Relationship between Sleep Apnea, Fat Distribution, and Insulin Resistance in Obese Children

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Background: Obstructive sleep apnea (OSA) is associated with obesity, inflammation, and insulin resistance. The role of fat distribution in OSA pathogenesis has not been established in children. The objective of the study is to examine the relationship between fat distribution, OSA, and insulin resistance in an unselected population of obese children.

Methods: All obese (BMI > 95th percentile) children (ages 5-18 y) seen at a pediatric obesity clinic were invited to participate. Subjects underwent polysomnography, and were tested for dyslipidemia, inflammation, and insulin resistance measured by the homeostasis model assessment (HOMA). In a subset of subjects, magnetic resonance (MRI) imaging was used to determine the abdominal visceral and subcutaneous adipose tissue areas and magnetic resonance spectroscopy (MRS) spectroscopy was used to intramyocellular lipids in leg muscles.

Measurements and Main Results: 31 obese subjects enrolled and completed polysomnography and serum testing,

and 19 subjects underwent MRI/MRS. The mean age was 12.6 ± 3.0 y and the mean body mass index (BMI) was 39.5 ± 11.2 kg/m². Forty-eight percent had OSA (mean apnea hypopnea index [AHI] 6.26 ± 6.77 events/h). Subjects with OSA had significantly increased BMI, log HOMA, triglycerides, and leptin compared to those without OSA. In regression analysis, only BMI z-score was associated with log HOMA. In the subset of patients with imaging data, visceral fat area was strongly predictive of AHI ($p = 0.003$, $r^2 = 0.556$). BMI z-score, gender, and age were not predictive.

Conclusions: Visceral fat distribution is independently predictive of OSA severity in obese children.

Keywords: Obstructive sleep apnea, obesity, pediatrics, metabolic syndrome

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obesity is a significant risk factor for obstructive sleep apnea in children but not all obese children suffer from OSA. Studies of fat distribution in adults have shown visceral adiposity to be strongly associated with OSA. Body fat distribution may explain the relationship between obesity and OSA in children.

Study Impact: This study demonstrates that visceral adiposity, as measured by magnetic resonance imaging at L4, is a significant predictor of OSA severity independent of body mass index. Further examination of fat distribution may enable prediction of OSA risk in obese children and further understanding of the pathogenesis of OSA in this population.

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete airway obstruction resulting in hypoxemia, hypercapnia, and respiratory arousal.¹ It is a relatively common condition, with an estimated prevalence of 1% to 3% in otherwise healthy children.² The risk of OSA is greatly increased by obesity in children, with an estimated prevalence of 36% in obese children.³⁻⁵ The prevalence in obese patients with snoring or other signs of apnea is estimated to be much higher.⁵ Interestingly, many severely obese children do not have OSA, indicating that different fat distribution phenotypes may exist. Thus, precise determination of fat distribution may identify which obese children are at risk for OSA. Furthermore, specific phenotypes of fat distribution may explain the mechanistic relationship between obesity and OSA.

Obesity confers significant cardiovascular, metabolic, and neurocognitive morbidity in the pediatric population, and is defined in the pediatric population by the presence of a body mass index (BMI) > 95th% for age. In the United States, the prevalence of childhood obesity is estimated to be 16.9%.⁶ Obesity in children is associated with an increased prevalence of insulin

resistance,⁷ hypertension,⁸ and dyslipidemia.⁹ This constellation of conditions has been termed the metabolic syndrome, and affects as many as 30% to 50% of obese children.⁹

A variety of studies have indicated a clear relationship between OSA and insulin resistance, but the pathophysiology of this relationship has not been established. Multiple studies have demonstrated a clear relationship between OSA, insulin resistance, and inflammation in obese and non-obese children.¹⁰⁻¹⁴ Intermittent hypoxemia predisposes to insulin resistance in ani-

imals and humans,^{15,16} and sleep fragmentation increases insulin resistance in healthy controls.¹⁵⁻¹⁸ Visceral fat has been proposed as a potential mediator of the relationship, because both OSA and insulin resistance are more closely associated with the size of visceral fat deposits than with BMI alone.¹⁹⁻²¹

Previous studies examining the relationship between fat distribution and OSA relied on measurements of waist/hip ratios and total body fat,^{13,22,23} and have not found a clear cut relationship between fat distribution and OSA. In children, both visceral adiposity and intramyocellular lipid content, a measure of fat accumulation at the cellular level determined by spectroscopy, has been shown to be a strong predictor of insulin resistance.^{7,24} These techniques have not been used in the assessment of fat distribution as it may relate to OSA.

The goals of this study were to examine two hypotheses. Our primary hypothesis was that visceral adiposity and intramyocellular lipid are predictive of OSA severity, as measured by the apnea hypopnea index (AHI). The secondary hypothesis was that OSA, as measured by the AHI is associated with insulin resistance (measured by the homeostasis model assessment [HOMA]), among children referred to a pediatric obesity clinic unselected for sleep symptoms. Such information may permit more precise determination of OSA risk in obese children by defining the relationship between body fat distribution and upper airway obstruction. Additionally, it may explain why many obese children do not suffer from OSA.

METHODS

This study was approved by the Institutional Review Board of Massachusetts General Hospital (Protocol #: 2005P002112). Subjects between age 5 and 18 years of age with BMI > 95th percentile for age were recruited prospectively from patients seen at the Massachusetts General Hospital Weight Center. All patients presenting to the clinic were offered enrollment independent of sleep symptoms. Exclusion criteria included current use of CPAP or bilevel PAP for OSA, presence of hardware to prevent MRI scanning, and serious medical conditions. Participants completed a survey about sleep related symptoms modeled on the survey in Tausman et al.¹² and underwent a complete physical examination. The survey included a basic inventory of sleep related complaints as snoring, parasomnias, and bed time resistance, as well as information about usual bedtime and wake time. To assess our secondary hypothesis, we used lab values obtained as part of the routine evaluation in the Weight Center, which were comprised of fasting lipid, glucose, insulin, and leptin values. The lipid and glucose values were obtained via analysis on a Hitachi 917 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). High-sensitivity C-reactive protein (hsCRP) level was determined by using a Hitachi 917 analyzer (San Jose, CA) using reagents and calibrators from Equal Diagnostics (Exton, PA).²⁵ Leptin values were obtained using double antibody radioimmune assay (Esoterix Laboratory Services, Calabasas Hills, CA).²⁶ Insulin levels were determined via a double antibody chemiluminescent immunoassay on an Immulite 2000 (Siemens, Deerfield, IL).²⁷ Insulin resistance was estimated using the HOMA, calculated as (fasting insulin (mU/mL) × fasting glucose (mmol/L))/22.5. A HOMA

value > 3.16 in children and > 2.5 in adults is suggestive of insulin resistance.²⁸

Polysomnography

All patients underwent overnight polysomnography. The studies were performed with a computerized system (Grass Instruments, Braintree, MA). During polysomnography, the following parameters were measured: electroencephalogram (C3/A2, O1/A2, F1/A2); right and left electrooculogram; submental electromyogram (EMG); tibial EMG; surface intercostal EMG; electrocardiogram; chest/abdominal wall motion (piezoelectric transducers or respiratory inductance plethysmography), nasal pressure (Validyne, Northridge, CA), thermistor, end-tidal CO₂ (Novamatrix COSMO, Wallingford, CT); arterial oxygen saturation (Novamatrix COSMO); and videotaping. Events were scored using the criteria of Rechtschaffen and Kales,²⁹ and reviewed by a physician board certified in sleep medicine (EK). The physician reviewing the polysomnograms was naïve to the fat distribution, metabolic status, and BMI of the subjects. OSA was defined as an AHI > 2 per hour. Hypopneas were scored when a 50% decrement in nasal pressure was noted in association with arousal or a 3% desaturation.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was performed on a subset of subjects for body fat distribution measurement. Intravenous contrast was not used. A single cross-sectional MR image at L4 was utilized to assess distribution of adipose tissue. Scans were performed with a 1.5T MR device (GE Medical Systems, Milwaukee, WI). A triplane localizer image of the abdomen was obtained to identify L4, which served as a landmark for a single-slice image at this level. Fat attenuation values were set for intra-abdominal visceral and subcutaneous fat areas based on tracings obtained utilizing commercial software (VITRAK, Merge/eFilm, WI). Abdominal visceral (VAT) and abdominal subcutaneous adipose tissue (SAT) (both as cm²) and the ratio of VAT to total abdominal adipose tissue (TAT) areas were measured.

The region of interest for magnetic resonance spectroscopy (MRS) was identified using T1-weighted images of the right calf. Localization was performed on the slice containing the largest cross-sectional area of the tibialis anterior and soleus muscles. The region of interest was positioned to include a muscle volume avoiding visible interstitial tissue, fat, and vessels. The volume of the voxel used was 3.4 mL (15 × 15 × 15 mm).

Processing of the MRS data was performed on a Linux workstation running LCModel software for spectral analysis. The intramyocellular lipid peak was scaled to unsuppressed water peak using the LCModel routine, and the measurement performed on soleus (S-IMCL([W])) and tibialis anterior (T-IMCL([W])) muscles of the right leg. The physicians reviewing the imaging studies (BJT, MT) were naïve to the polysomnographic status, BMI, and lab results of the patients being studied.

Analysis

Data were entered into a Microsoft Excel spreadsheet and analyzed using SigmaStat software (Systat, Chicago, IL). To assess the primary hypothesis, multiple regression analysis was used to model the relationship between fat partitioning,

Table 1—Demographics and polysomnography values

	No OSA	OSA	p-value
N	16	15	
Age (years)	12.6 ± 2.73	12.7 ± 2.64	0.93
Gender (% male)	0.38	0.53	
Race/Ethnicity (%):			
White	56.0	47.0	
African American	19.0	20.0	
Asian	0.0	7.0	
Hispanic	50.0	33.0	
BMI (kg/m ²)	35.4 ± 5.8	43.9 ± 13.9	0.04
BMI Z-score	2.44 ± 0.27	2.78 ± 0.39	0.01
AHI (events/h)	0.48 ± 0.30	6.26 ± 6.77	0.02
AHI+ RERA (events/h)	2.9 ± 1.32	8.07 ± 7.33	0.05
Arousal index (events/h)	8.44 ± 2.12	13.79 ± 9.13	0.10
SpO ₂ 90% (min)	0.0 ± 0.0	5.73 ± 13.06	0.20
SpO ₂ Nadir	93.24 ± 2.44	85.52 ± 11.1	0.06

All values expressed as mean ± standard deviation

Table 2—MRI subgroup

	No OSA	OSA	p-value
N	9	10	
Age (years)	12.4 ± 2.96	12.2 ± 3.58	0.87
Gender (% male)	0.56	0.50	
BMI (kg/m ²)	34.28 ± 5.83	38.81 ± 8.01	0.17
BMI Z-score	2.41 ± 0.26	2.63 ± 0.26	0.08
Subcutaneous fat (SAT) (cm ²)	450.72 ± 161.75	545.57 ± 51.79	0.21
Visceral fat (VAT) (cm ²)	86.37 ± 39.92	127.52 ± 50.02	0.063
VAT/TAT	0.167 ± 0.061	0.187 ± 0.038	0.42
Tibialis anterior IMCL (% of water signal)	123.62 ± 58.98	111.33 ± 46.82	0.62
Soleus IMCL (% of water signal)	578.37 ± 321.39	583.38 ± 161.4	0.97

All values expressed as mean ± standard deviation

measures of OSA, and insulin resistance. For evaluation of the secondary hypothesis, a 2-tailed Student *t*-test was used for comparison of continuous variables from routine Weight Center between patients with and without OSA.

RESULTS

Ninety-one subjects were screened during the study period. Three patients were excluded from the study; two patients were using positive airway pressure therapy (one on CPAP and one on bilevel). One patient did not have a BMI ≥ 95% for age and thus did not meet the criteria for obesity. No one was excluded for serious medical conditions. This reflects the clinic population of the Weight Center, which is generally composed of obese non-syndromic children.

Thirty-two subjects declined participation. Fifty-five patients initially provided consent. Five patients withdrew (one was afraid of performing the MRI; two patients could not tolerate the sleep lab equipment; and two did not provide a reason). Of the remaining 51 patients, 31 patients completed the study. Multiple attempts were made to complete the studies on the remaining 20 patients, including via email, multiple phone messages, and letters. After the letter was sent, patients were deemed “lost to follow-up” after a two month period without a response. In total, 34% of the screened clinic patients completed the study.

Twenty-nine percent of the patients had a history of adenotonsillectomy. There was no difference in this proportion between the groups with and without OSA. A total of 31 patients enrolled in the study and completed the polysomnogram (**Table 1**). The mean age was 12.6 ± 3.15 years. Forty-five percent of the enrolled subjects were male. The BMI of patients with OSA (defined as AHI > 2/h) was significantly higher than those without OSA (43.9 ± 13.9 kg/m² and 39.5 ± 11.2 kg/m², respectively, *p* = 0.04).

Primary Outcomes: Fat Distribution Group Data (n = 19)

Due to resource limitations, only the first 21 patients were offered MRI. Nineteen patients completed the MRI; 2 patients were ineligible for the MRI because their weight exceeded the safety limit for the equipment (425 lb). **Table 2** shows the characteristics of the subjects who had MRI studies. Examples of children with high and low visceral adiposity are shown in **Figure 1**.

The subgroup of subjects who had MRI did not differ significantly in BMI z-score, gender, or polysomnographic variables from those that did not have MRI. However, their leptin was significantly lower compared with the subjects who did not have MRI (27.0 ± 9.6 vs. 41.9 ± 10.0, respectively, *p* = 0.0004).

VAT was positively associated with log HOMA (Pearson correlation coefficient = 0.458, *p* = 0.00147). The 2 measures of intramyocellular lipid content relative to water in the tibialis anterior (TIMCLW) and soleus (SIMCLW) were not associated with AHI or log HOMA. Multiple linear regression performed with age, gender, BMI z score, AHI, and VAT, as covariates showed AHI to be the only significant predictor of log HOMA in the model (*p* < 0.001, *r*² = 0.619).

To assess the relationship between fat distribution, weight, and severity of OSA, linear regression was performed with AHI as the dependent variable, and including gender, age, BMI z score, and VAT. Only VAT (*p* = 0.003), but not BMI z score, gender, or age, was a significant independent predictor of AHI (*r*² = 0.556).

Secondary Outcomes: Metabolic Marker Group Data (n = 31)

Fasting insulin, HOMA, triglycerides, and leptin were all significantly higher in the subjects with OSA than those without OSA, whereas CRP was not (**Table 3**).

To examine the relationship between measures of OSA and HOMA, linear regression was performed with log HOMA as the dependent variable. Gender (*p* = 0.562), AHI (*p* = 0.620), and age (*p* = 0.793) did not significantly correlate with log HOMA, although BMI z-score approached significance (*p* = 0.062, *r*² = 0.224).

Figure 1—Example of fat distribution in obese children with and without obstructive sleep apnea

(A) Marked visceral adiposity: 16-year-old Hispanic female. BMI 43 kg/m². AHI = 25/h. VAT = 229.1 cm²; SAT = 632.1 cm²; VAT/TAT = 0.266. **(B)** 16-year-old white female. BMI 38 kg/m². AHI = 0/h. VAT = 29.4 cm²; SAT = 612.7 cm²; VAT/TAT = 0.048. Visceral fat is highlighted in red; subcutaneous in green. AHI, apnea-hypopnea index; BMI, body mass index; VAT, visceral adipose tissue.

The relationship between AHI and weight was compared via multiple linear regression, using AHI as the dependent variable and including age, BMI z-score, and gender as covariates. Only BMI z-score was significantly predictive of AHI ($p = 0.016$, $r^2 = 0.205$).

DISCUSSION

This study was the first to use highly sensitive imaging techniques to quantify fat distribution in obese children with OSA. We observed a strong relationship between visceral adiposity and OSA, independent of BMI, which may explain why some obese children develop OSA and some do not.

Our results confirm multiple prior studies in adults in children showing a significant correlation between OSA and markers of the metabolic syndrome, including increased insulin resistance (as measured by fasting insulin and HOMA), dyslipidemia (as measured by elevated triglycerides and a trend towards lower HDL), and elevated leptin levels. Unlike the

Table 3—Secondary measures: lab values

	No OSA	OSA	p-value
Fasting blood sugar (mg/dL)	89.25 ± 7.58	90.53 ± 10.8	0.71
Fasting insulin (uU/mL)	13.375 ± 0.59	33.07 ± 24.66	0.01
HOMA	2.81 ± 2.92	6.58 ± 4.33	0.02
C reactive protein (mg/L)	3.82 ± 1.95	5.57 ± 2.58	0.12
Total cholesterol (mg/dL)	161.9 ± 34.4	166.7 ± 17.15	0.71
LDL (mg/dL)	90.44 ± 27.13	99.4 ± 20.15	0.43
HDL (mg/dL)	50.89 ± 18.41	37.7 ± 6.86	0.07
Triglycerides (mg/dL)	102.56 ± 33.22	147.5 ± 39.61	0.02
AST (U/L)	30.63 ± 14.43	39.6 ± 15.72	0.23
ALT (U/L)	45.13 ± 25.94	51.2 ± 28.51	0.64
Leptin (ng/mL)	21.18 ± 7.77	32.19 ± 8.27	0.01

All values expressed as mean ± standard deviation

majority of studies of obese children with sleep apnea, we recruited a population from a tertiary care obesity center composed exclusively of morbidly obese children unselected for sleep symptoms or snoring. In this range of obese subjects, thus, these values confirm that further evaluation of metabolic syndrome parameters in this subpopulation of obese children is worth pursuing. In this group, BMI z-score was an independent determinant of OSA, as is true in children over a wider range of BMI.^{3-5,30}

One proposed mechanism for the association between obesity and OSA is narrowing of the upper airway due to fat deposition.³¹ In children, sleep apnea may be caused by somewhat different mechanisms. Limited pediatric data suggest that adenotonsillar hypertrophy and the soft palate are responsible for a significant component of the obstruction, even in obese children.³² Indeed, adenotonsillectomy is beneficial in many obese children with OSA,³³ though residual OSA is common in these children postoperatively.³⁴

The relationship between OSA and body fat distribution has primarily been investigated in adults. In adults, the preponderance of data support the association between visceral adiposity and OSA.^{19,21,35,36} In addition, both visceral adiposity and OSA predispose to manifestations of the metabolic syndrome such as insulin resistance and dyslipidemia.^{21,36} Studies in adults have found that visceral adiposity correlated more strongly than BMI with the presence of OSA.^{20,37} Previous studies in children that used only anthropometric measures of adiposity have not demonstrated an association between fat distribution and OSA. Specifically, Li and colleagues found that obese children with OSA were older, heavier, and had larger waist circumferences than their peers; but an independent relationship between waist circumference and OSA was not confirmed after adjusting for the other covariates.²² A study by Verhulst and colleagues found that OSA was associated with several elements of the metabolic syndrome, but this was independent of waist circumference.¹⁴ Another study by the same authors demonstrated that several measures of abdominal adiposity (waist circumference, waist-to-hip ratio, and percent fat mass measured by bioelectric impedance) correlated with oxygen desaturations associated with brief respiratory pauses, but not OSA.¹³ By contrast, our study,

which employed more sensitive measures of fat distribution (MRI and MRS), demonstrated an association between visceral adiposity (VAT) and OSA (AHI).

As in multiple prior studies, the AHI was associated with insulin resistance and dyslipidemia in our subjects in the MRI group.^{10,14,22,38} However, regression analysis in our complete sample showed that only BMI z-score and not AHI, age, or gender approached significance as a predictor of log HOMA. Moreover, our study did not show that AHI was predictive of inflammation as measured by C-reactive protein. The subjects in our study had a high level of inflammation, likely due to their severe obesity compared with other study populations. This is consistent with several other studies that found that the BMI, and not measures of OSA, were the primary determinants of insulin resistance³⁹ and inflammation.⁴⁰

Our study is limited by a small sample size. Although we attempted to include all patients seen in the clinic, it is possible that selection bias is present, given that we captured about a third of patients seen in the clinic. Additionally, there was significant age heterogeneity. This resulted in large variation in the study data and a lack of power. Other factors pertinent to the relationship between sleep and metabolic factors, such as habitual sleep duration, were not precisely assessed. We had a heterogeneous sample in terms of race and ethnicity, but our small size did not permit determination of the influence of these factors. Moreover, these patients were moderately to severely obese, and had a high baseline inflammatory burden, as indicated by the marked elevation of C reactive protein. Such a high inflammatory burden likely masked the contribution of OSA. Thus, patients with a lesser degree of obesity paradoxically might have had a stronger relationship between fat distribution, OSA, and insulin resistance. We also did not observe the correlation between measures of cellular fat partitioning (S-IMCL[W]) and T-IMCL[W]) and insulin resistance observed by prior authors, which may have been a function of our small sample size. Additionally, although we did not seek to select subjects based on sleep symptoms, some selection bias may be present, as patients with subjective sleep complaints may have been more likely to participate in the study. Finally, the overall severity of sleep apnea was low in our sample, with oxygen desaturations being relatively rare and mild. Intermittent hypoxemia seems to cause insulin resistance in animals^{12,16} and humans,¹⁵ possibly through the generation of reactive oxygen species. Thus, the lack of frequent desaturations in our study population may explain the weak relationship between AHI and HOMA.

Our study showed that body fat distribution, as measured by the area of visceral adiposity at L4, is a strong predictor of obstructive sleep apnea and likely contributes to the relationship between obesity and OSA in children. Future research should be undertaken to understand the influence of fat distribution on lung function and upper airway collapsibility, and to look for proxy measures of visceral adiposity as a means to predict sleep apnea in obese children.

ABBREVIATIONS

OSA, Obstructive sleep apnea
BMI, Body mass index

LDL, Low density lipoprotein
HDL, High density lipoprotein
AHI, Apnea-hypopnea index
SpO₂, Peripheral oxygen saturation
MRI, Magnetic resonance imaging
MRS, Magnetic resonance spectroscopy
HOMA, Homeostasis model assessment
VAT, Visceral adipose tissue
SAT, Subcutaneous adipose tissue
TAT, Total adipose tissue
S-IMCL (W), Ratio of soleus intramyocellular peak to water peak
T-IMCL (W), Ratio of tibialis anterior intramyocellular peak to water peak

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