*	0.504**	−0.585**

P=0.05.

** P<0.05.

*** *P*<0.01.