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Impact of Adenotonsillectomy on Insulin Resistance and Lipoprotein Profile in Nonobese and Obese Children

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BACKGROUND: OSA associates with insulin resistance (IR), hyperglycemia, and dyslipidemia consistently in adults, but inconsistently in children. We set out to quantify the impact of OSA treatment upon obesity and metabolic outcomes and thus assess causality.

METHODS: Sixty-nine children with OSA; mean age, 5.9 years (range, 3-12.6); 55% boys; and 68% nonobese (NOB) underwent baseline overnight polysomnography, anthropometric and metabolic measurements, adenotonsillectomy (T&A), and follow-up testing a mean 7.9 months (range, 2-20) later.

RESULTS: Fifty-three children (77% of study cohort; 91% of obese children) had residual OSA (apnea-hypopnea index $>$ 1 event/h) post-T&A. Fasting plasma insulin (FPI, 14.4 $\pm$ 9.4 $\rightarrow$ 12.6 $\pm$ 9.7 μIU/mL, $P = .008$), homeostasis model assessment-IR (3.05 $\pm$ 2.13 $\rightarrow$ 2.62 $\pm$ 2.22, $P = .005$), and high-density lipoprotein (HDL) (51.0 $\pm$ 12.9 $\rightarrow$ 56.5 $\pm$ 14.4 mg/dL, $P = .007$) improved despite increased BMI z score (1.43 $\pm$ 0.78 $\rightarrow$ 1.52 $\pm$ 0.62, $P = .001$); changes did not differ significantly between sexes or NOB and obese participants; however, post-T&A BMI z score rather than apnea-hypopnea index was the main predictor of levels of follow-up FPI, HDL, and other metabolic parameters. Higher baseline FPI and BMI-z predicted likelihood of residual OSA; conversely, on regression analysis, follow-up IR, HDL, and triglycerides were predicted by BMI z score, not residual OSA.

CONCLUSIONS: T&A improved IR and HDL, and residual OSA is predicted by baseline FPI and BMI z score, indicating a causal relationship; however, following T&A, residual metabolic dysfunction related to underlying adiposity rather than remaining sleep-disordered breathing. Finally, T&A cured OSA in $<$ 25% of all children and only 10% of obese children; post-T&A polysomnography is indicated to assess which children still require treatment.

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KEY WORDS: adenotonsillectomy; children; insulin resistance; lipids; OSA

ABBREVIATIONS: AHI = apnea-hypopnea index; CHAT = Randomized Controlled Study of Adenotonsillectomy for Childhood Sleep Apnea; CV = coefficient of variation; FPG = fasting plasma glucose; FPI = fasting plasma insulin; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; IR = insulin resistance; LDL = low-density lipoprotein; MetSyn = the metabolic syndrome; NOB = nonobese; PSG = polysomnography; T&A = adenotonsillectomy; T2DM = type 2 diabetes mellitus; TChol = total cholesterol; TG = triglyceride; TST = total sleep time

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The prevalence of pediatric obesity[1] and concomitant comorbidities, including type 2 diabetes mellitus (T2DM),[2] dyslipidemia, and the metabolic syndrome (MetSyn),[3] has increased in recent decades. Another common comorbidity of obesity is OSA, characterized by repetitive upper airway collapse during sleep, episodic oxyhemoglobin desaturations, and sleep fragmentation.[4] OSA in adults is associated with increased risk of insulin resistance (IR),[5,6] MetSyn,[7,8] and T2DM[6,7] and poorer glycemic control in adults with existing T2DM.[9-11] Similarly, OSA prevalence is greater among adults with T2DM[12] vs community-based cohorts.[13] Treating OSA in adults using CPAP improves IR, although the impact on glycemia is more unpredictable.[14] In children, the association of OSA with IR and MetSyn has been inconsistent: some studies have found that OSA increases risk of IR[15] and dyslipidemia,[16] whereas others have found that IR and MetSyn are primarily determined by obesity.[17,18] Most studies have examined associations rather than causal relationships. However, the few interventional studies of metabolic outcome in children with OSA after adenotonsillectomy (T&A, the gold standard pediatric OSA treatment) have had similarly contradictory results.[19-22] Thus, we set out to prospectively study a cohort of children with OSA and examine the contribution of OSA to IR, glucose homeostasis, and dyslipidemia independently of body habitus by assessing changes in metabolic and anthropometric parameters following T&A.

Materials and Methods

This was an observational study of otherwise healthy, habitually snoring children, and was approved by the University of Chicago Institutional Review Board Committee (protocol #09-115-B-AM029). Habitually snoring children ages 3 to 16 years who were found to have clinically significant OSA after baseline polysomnography were prospectively recruited. Children with chronic medical conditions (eg, genetic syndromes, craniofacial anomalies, chronic illnesses excepting well-controlled asthma on no controller medications) were excluded. Children receiving medications potentially affecting sleep, lipids, insulin, or glucose homeostasis (eg, systemic glucocorticoids within a month of the study) were also excluded. Informed consent and age-appropriate assent were obtained. In our center, all children undergoing evaluation for suspected OSA undergo anthropometric measurements (height and weight), overnight polysomnography (PSG), and fasting blood draw for insulin, glucose, and lipoprotein profile at baseline. Children who were found to have OSA (apnea-hypopnea index [AHI] $>$ 1.0 event/h) with adenotonsillar hypertrophy requiring T&A were approached for enrollment. Those who consented were recruited into the study, underwent clinical T&A, and returned for follow-up research PSG and anthropometric and metabolic evaluations.

Height was assessed via a wall-mounted stadiometer. Weight was assessed by electronic scale. BMI was calculated as BMI = kg/m^2. Age- and sex-adjusted standard scores (z scores) for BMI were calculated using Centers for Disease Control and Prevention 2000 growth chart reference data.[23] Participants with a BMI z score $\geq$ 1.64, corresponding to BMI $\geq$ 95th percentile for age and sex, were considered to be obese[24]; other children were classified as nonobese (NOB).

All participants underwent overnight PSG, conducted and scored as previously reported.[25] Sleep architecture, respiratory events, and arousals were scored using standard pediatric criteria.[26] Apneas were defined as $\geq$ 90% airflow decrement lasting at least two breaths, and hypopneas were defined as $>$ 50% decrement in nasal airflow accompanied by a 3% desaturation and/or an EEG arousal. Arousals were defined per the revised American Academy of Sleep Medicine guidelines[26]; arousal indices (arousals/h of sleep) were calculated. Children with AHI (number of apneas and hypopneas per hour of sleep) $<$ 1.0, $\geq$ 1, $<$ 5, and $\geq$ 5 events/hour total sleep time (TST) were deemed to have normal breathing during sleep, mild OSA, and moderate-severe OSA, respectively.[18] Only children with moderate-severe OSA were enrolled in this interventional study.

Following overnight PSG, participants underwent a fasting blood draw. Fasting plasma insulin levels were measured via solid-phase, two-site chemiluminescent immunometric assay (Immulite 2000; Siemens Healthcare Diagnostics), range 2 to 300 μIU/mL, intra-assay coefficient of variation (CV) $\leq$ 8.0%. Fasting plasma glucose (FPG) was measured via ultraviolet enzymatic method with hexokinase (Roche Cobas 8000 702 platform), range 10 to 1,200 mg/dL, CV $\leq$ 5%. High-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TChol), and triglycerides (TGs) were measured via homogenous enzymatic colorimetric assays (Roche Cobas 8000 502 platform). Analytical measuring range and assay CVs follow.

- TChol: range, 3.86 to 800 mg/dL; CV $\leq$ 1.6%.
- HDL cholesterol: range, 3 to 120 mg/dL; CV $\leq$ 1.5%.
- LDL cholesterol: range, 3.86 to 548 mg/dL; range $\leq$ 2.7%.
- TG: range, 8.85–885 mg/dL; CV $\leq$ 2 .0%.

TChol/HDL, LDL/HDL, and TG/HDL ratios were calculated, with higher values denoting greater cardiovascular risk.[27]

Calculated insulin sensitivity parameters included the following:

- Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as: fasting plasma index [FPI] (μIU/mL) × FPG (mg/dL)/405.[28]
- The McAuley index, a measure incorporating a weighted combination of FPI and TGs,[29] was calculated as: exp[2.63 – 0.28 ln(FPI in μIU/mL) – 0.31 ln(TG [mmol/L]). Lower values indicate greater IR.

Statistical analyses were performed using IBM SPSS Statistics v22.0 (IBM SPSS). Normality of distribution of continuous variables was assessed; skewed variables were natural log-transformed. Paired t tests or related samples Wilcoxon signed-rank tests were used to assess changes pre- and post-T&A in normally distributed and skewed variables, respectively. Because susceptibility to OSA-related

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metabolic sequelae could vary by obesity status and/or sex, independent sample *t* tests/Mann Whitney *U* test were used to assess differences among NOB and obese participants and among boys and girls of sleep and metabolic variables pre- and post-T&A and of the pre-post delta values; χ^2 analysis was used to compare categorical characteristics among residual OSA groups. Correlation coefficients were used to examine associations between residual AHI and pre-T&A metabolic measures of interest, including anthropometric and metabolic variables, to assess which would associate with residual OSA. Stepwise linear regression models were constructed to assess relationships between post-T&A AHI and metabolic measures. *P* value $< .05$ was used as the cutoff for statistical significance. Finally, subjects were divided into three groups of residual OSA severity (none, mild, and moderate-severe OSA), and χ^2 (categorical variables) and ANOVA/Kruskal-Wallis tests (continuous variables) were performed to ascertain how many in each group had improvement, no change, or worsening of the metabolic outcomes of interest.

Results

One hundred fourteen subjects with moderate-severe baseline OSA consented to participate in the study; of these, 69 children completed all pre- and post-T&A testing. There were no significant sex, race, ethnicity, age, BMI *z* score, metabolic, or PSG differences between those who completed all study visits and those who did not. Thirty-eight (55%) of study participants were boys, 50 (72%) were NOB at baseline, and 47 (68%) were NOB at follow-up (net three participants became obese in the interim). Fifty (72%) were Caucasian, 16 (23%) were African American, and seven (10%) were Hispanic. Baseline age, BMI *z* score, and baseline PSG measures are shown in Table 1, column 1. Participants returned for follow-up PSG and evaluation a mean of 7.9 ± 3.1 months (range, 2.2-12.2 months) post-T&A. Age, ethnicity, and baseline PSG variables did not differ among boys and girls or between NOB vs obese participants (data not shown); baseline metabolic variables differed as anticipated between NOB and obese participants, with higher glucose and insulin levels, higher HOMA-IR and lower McAuley index (signifying greater IR), trend toward higher TGs, higher total and LDL cholesterol, and lower HDL cholesterol in participants with obesity (e-Table 1).

Changes in OSA Measures Following T&A

Several PSG measures improved significantly following T&A (polysomnographic and age changes depicted in Table 1). Post-T&A PSG variables and pre-post changes in PSG variables were similar among boys and girls and NOB vs obese children (data not shown). Of note, although OSA improved significantly with surgery, the mean residual AHI post-T&A was still consistent with moderate OSA. Following T&A, 16 children (23% of study cohort; 14 NOB, two obese) had complete OSA resolution, whereas 53 (77% of study cohort) had residual OSA. Of these, 23 children (15 NOB, eight obese) had mild residual OSA and 30 (18 NOB, 12 obese) had residual moderate-severe OSA (AHI < 1, 1-5, and >5/h TST), although even in the moderate-severe OSA group (residual AHI > 5 events/h TST), mean AHI decline from 22.9 ± 15.6 to 5.9 ± 6.5/h TST. Proportions of NOB and obese participants did not differ among residual OSA subgroups (χ^2 $P = .21$), nor between those with and without residual OSA ($P = .12$). Proportions of boys vs girls in the residual AHI groups did not differ (data not shown).

Body Habitus and Metabolic Alterations Following T&A: Changes in metabolic parameters after T&A are shown in Table 2. BMI *z* score increased significantly,

TABLE 1] Age and Polysomnographic Measures Pre- and Post-T&A

Variable	Pre-T&A Value	Post-T&A Value	*P* Value	Mean Delta (Post-Pre T&A)
No.	69	69		
Age, y	6.33 ± 2.04 (3.8-12.2)	6.99 ± 2.05 (4.2-12.6)	< .0005	0.66 ± 0.26 (0.18-1.68)
AHI, events/h TST	22.2 ± 15.6 (3.6-70.3)[a]	5.9 ± 6.5 (0.2-34.6)[a]	< .0005[a]	−16.3 ± 16.4‡ (−69.5 to 20.9)
Lowest SpO_2, %	82.2 ± 7.4 (50-93)[a]	88.5 ± 6.9 (72-97)	< .0005[a]	6.3 ± 10.0 (−15.0 to 43)
Spontaneous ArI	9.9 ± 3.4 (1.6-24.4)[a]	12.1 ± 4.9 (1.8-36.4)[a]	< .0005[a]	2.2 ± 5.2 (−9.3 to 23.9)[a]
Respiratory ArI	5.5 ± 4.3 (0.1-26.5)[a]	1.4 ± 2.0 (0-13.0)[a]	< .0005[a]	−4.1 ± 4.7 (−25.9 to 7.3)[a]
Total ArI	16.4 ± 5.7 (6.9-39.1)[a]	12.0 ± 4.6 (2.8-37.4)[a]	< .0005[a]	−4.3 ± 7.0 (−28.2 to 12.9)[a]
Peak E_TCO_2	49.6 ± 5.5 (33.5-65.3)	47.3 ± 4.9 (36.5-62.3)	.009	−2.3 ± 7.0‡ (−14.8 to 26.4)

Data represent mean ± SD (range). AHI = apnea-hypopnea index; ArI = arousal index; E_TCO_2 = end-tidal CO_2; SpO_2 = oxyhemoglobin saturation; T&A = adenotonsillectomy; TST = total sleep time.
[a]Non-normal distribution by nonparametric testing.

TABLE 2] Changes in BMI *z* Score and Metabolic Variables Following T&A

Variable	Pre T&A Value	Post-T&A Value	*P* Value	Mean Delta (Post-Pre)
No.	69	69		
BMI *z* score	1.43 ± 0.78 (−1.29 to 4.45)	1.52 ± 0.62‡ (−0.74 to 4.17)	.001[a]	0.09 ± 0.88
Fasting plasma glucose, mg/dL	84.6 ± 9.0 (67-112)	82.3 ± 9.3 (57-103)	.21	−2.3 ± 11.9 (−32 to 30)
Fasting plasma insulin, μIU/mL	**14.4 ± 9.4 (2.0-49.0)[a]**	**12.6 ± 9.7 (2.0-45.0)**	**.008[a]**	−1.8 ± 10.5[a] (−27 to 32)
HOMA-IR	**3.05 ± 2.13 (0.39-11.25)[a]**	**2.62 ± 2.22 (0.28-11.11)[a]**	**.005[a]**	−0.43 ± 2.33[a] (−5.41 to 8.03)
McAuley Index	7.56 ± 1.73 (3.94-12.46)	8.06 ± 1.98 (4.36-13.17)	.053	0.50 ± 2.05 (−4.26 to 7.22)
Total cholesterol (mg/dL)	157.6 ± 31.2 (105-249)	155.5 ± 28.7[a] (118-269)	.60[a]	−2.1 ± 33.3 (−75 to 65)
Triglycerides, mg/dL	75.8 ± 23.4[a] (43-207)	77.6 ± 22.8[a] (45-179)	.54[a]	1.8 ± 30.0[a] (−121 to 103)
HDL cholesterol, mg/dL	**51.0 ± 12.9 (25-87)**	**56.5 ± 14.4 (25-91)**	**.007**	5.5 ± 16.1 (−29 to 54)
LDL cholesterol, mg/dL	108.8 ± 34.1 (39.9-216.3)	103.5 ± 31.1 (47.4-205.0)	.24	−5.2 ± 35.7 (−107.9-94)
TChol/HDL ratio	**3.31 ± 1.02 (1.57-5.79)**	**2.92 ± 0.96 (1.48-5.67)**	**.001**	−0.38 ± 0.95 (−3.32 to 1.10)
LDL/HDL ratio	**2.30 ± 0.99 (0.60-5.03)**	**1.98 ± 0.91[a] (0.59-5.69)**	**.012[a]**	−0.31 ± 1.01 (−3.45 to 2.69)
TG/HDL ratio	1.60 ± 0.78[a] (0.72-5.60)	1.51 ± 0.78[a] (0.56-4.97)	.093[a]	−0.09 ± 0.88‡ (−3.21 to 3.16)

Data represent mean ± SD (range). Numbers in bold are significantly different between the pre- and post-T&A conditions. HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; LDL = low-density lipoprotein; TChol = total cholesterol; TG = triglycerides. See Table 1 legend for expansion of other abbreviations.
[a]Non-normal distribution assessed by nonparametric test.

whereas FPI and HOMA-IR were significantly lower and McAuley index trended toward being higher, indicating improved IR. FPG did not change significantly. The degree of change in metabolic parameters did not differ between boys and girls or between NOB and obese study participants (data not shown). HDL was significantly higher and TChol/HDL and LDL/HDL ratios significantly lower, indicating more favorable lipoprotein profiles.

Predictors of Residual OSA: We examined associations between baseline age, BMI *z* score and metabolic parameters and post-T&A AHI to assess whether any baseline variable predicted posttreatment OSA (Table 3). FPI and HOMA-IR were strongly positively associated with post-T&A AHI; trends were seen toward associations between follow-up AHI and BMI *z* score and McAuley index. Correlation analyses between post-T&A AHI and anthropometric variables showed a trend toward association of post-T&A AHI with BMI *z* score ($r = 0.202$, $P = .096$), but no relationships with age,

TABLE 3] Associations Between Baseline Parameters and Residual AHI

Variable	AHI
Age, y	0.093
BMI *z* score	0.227 ($P = .061$)
Glucose, mg/dL	0.024
Insulin, μIU/mL	**0.263 ($P = .029$)**
HOMA-IR	**0.258 ($P = .033$)**
McAuley Index	−0.204 ($P = .092$)
TG, mg/dL	−0.111
TChol, mg/dL	−0.023
HDL, mg/dL	−0.159
LDL, mg/dL	0.029
TChol:HDL ratio	0.142
LDL:HDL ratio	0.144
TG:HDL ratio	−0.023

Data represent Spearman's rho correlation coefficients. Only *P* values of < .1 are reported. Numbers in bold represent significant correlations. See Table 1 and 2 legends for expansion of abbreviations.

TABLE 4] Demographic, Metabolic, and Sleep Results Across Residual AHI Groups

Variable	AHI 0-1/h TST: No OSA (n = 16)	AHI 1-5/h TST: Mild OSA (n = 23)	AHI >5/h TST: Moderate-Severe OSA (n = 30)
Baseline demographic, metabolic variables			
Baseline age, y	6.34 ± 2.03 (4.0-11.7)	6.14 ± 2.60 (3.8-16.2)	6.47 ± 2.34 (3.8-14.1)
Baseline BMI *z* score[a]	1.05 ± 0.72 (−1.01 to 1.94)	1.53 ± 0.96 (−1.29 to 4.45)	1.56 ± 0.52 (0.89-2.87)[b]
Baseline FPG, mg/dL	84.8 ± 9.5 (69-100)	85.8 ± 8.5 (68-101)	83.9 ± 9.1 (67-112)
Baseline FPI, μIU/mL[a]	10.3 ± 7.6 (2.0-27.0)	14.1 ± 8.1 (4.0-35.0)	16.2 ± 10.7 (4.0-49.0)
Baseline LN FPI	**2.04 ± 0.82 (0.69-3.30)**	**2.49 ± 0.60 (1.39-3.56)**	**3.59 ± 0.63 (1.39-3.89)**[c]
Baseline HOMA-IR[a]	2.20 ± 1.76 (0.39-6.53)	2.94 ± 1.65 (0.94-6.91)	3.46 ± 2.50 (0.78-11.25)
Baseline McAuley Index	8.47 ± 2.36 (5.66-12.46)	7.56 ± 1.69 (3.94-10.67)	7.28 ± 1.37 (5.13-10.26)[b]
Baseline TG, mg/dL[a]	77.9 ± 17.9 (43-116)	77.0 ± 35.5 (48-207)	73.2 ± 11.8 (55-105)
Baseline TChol, mg/dL	160.0 ± 34.2 (105-212)	153.5 ± 23.7 (110-198)	159.7 ± 31.0 (117-249)
Baseline HDL cholesterol, mg/dL	54.9 ± 13.1 (37-81)	50.7 ± 13.4 (34-87)	49.5 ± 12.4 (25-76)
Baseline LDL cholesterol, mg/dL	108.4 ± 38.7 (39.9-176.4)	103.9 ± 25.8 (58.8-167.0)	111.8 ± 37.3 (50.4-216.3)
Baseline TChol/HDL ratio	3.05 ± 0.93 (1.57-4.82)	3.30 ± 1.0 (1.64-5.11)	3.43 ± 1.09 (1.63-5.79)
Baseline LDL/HDL ratio	2.06 ± 0.96 (0.60-4.01)	2.25 ± 0.91 (0.68-4.28)	2.42 ± 1.07 (0.66-5.03)
Baseline TG/HDL ratio[a]	1.50 ± 0.59 (0.98-3.14)	1.66 ± 1.11 (0.82-5.96)	1.59 ± 0.54 (0.72-2.96)
Baseline sleep variables			
Baseline AHI, events/h TST[a]	20.3 ± 16.5 (6.2-70.3)	22.6 ± 18.0 (7.4-66.1)	22.9 ± 15.6 (3.6-45.8)
Baseline lowest SpO_2 (%)[a]	82.0 ± 7.0 (68-92)	81.7 ± 8.9 (50-93)	82.7 ± 6.6 (61-92)
Baseline spontaneous ArI, events/h TST[a]	9.7 ± 2.6 (5.3-13.3)	11.5 ± 4.1 (5.9-24.4)	8.9 ± 2.9 (1.6-14.3)[b]
Baseline respiratory ArI, events/h TST[a]	5.8 ± 5.7 (2.1-26.5)	5.9 ± 5.1 (0.1-25.3)	5.2 ± 2.4 (1.8-14.7)
Baseline total ArI, events/h TST[a]	16.3 ± 6.2 (10.6-37.6)	18.3 ± 7.2 (9.0-39.1)	15.0 ± 5.7 (6.9-23.0)
Post T&A demographic, metabolic variables			
Follow-up age, y[a]	6.98 ± 2.03 (4.8-12.5)	6.71 ± 2.62 (4.4-16.6)	7.2 ± 2.35 (4.2-14.8)
Follow-up BMI *z* score[a]	1.17 ± 0.62 (−0.74 to 1.96)	1.69 ± 0.69 (0.71-4.17)	1.57 ± 0.48 (0.93-2.82)[b]
Follow-up FPG, mg/dL	80.9 ± 7.5 (68-98)	84.7 ± 8.5 (65-100)	81.2 ± 10.6 (57-103)
Follow-up FPI, μIU/mL[a]	9.9 ± 7.1 (3.0-27.0)	14.1 ± 11.1 (2.0-45.0)	13.0 ± 9.9 (2.0-42.0)
Follow-up LN FPI	2.07 ± 0.67 (1.10-3.30)	2.40 ± 0.82 (0.69-3.81)	2.28 ± 0.80 (0.69-3.74)
Follow-up HOMA-IR[a]	1.99 ± 1.47 (0.64-5.80)	3.13 ± 2.66 (0.39-11.11)	2.61 ± 2.21 (0.28-10.37)
Follow-up McAuley Index	8.65 ± 1.91 (5.85-11.61)	7.78 ± 2.04 (4.94-11.69)	7.93 ± 1.99 (4.36-13.17)

(Continued)

TABLE 4] *(Continued)*

Variable	AHI 0-1/h TST: No OSA (n = 16)	AHI 1-5/h TST: Mild OSA (n = 23)	AHI >5/h TST: Moderate-Severe OSA (n = 30)
Follow-up TG, mg/dL[a]	**68.6 ± 12.9 (45-94)**	**80.6 ± 15.4 (45-111)**	**80.2 ± 29.7 (46-179)**[c]
Follow-up TChol, mg/dL[a]	148.2 ± 22.5 (122-206)	154.7 ± 22.1 (120-204)	159.9 ± 35.2 (118-269)
Follow-up HDL cholesterol, mg/dL	58.8 ± 12.8 (36-81)	55.5 ± 15.7 (25-85)	56.1 ± 14.7 (35-91)
Follow-up LDL cholesterol, mg/dL	98.2 ± 26.6 (64-160)	102.7 ± 31.5 (59-205)	105.7 ± 33.4 (47-178)
Follow-up TChol/HDL ratio	2.67 ± 0.82 (1.61-4.92)	2.02 ± 1.04 (1.76-5.67)	3.04 ± 1.00 (1.48-5.50)
Follow-up LDL/HDL ratio[a]	1.82 ± 0.82 (0.79-3.34)	2.06 ± 1.08 (0.83-5.69)	2.04 ± 0.87 (0.59-4.11)
Follow-up TG/HDL ratio[a]	1.26 ± 0.47 (0.56-2.05)	1.63 ± 0.80 (0.87-4.08)	1.57 ± 0.88 (0.65-4.97)
Post-T&A sleep variables			
Follow-up AHI, events/h TST[a]	**0.50 ± 0.22 (0.2-0.8)**	**2.52 ± 1.23 (1.0-4.9)**	**5.9 ± 6.5 (5.7-34.6)**[d]
Follow-up lowest SpO_2, %	**95.9 ± 1.0 (94-97)**	**90.6 ± 4.9 (77-97)**	**82.9 ± 5.2 (72-91)**[d]
Follow-up spontaneous ArI, events/h TST[a]	13.5 ± 2.9 (6.6-16.6)	12.3 ± 6.8 (3.7-36.4)	10.9 ± 4.0 (1.8-17.2)[b]
Follow-up respiratory ArI, events/h TST[a]	**0.2 ± 0.3 (0-1)**	**1.6 ± 1.6 (0-5)**	**2.0 ± 2.5 (0-13)**[d]
Follow-up total ArI, events/h TST[a]	12.1 ± 2.3 (6.7-14.7)	12.5 ± 6.5 (4.7-37.4)	11.3 ± 3.7 (2.9-21.9)
Change (delta) in age and metabolic variables, post-pre			
Delta age, y	0.64 ± 0.15 (0.4-0.88)	0.57 ± 0.25 (0.18-1.20)	0.72 ± 0.29 (0.20-1.68)[b] *f*
Delta BMI *z* score[a]	0.12 ± 0.16 (−0.07 to 0.54)	0.16 ± 0.45 (−0.40 to 2.0)	0.01 ± 0.17 (−0.45 to 0.41)
Delta FPG, mg/dL	−3.9 ± 14.8 (−30 to 29)	−1.0 ± 10.7 (−24 to 30)	−2.4 ± 11.3 (−32 to 21)
Delta FPI, μIU/mL[a]	−0.4 ± 4.3 (−9 to 6)	−1.0 ± 13.4 (−25 to 31)	−3.2 ± 10.8 (−27 to 32)
Delta LN FPI	0.03 ± 0.53 (−0.75 to 0.92)	−0.21 ± 0.99 (−2.6 to 1.79)	−0.32 ± 0.78 (−2.67 to 1.61)
Delta HOMA-IR[a]	−0.21 ± 1.19 (−2.5 to 2.02)	−0.06 ± 3.15 (−5.41 to 8.03)	−0.80 ± 2.17 (−5.16 to 5.93)
Delta McAuley Index	0.17+1.89 (−3.81 to 3.68)	0.54 ± 2.34 (−4.26 to 6.09)	0.66 ± 1.98 (3.90-7.22)
Delta TG, mg/dL[a]	−9.2 ± 24.6 (−62 to 31)	2.8 ± 34.5 (−121 to 52)	6.9 ± 28.4 (−31 to 103)[b]
Delta TChol, mg/dL	−11.5 ± 36.0 (−69.4 to 44.0)	1.5 ± 31.5 (−73.0 to 67.0)	0.2 ± 33.5 (−75.0 to 61.9)
Delta HDL cholesterol, mg/dL	3.8 ± 17.5 (−20 to 39)	5.2 ± 16.1 (−29 to 32)	6.6 ± 15.7 (−27 to 54)
Delta LDL cholesterol, mg/dL	−8.0 ± 30.1 (−58.6 to 36.7)	−2.0 ± 39.5 (−107.9 to 94)	−6.1 ± 36.4 (−82 to 70.8)
Delta TChol/HDL ratio	−0.38 ± 0.84 (−2.48 to 0.75)	−0.37 ± 0.96 (−3.32 to 1.10)	−0.39 ± 1.02 (−3.15 to 1.04)
Delta LDL/HDL ratio	−0.17 ± 0.67 (−1.65 to 0.85)	−0.28 ± 1.15 (−3.45 to 2.69)	−0.41 ± 1.06 (−3.23 to 1.54)
Delta TG/HDL ratio[a]	−0.25 ± 0.76 (−2.42 to 0.70)	−0.07 ± 0.96 (−3.21 to 2.04)	−0.03 ± 0.91 (−1.48 to 3.16)

(Continued)

TABLE 4 *(Continued)*

Variable	AHI 0-1/h TST: No OSA (n = 16)	AHI 1-5/h TST: Mild OSA (n = 23)	AHI >5/h TST: Moderate-Severe OSA (n = 30)
Change in sleep variables			
Delta AHI, events/h TST	**−19.8 ± 16.4 (−69.4 to 5.9)**	**−20.0 ± 18.1 (−63.7 to 3.7)**	**−11.5 ± 14.2 (−34.6 to 20.9)**[d]
Delta lowest SpO_2, %	**13.9 ± 6.8 (5.3-28.1)**	**8.9 ± 9.9 (−7.1 to 43.0)**	**0.2 ± 7.8 (−15.4 to 20.8)**[d]
Delta spontaneous ArI, events/h TST[a]	4.1 ± 3.2 (−1.4 to 10.0)	1.2 ± 7.4 (−9.3 to 23.9)	2.0 ± 3.7 (−6.4 to 11.4)[c]
Delta respiratory ArI, events/h TST[a]	−5.6 ± 5.7 (−25.9 to 1.5)	−4.3 ± 5.4 (−22.6 to 2.0)	−3.2 ± 3.3 (−25.9 to 7.3)
Delta total ArI, events/h TST[a]	−3.9 ± 6.8 (−27.7 to 0)	−5.4 ± 9.6 (−28.2 to 12.9)	−3.8 ± 4.6 (−12.4 to 4.7)

Data represent mean ± SD. Numbers in bold are significantly different between study participants across residual OSA groups. AI = apnea index; FPG = fasting plasma glucose; FPI = fasting plasma insulin; OAI = obstructive apnea index. See Table 1 and 2 legends for expansion of abbreviations.

[a]Non-normal distribution using nonparametric testing (Kruskal-Wallis).

[b]P between .05 and .1,

[c]$P < .05$, and

[d]$P < .01$ for ANOVA/Kruskal-Wallis comparisons across OSA groups.

insulin sensitivity, glucose levels, or lipid levels (data not shown). On stepwise linear regression models, FPI significantly predicted residual AHI, whereas BMI z score did not: model adjusted $R^2 = 0.086$, FPI β-coefficient = 0.315 ($P = .008$), and BMI z score β-coefficient = 0.17 ($P = .19$).

We also examined demographic, metabolic, and sleep parameters at baseline and at follow-up across the groups of subjects who had no OSA, mild OSA, and moderate-severe OSA on follow-up PSG (Tables 4, 5) to explore whether subtle baseline differences or postoperative metabolic markers might predict likelihood of residual OSA. We found a trend toward lower BMI z score pre-T&A in participants who exhibited complete OSA resolution (Kruskal-Wallis $P = .053$). Of baseline metabolic variables, only FPI differed, with lowest values in those who would go on to have OSA resolution and highest in those who would go on to have the most severe persistent OSA (Table 4, Fig 1A); a parallel trend was seen with McAuley index values, with highest values (denoting greatest insulin sensitivity) in those who would have no OSA on follow-up. No baseline PSG variables differed significantly among the post-T&A ad hoc groups. Post-T&A PSG variables differed significantly as anticipated: lowest AHI (the group defining criterion) and respiratory arousal index levels and highest oxyhemoglobin saturation nadir levels were seen in those without OSA. Post-T&A, TGs differed significantly among post-T&A OSA groups, with lowest levels seen in those with no OSA at follow-up, but with no differences among those with mild vs moderate-severe OSA (Table 4, Fig 1B); other post-T&A metabolic parameters, including FPI, did not differ among the groups. On regression analyses, follow-up BMI z score was found to be the primary predictor of post-T&A fasting insulin, HOMA-IR, McAuley index, TGs, and HDL; neither age nor post-T&A AHI was a significant predictor of any of these metabolic variables (data not shown).

Discussion

In this study, we found that T&A improved insulin sensitivity and HDL levels, but not fasting glucose or other lipoprotein levels despite a parallel increase in BMI z scores, suggesting that OSA is causally involved in creating an adverse metabolic state independent from obesity because the metabolic changes did not differ significantly between NOB and obese children or between boys and girls. Fasting insulin was most strongly associated with post-T&A AHI, such that more

TABLE 5] Residual OSA Group Comparisons: Percentage Improved, Unchanged, and Worsened

Variable	Delta (Δ) Indicating Significant Change Pre- vs Post-T&A	Residual AHI 0-1/h TST; No OSA (n = 16)			Residual AHI 1-5/h TST; Mild OSA (n = 23)			Residual AHI >5/h TST; Moderate-Severe OSA (n = 30)		
		% Better	% Worse	% No change	% Better	% Worse	% No change	% Better	% Worse	% No change
AHI	≥ 1.5 events/h TST	100	0	0	100	0	0	86.70	6.70	6.70
BMI *z* score	> 0.05	6.25	56.25	37.50	17.40	60.90	21.70	33.30	20	46.70
FPG, mg/dL	≥ 5 mg/dL	37.50	25	37.50	30.40	17.40	52.20	41.40	27.60	31.00
FPI, μIU/mL[a]	> 5 μIU/mL	6.25	18.75	75	38.10	14.30	47.60	36.70	16.70	46.70
HOMA-IR[a]	≥ 0.3	50	31.25	18.7%	57.10	19	23.80	65.50	20.70	13.80
McAuley Index	> 0.25	50	31.25%	18.75	42.10	31.60	26.30	60	26.70	13.30
Total cholesterol	> 10 mg/dL	37.50	31.25	31.25	31.80	36.40	31.80	43.30	23.30	33.30
HDL cholesterol	> 10 mg/dL	37.50	25	37.50	36.40	22.70	40.90	40	13.30	46.70
LDL cholesterol	> 10 mg/dL	53.30	33.30	13.30	33.30	33.30	33.30	43.30	26.70	30
TG	> 10 mg/dL	56.25	18.75	25	13.60	50	36.40	20	26.70	53.30
TChol/HDL ratio	> 0.4	37.50	6.25	56.25	42.90	23.80	33.30	50	23.30	26.70
TG/HDL ratio[a]	> 0.44	18.75	12.50	68.75	18.20	13.60	68.10	26.70	20	53.30
LDL/HDL ratio	> 0.3	33	20	46.70	47.60	23.80	28.60	58.60	27.90	13.80

Data represent percentages in each group experiencing a significant improvement, worsening, or no change in the outcome variable in question in each residual OSA group. See Table 1, 2, and 4 legends for expansion of abbreviations.

[a]Non-normal distribution assessed by nonparametric test.

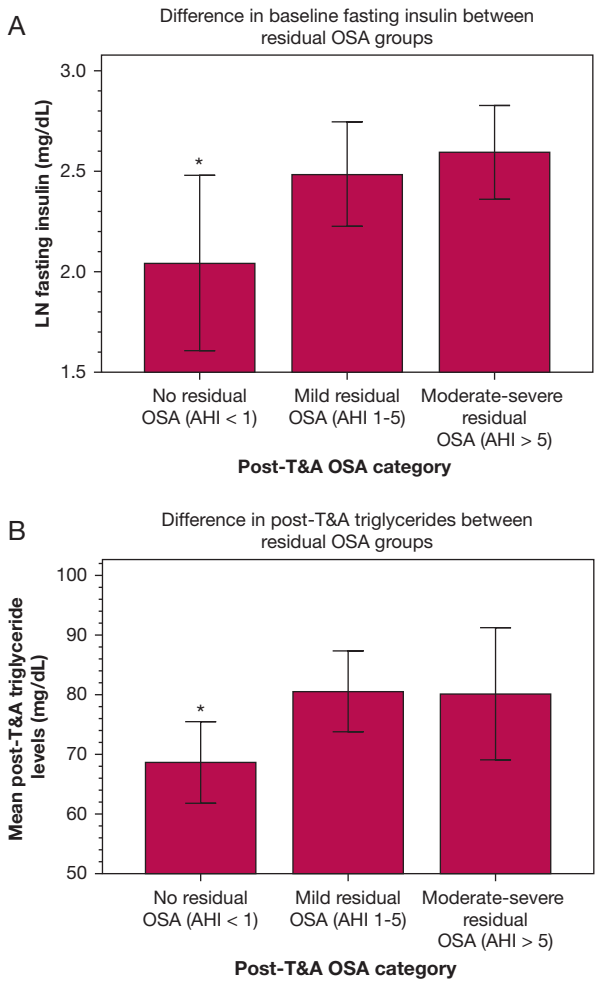

Figure 1 – *(A) Difference in baseline fasting insulin between residual OSA groups. (B) Difference in post-adenotonsillectomy (T&A) triglycerides between residual OSA groups. AHI = apnea-hypopnea index; LN = natural log. *P < .05 vs the other two groups.*

children with IR were more likely to have residual OSA. No baseline PSG variable predicted who would be at higher risk of having residual OSA at follow-up. Finally, although T&A ameliorated the severity of OSA, it was not highly efficacious at resolving OSA in a substantial proportion: only 23% of children studied (10% of obese and 30% of NOB) experienced full OSA resolution following T&A, and 43% (38% of NOB, 54% of obese) still had moderate-severe OSA.

OSA, Body Habitus, and Impact of T&A

Similar to previous studies,[30] more overweight children were at greater risk of residual OSA post-T&A. However, children with more significant residual OSA were less likely to gain weight after surgery compared with children with mild or no OSA. OSA can increase energy expenditure,[31] which improves following OSA treatment[32]; in children, OSA can even cause failure to thrive, and weight gain can improve following T&A.[32] Thus, it is unsurprising that excess weight gain can be exacerbated by effective OSA treatment.

Metabolic Changes Following T&A

Remarkably, despite the weight gain in our study cohort at follow-up, IR measures and HDL improved significantly post-T&A (these positive changes were seen even in the group with residual moderate-severe OSA, although it should be noted that OSA still improved considerably even in this group following T&A). These changes suggest that OSA per se directly affects metabolic homeostasis, although following T&A, residual IR and dyslipidemia were primarily determined by adiposity rather than AHI. Thus, the current study adds further to the list of contradictory pediatric studies focused on OSA and metabolic function, whereby some have reported significant associations between OSA and IR independently of obesity, whereas others have found no independent associations.[18,33] Studies examining the impact of OSA treatment upon metabolic derangements in children have been similarly contradictory; we previously reported improvements in TChol, HDL, and LDL in all children, but with TG and IR improvements only in obese children,[19] whereas other studies have found no improvements in IR.[22] The Randomized Controlled Study of Adenotonsillectomy for Childhood Sleep Apnea (CHAT) study, the largest pediatric study to date examining the effect of T&A on OSA in children, found no improvement in lipoproteins or other cardiometabolic markers in children 5 to 9 years of age with OSA undergoing T&A.[34] However, the CHAT study differed from ours in several ways: the age cutoff of the CHAT study was younger (up to 9 years in the CHAT study vs up to 12.6 years in ours), included a larger proportion of African American vs Caucasian children (53% African American and 35% Caucasian vs 23% African American and 72% Caucasian in our group.) The differences in age distribution between our study and the CHAT study may account for some of the discrepancies: younger children may be less likely to exhibit significant metabolic changes after T&A than older children. The difference in racial makeup of study participants may also be important: African American children are more likely to be IR than Caucasian children[35] and may be at higher risk for residual OSA[36] than Caucasians. Finally, the younger age group of the CHAT study means that the majority of participants were likely prepubertal or at most in early puberty; our study included adolescents of pubertal age. The distinction between prepubertal and pubertal status is

potentially critical because studies examining associations in adolescents as opposed to prepubertal children have consistently found associations between OSA and IR independently of obesity.[18,33,37] The endocrine milieu and body composition change considerably with puberty, accompanied by considerably increased IR[38] and increased TGs and lower HDL and LDL levels[39]; thus, relationships with risk factors such as obesity or OSA could certainly differ in prepubertal vs pubertal cohorts. The prevalent OSA phenotype also changes with puberty, with a decline in the proportion of OSA attributable to lymphadenoidal hypertrophy and a rise in the proportion of OSA phenotype more related to obesity.[40] Few studies of OSA's metabolic sequelae have separated prepubertal and pubertal children and formally assessed pubertal staging,[37] and no study of which we are aware has examined the impact of T&A on metabolic sequelae of OSA exclusively in adolescents.

Potential Predictors of Residual OSA

Of the factors examined, higher baseline insulin was most predictive of likelihood of residual OSA at follow-up, more than baseline BMI *z* score. In other studies examining metabolic changes in children with OSA following T&A, obesity,[30,41] AHI,[41] and older age[30,41] at diagnosis were associated with greater likelihood of persistent OSA[30]; this is the first study to our knowledge in which baseline insulin was identified as being predictive of likelihood of residual OSA. Classically, OSA is thought to alter insulin sensitivity and glucose homeostasis via sleep fragmentation[42] and intermittent hypoxia[43] that induce sympathetic activation,[44] catecholamine elevation, oxidative stress and inflammation,[45] increased glucocorticoid levels,[46] and adipose tissue hypoxia.[47] Our findings suggest that there may also be a reciprocal relationship, whereby IR helps maintain OSA independently of obesity. In adults, exercise can reduce the frequency of apneas independently of obesity, age or sex,[48] and women with polycystic ovary syndrome, a disorder of androgen excess in which IR is a key underlying anomaly, are more likely to have OSA than BMI-matched women without polycystic ovary syndrome,[49] supporting the possibility that IR per se could exacerbate OSA, although the degree to which this is additive to the effect of BMI following T&A is unclear. Future studies should explore whether IR predicts likelihood of OSA persistence in children following treatment, especially in a pubertal cohort.

Impact of T&A on OSA

Finally, we found that 77% of all children studied and 90% of those with obesity still had OSA following T&A. Our findings add to a growing body of literature reporting that, following T&A, many children still have residual OSA.[30,50] Although T&A remains the gold standard first line of treatment for pediatric OSA and indeed ameliorates OSA severity, it has now been repeatedly demonstrated that T&A is not curative for a substantial majority; postoperative PSG is therefore necessary to assess who still has OSA.[30,50]

Strengths and Limitations: Our study had a number of strengths. First, we examined potential causality by assessing metabolic changes after intervention aiming to improve or cure OSA and thus to assess the contribution of OSA to IR, hyperglycemia, and dyslipidemia independently of obesity. OSA diagnosis was based on the gold standard in-laboratory overnight PSG. We also studied several NOB children who are at lower a priori risk of IR and MetSyn and were able to evaluate the contribution of OSA to IR without the confounder of obesity. Our study also had several limitations. First, of the 114 children who initially consented to participate, only 69 returned for follow-up evaluation (approximately 60%); however, those who did not return for follow-up visits did not differ demographically, anthropometrically, metabolically, or in OSA severity from those who did return, so attrition is unlikely to have significantly biased our results. Also, the wide age distribution of our cohort could have affected interpretation of IR, hyperglycemia, and dyslipidemia, given the mixture of prepubertal and pubertal children. We also did not examine the participants' diet and physical activity pre- and post-T&A, and thus cannot exclude the possibility that some participants significantly changed their food intake patterns and overall activity lifestyle following T&A. Lymphadenoidal hypertrophy also has been found to decline in adolescence,[51] although adolescents with OSA vs without OSA are more likely to have adenotonsillar hypertrophy[52]; this variability may have affected how the underlying primary contributors to upper airway dysfunction impinge upon metabolic function. Furthermore, glycosylated hemoglobin was not examined, so the impact of OSA treatment on longstanding glycemia could not be assessed. Children who were found to have clinically significant OSA on follow-up PSG were offered CPAP as per clinical routine by their sleep medicine physicians; however, this was not part of our study and thus we do not have data regarding

the impact of CPAP on metabolic outcomes in children with residual OSA. The metabolic impact of CPAP in children should be examined in future studies. Finally, only 22 subjects were obese, limiting our power to assess for separate relationships between OSA and metabolic sequelae in this population.

In conclusion, we found that T&A significantly improved IR and HDL, and that baseline FPI predicted residual OSA independently from BMI *z* score, suggesting that IR may contribute to worsening of untreated OSA. Future studies are clearly needed to better delineate putative associations between OSA and IR, especially in the context of puberty onset and progression and its related changes. Finally, we found that OSA persisted following T&A in the majority of children, especially those with obesity; the high prevalence of remaining OSA post-T&A not only demonstrates that T&A is not fully efficacious at resolving OSA, but suggests that objective follow-up assessment of sleep-breathing patterns is indicated after adenotonsillectomy.

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Author contributions: L. K.-G. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and serves as guarantor for the manuscript. D. K., D. G., and L. K.-G. contributed to study design, data analysis, and writing the manuscript. M. F. P. and R. B. contributed to data acquisition and to revising the manuscript.

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Additional information: The e-Table can be found in the Supplemental Materials section of the online article.

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