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Obstructive Sleep Apnea and Hypoxemia are Associated with Advanced Liver Histology in Pediatric Non-Alcoholic Fatty Liver Disease

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Abstract

Objective—To determine if obstructive sleep apnea (OSA) and/or nocturnal hypoxemia were associated with the severity of liver injury in pediatric non-alcoholic fatty liver disease (NAFLD).

Study design—Obese children ages 10–18 years with liver biopsy proven NAFLD were enrolled. Demographic, clinical and laboratory data were collected, polysomnography performed, and liver histology scored. Subjects were divided into those with and without OSA/hypoxemia for analyses.

Results—Of 25 subjects with NAFLD, OSA/hypoxemia was present in 15 (60%) subjects (mean age 12.8 ± 1.9 years, 68% male, 88% Hispanic, BMI z score 2.3 ± 0.3). Subjects with and without OSA/hypoxemia had similar aminotransferases, serum lipids, inflammatory and insulin resistance markers. Although there were no differences between groups in histologic severity of steatosis, inflammation, ballooning degeneration, NAFLD Activity Score (NAS) or histologic grade, subjects with OSA/hypoxemia had significantly more severe hepatic fibrosis. Moreover, oxygen saturation nadir during polysomnography was related to hepatic fibrosis stage ($r = -0.49$, $p = 0.01$) and AST ($r = 0.42$, $p < 0.05$). Increasing % time with oxygen saturations $\geq 90\%$ was related to

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NAFLD inflammation grade ($r=0.44$, $p=0.03$), degree of hepatic steatosis ($r=0.50$, $p=0.01$), NAS ($r=0.42$, $p=0.04$), and AST and ALT ($r=0.56$ and 0.44 , $p=0.004$ and 0.03).

Conclusions—Moderate OSA/hypoxemia commonly occur in pediatric patients with biopsy proven NAFLD. OSA and the severity/duration of hypoxemia are associated with biochemical and histologic measures of NAFLD severity.

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathologic condition characterized by abnormal lipid deposition in hepatocytes in the absence of excess alcohol intake. It is the most common chronic liver disease affecting both children and adults and is associated with the obesity epidemic (1). NAFLD comprises a spectrum of diseases, ranging from isolated hepatic steatosis to non-alcoholic steatohepatitis (NASH), defined as steatosis, hepatocyte ballooning and inflammation, which can be associated with fibrosis and may progress to cirrhosis (1). NAFLD affects up to 9.6% of all children and 38% of obese children (2). Although isolated hepatic steatosis may have no significant consequences, NASH may progress to liver fibrosis and cirrhosis in about 20% of cases and is associated with hepatocellular carcinoma in adults (1, 3). Risk factors for pediatric NAFLD include Hispanic race, male sex, insulin resistance and obesity (4).

Obstructive sleep apnea (OSA), characterized by recurrent partial or complete upper airway obstruction during sleep, affects 1.2–5.7% of the general pediatric population (5–12). In addition, a relationship between obesity and obstructive sleep apnea has been shown in two large population based studies utilizing polysomnography (5, 10). Symptoms include daytime sleepiness, poor school performance and snoring, though many children are asymptomatic. Affected patients experience repeated episodes of nocturnal hypoxemia alternating with normoxia (so called chronic intermittent hypoxemia), resembling the pathophysiologic mechanisms involved in ischemia/reperfusion tissue injury (13, 14).

The relationship between NAFLD and OSA extends beyond their simple co-existence as obesity related co-morbidities. Obese mice fed a high fat and high cholesterol diet develop steatosis and, when exposed to chronic intermittent hypoxia, develop significant increases in ALT, hepatic inflammation and fibrosis (15, 16). Elevated serum aminotransferases are present in 20–50% of adults with OSA (11–13) and there is an increased prevalence of OSA in adults with NASH. In addition, morbidly obese adults with moderate to severe OSA and hypoxemia have more severe hepatic inflammation seen histologically than those with OSA without hypoxemia (17). Precious little, however, is known about the relationship of sleep disordered breathing and pediatric NAFLD. A single study from a selected sleep medicine clinic population reported that 91% of obese children with increased aminotransferases have OSA, although liver histology was not evaluated (18, 19).

Because of the potential that oxidative stress induced by hypoxia/re-oxygenation is a factor in the progression from fatty liver to NASH, this study was conducted to explore the relationship between pediatric NAFLD and sleep disordered breathing. We hypothesized that obstructive sleep apnea and/or nocturnal hypoxemia would be associated with the severity of biochemical or histologic evidence of liver injury in pediatric NAFLD.

Methods

Pediatric patients cared for at the Children's Hospital Colorado Pediatric Liver Center between June 2009 and January 2013 were enrolled if they had suspected NAFLD and were scheduled to undergo a clinically indicated liver biopsy (Figure 1; available at www.jpeds.com). In our center, NAFLD is suspected in overweight or obese children (Body Mass Index (BMI) > 85% for age and sex), with chronically elevated aminotransferases, who have negative screening for Wilson's disease, autoimmune hepatitis, viral hepatitis, and alpha-1 antitrypsin deficiency. Study subjects were males and females, ages 8 through 18 years, and Tanner stage 2–4. This Tanner stage range was chosen to minimize variations in insulin sensitivity that may confound the interpretation of potential associations between OSA/hypoxia and NAFLD. Subjects were excluded if they had Wilson disease, alpha-1-antitrypsin deficiency, viral hepatitis, autoimmune hepatitis, another known chronic liver disease or cholelithiasis, or if they received anti-convulsants, sedatives, oral or intravenous steroids, drugs that promote or reduce insulin resistance (including insulin sensitizers, thiazolidenediones and metformin), or medications known to induce hepatic steatosis (steroids, amiodarone or total parenteral nutrition) in the past 2 weeks. Additional exclusion criteria included current use of CPAP (continuous positive airway pressure), insulin dependent diabetes, regular tobacco or alcohol use, neuromuscular disorders, and genetic or craniofacial abnormalities. This study was approved by the Colorado Multiple Institutional Review Board and informed consent was obtained from parents/guardians and written assent from all subjects.

Demographic and medical history data, including results of clinical testing for autoimmune hepatitis, alpha-1-antitrypsin deficiency, Wilson's disease and viral hepatitis, and abdominal ultrasound or CT imaging, were obtained. Subjects were asked about clinical symptoms of sleep apnea (snoring, witnessed apnea, non-restorative sleep, and daytime sleepiness). Height, weight, waist and hip circumference were measured and BMI was calculated. BMI z scores were determined based on age and sex from data from the Centers for Disease Control and Prevention (20). Waist measurements were taken at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin. Hip measurements were taken at the fullest part of the hips.

Liver biopsies were performed for clinical indications by standard percutaneous technique. Liver histology (H and E and Masson's trichrome stain) was reviewed and scored by a single pediatric pathologist blinded to patient information. Biopsies with histologically confirmed NAFLD (defined as ≥ 5% of hepatocytes containing macrovesicular fat) were assigned a grade of necro-inflammation (0–3) and a stage of fibrosis (0–4) based on the standard histologic criteria of Brunt et al (21). Biopsies were also scored for the following criteria established by the NASH Clinical Research Network (22): steatosis (Grade 0 [$<5\%$ of hepatocytes containing macrovesicular fat], grade 1 [5–33%], grade 2 [34–66%], grade 3 [$>66\%$]); lobular inflammation (Grade 0 [no foci of inflammation], grade 1 [<2 foci per high powered field (HPF)], grade 2 [2–4 foci per HPF], grade 3 [>4 foci per HPF]); ballooning degeneration (grade 0 [none], grade 1 [few balloon cells], grade 2 [many/prominent balloon cells]). A NAFLD Activity Score (NAS) was calculated by summing the scores for steatosis, lobular inflammation and ballooning degeneration (22). Fibrosis was

scored as stage 0 [none], stage 1a [mild perisinusoidal], stage 1b [moderate perisinusoidal], stage 1c [portal/periportal fibrosis only], stage 2 [zone 3 and periportal], stage 3 [bridging fibrosis] and stage 4 [cirrhosis] (20). Subjects were also classified as either Type 1 (classic adult pattern), Type 2 (portal based) or an overlap of the two NASH histologic subtypes (23).

Subjects with histologically confirmed NAFLD underwent a standard multi-channel sleep study (polysomnogram), which was scored by a research trained technician and interpreted by a single sleep medicine physician, both of whom were masked to liver biopsy results. The following data were analyzed: total sleep time, percent REM sleep, apnea/hypopnea index (AHI), oxygen nadir, percent of time O_2 saturation (SpO_2) $\geq 90\%$ and $\geq 95\%$, end tidal carbon dioxide time > 50 mmHg, oxygen desaturation index (the number of SpO_2 drops below 95% by pulse oximeter), and arousal index. The presence of OSA was defined as an apnea/hypopnea index (AHI) > 1.0 , indicating total apneas and hypopneas per hour of total sleep time (24, 25). Apnea was defined as cessation of airflow over ≥ 2 attempted respiratory cycles and hypopnea was defined as a decrease in nasal pressure of $\geq 50\%$, with a corresponding decrease in oxygen saturation of $\geq 3\%$ and/or arousal. Hypoxemia was defined as $SpO_2 < 90\%$ for $\geq 1\%$ of total sleep time.

The morning following the sleep study, fasting blood specimens were obtained for ALT, AST, GGT, ultra-sensitive CRP, lipid profile (total cholesterol, triglyceride, HDL), glucose and insulin. Fasting glucose and insulin levels were used to estimate insulin resistance at baseline using the homeostasis model assessment of insulin resistance (HOMA-IR) (26).

Statistical analyses were performed using SAS 9.3 software (SAS Institute Inc, Cary, NC, USA). Descriptive statistics are presented in tables as either mean $\pm$ SD for continuous measures or percentages for categorical responses. Two sample t-test, chi square or Fisher exact test were used, as appropriate, to assess the difference between subjects with and without OSA/hypoxemia. Pearson correlation coefficient was used to quantify the correlations between ALT, AST and histologic parameters with polysomnographic parameters. Arcsine-root transformation was applied to proportional type polysomnographic data, such as percent time with $SpO_2 < 90\%$. Results, however, were presented in the original scale for ease of interpretation. A p value < 0.05 was considered statistically significant.

Results

Obese subjects with liver biopsy-confirmed NAFLD were studied ($n=25$). Their mean age was 12.8 ± 1.9 years, 17 were male (68%), 22 were Hispanic (88%), with a mean BMI z score of 2.3 ± 0.3 (Table). There were no differences in personal or family history of diabetes, hypertension, autoimmune disease, liver disease, OSA or obesity between subjects with and without OSA/hypoxemia (Table). Subjects with and without OSA/hypoxemia had similarly elevated aminotransferases, triglycerides, HDL, inflammatory markers and evidence of insulin resistance (Table). However, total serum cholesterol concentration was higher in those with OSA/hypoxemia ($p=0.03$). None of the subjects had evidence of gallstone disease on abdominal imaging.

Fifteen subjects (60%) met the study criteria for OSA and/or hypoxemia: 1 had isolated hypoxemia; 4 isolated OSA and 10 subjects had both OSA and hypoxemia. Those with confirmed OSA/hypoxemia reported more snoring ($p=0.045$), but otherwise had similar symptoms of sleep disordered breathing compared with those without OSA/hypoxemia (Table). Polysomnograms were of adequate length and time spent in REM sleep ($>12\%$ of total sleep time) to be considered valid studies, (Table) with mean total sleep time and percent REM sleep similar between both groups. Those with OSA/hypoxemia had a mean AHI score of 9.7 ± 7.8 versus 1.0 ± 0.7 in the group without OSA/hypoxemia ($p=0.0007$), indicating moderate to severe OSA in affected subjects. Subjects with OSA/hypoxemia also had significantly lower oxygen nadirs ($81.7 \pm 5.1\%$ versus $88.3 \pm 3.4\%$, $p=0.002$) and percent of sleep time spent with oxygen saturations less than 90% (3.5 ± 4.5 versus 0.4 ± 0.8 , $p=0.03$) compared with those without OSA/hypoxemia. These differences were not explained by differences in age, sex, ethnicity, BMI or clinical symptoms ($p=NS$).

Of the 25 enrolled subjects with NAFLD, 64% had definitive NASH (NAS = 5). There were no differences in the presence of OSA/hypoxemia between those with or without definitive NASH. Liver histology revealed no significant differences between those with and without OSA/hypoxemia in severity of steatosis, inflammation, ballooning degeneration, and NAS (mean NAS: 4.93 ± 1.2 versus 4.9 ± 1.1) or histologic grade (Figure 2, A). Subjects with OSA/hypoxemia, however, had significantly more advanced hepatic fibrosis than those without OSA/hypoxemia (Figure 2, B); 53% of those with OSA/hypoxemia had stage 2 or higher fibrosis compared with 10% of those without OSA/hypoxemia ($p=0.03$). There were no differences in the distribution of Type 1 versus Type 2 NAFLD pattern between those with and without OSA/hypoxemia.

We next examined the relationship (r values) between key polysomnographic measurements and AST and ALT in all enrolled subjects. A significant correlation was found between worsening oxygen nadir and higher AST ($r=-0.42$, $p=0.04$), with a trend towards a significant relationship with ALT ($r=-0.36$, $p=0.08$) (Figure 3, A and B). An increasing percentage of time with oxygen saturations $>90\%$ was associated with higher AST ($r=0.56$, $p=0.004$) and ALT ($r=0.44$, $p=0.03$) (Figure 3, C and D). There were no correlations between other results of the sleep study (AHI, arousal index) and either AST or ALT.

We next examined the relationship between polysomnographic measurements and histologic parameters. A significant correlation was found between NAFLD fibrosis stage and worsening oxygen nadir ($r=-0.49$, $p=0.01$; Figure 3, E) and a trend towards a significant relationship with percentage of time with oxygen saturations $>95\%$ ($r=0.37$, $p=0.08$). An increasing percentage of time with oxygen saturations $>90\%$ ($r=0.43$, $p=0.03$; Figure 3, F) and $>95\%$ ($r=0.46$, $p=0.02$) was significantly associated with NAFLD inflammation grade. An increasing percentage of time with oxygen saturations $>90\%$ ($r=0.40$, $p=0.05$) and $>95\%$ ($r=0.58$, $p=0.002$) was also significantly associated with degree of hepatic steatosis (Figure 3, G). Similarly, significant correlations were seen between NAS and increasing percentage of time with oxygen saturations $>90\%$ ($r=0.42$, $p=0.03$; Figure 3, H) and $>95\%$ ($r=0.53$, $p=0.01$). There were no correlations between the AHI, arousal index or oxygen desaturation index and histologic inflammation grade, fibrosis stage, degree of steatosis, ballooning or NAS.

Discussion

This study demonstrates that OSA and hypoxemia commonly affect pediatric patients with liver biopsy proven NAFLD. Histologic fibrosis was more severe in subjects with NAFLD with OSA/hypoxemia, compared with those without OSA/hypoxemia. Moreover, the severity and duration of hypoxemia were associated with both histologic measures of NAFLD disease severity and with elevated AST and ALT levels. These data suggest that the presence of OSA and severity and duration of nocturnal hypoxemia may be factors in the progression of NAFLD in obese children and adolescents. This is a plausible hypothesis inasmuch as hypoxia-reoxygenation is known to induce oxidative stress (27, 28), which has been associated with more advanced NAFLD in animal models and humans with NASH (29–32).

Relatively little is known about the relationship between obstructive sleep apnea and pediatric NAFLD. Verhulst et al (19) demonstrated a relationship between sleep disordered breathing and presumed NAFLD, based on the presence of obesity and elevated aminotransferases and/or a hyperechoic liver by ultrasonography. The Belgian children in this study, however, do not reflect the primarily Hispanic background of pediatric NAFLD patients in the United States (19). Kheirendash Gozal et al (18) studied a convenience sample of largely African American children being evaluated for snoring. In this study, 32% of obese children with OSA had elevated liver enzymes, and 91% of obese children with elevated aminotransferases had OSA. In both of these studies, elevated aminotransferases were primarily used to determine the presence of NAFLD, although NAFLD patients may have normal aminotransferases (18, 19). In addition, hepatic steatosis may be difficult to ascertain by ultrasonography in subjects with central adiposity; >30% hepatic fat may be necessary for detection using this imaging modality. Finally, these studies did not systematically exclude alternative causes of elevated ALT (18, 19). Our study expands upon existing knowledge by demonstrating a 60% prevalence of OSA/hypoxemia in patients with histologically confirmed pediatric NAFLD, all of whom had undergone a thorough evaluation for other liver diseases.

Liver biopsy remains the gold standard for both diagnosis and characterization of NAFLD disease severity. Studies in adult bariatric surgery populations examining the relationship between intra-operative hepatic histopathology and OSA have yielded mixed results (33–35). These studies focused on the obstructive component of sleep disordered breathing, characterized by the AHI. Kaallwitz et al (34) noted a higher AHI in patients with hepatic inflammation and fibrosis, but not with steatosis or ballooning degeneration. In a small cohort of subjects undergoing testing for sleep disordered breathing who subsequently underwent liver biopsy, Tanne et al (33) observed that severe OSA was independently associated with more severe steatosis, lobular necrosis and fibrosis. In contrast, Jouet et al (35) did not find a relationship between the AHI and steatosis, inflammation or fibrosis. Similarly, we did not find an independent association between AHI and degree of steatosis, inflammation, ballooning or fibrosis in pediatric NAFLD. Taken cumulatively, the relative importance of isolated airflow obstruction in the absence of hypoxia in NAFLD disease progression remains uncertain.

Intermittent hypoxemia may play a more critical role in the progression of NAFLD than simple airflow limitation. Verhulst et al (19) found a significant correlation between elevated ALT and both oxygen nadir and time spent with oxygen saturations <90% in overweight and obese children. We extend this observation, demonstrating significant correlations between both worsening oxygen nadir and time spent with oxygen saturations <90% and ALT and AST in children with biopsy proven NAFLD. Moreover, in morbidly obese adults undergoing bariatric surgery, an independent association was seen between markers of hypoxemia, including mean oxygen desaturations, oxygen nadir and oxygen desaturation index, and liver fibrosis (17, 36–38). Oxygen desaturations have also been associated with hepatic inflammation, hepatocyte ballooning and NAFLD Activity Score in other series of obese adults undergoing bariatric surgery (17, 37). Our findings in children with much lower degrees of obesity (mean BMI z score of 2.3 ± 0.3) demonstrate a significant inverse relationship between oxygen nadir and hepatic fibrosis. Moreover, the time spent with low oxygen saturations was strongly associated with NAFLD grade, steatosis and NAFLD Activity Score. As such, we demonstrate a relationship between nocturnal hypoxemia and more advanced liver histology in this exploratory analysis of pediatric NAFLD patients with non-morbid obesity.

Experimental evidence from animal studies supports a mechanistic role of hypoxemia in triggering progression from isolated fatty liver to NASH in children. In diet induced obesity models, mice repeatedly exposed to fluctuating ambient oxygen levels (to mimic oxyhemoglobin desaturations in humans) developed elevated aminotransferases, hepatic steatosis and hepatocellular swelling (15, 39). In addition, mice with hepatic steatosis exposed to intermittent hypoxia for 6 months developed significant liver fibrosis (15, 39). Furthermore, rodent models of NASH exposed to hypoxia demonstrate enhanced hepatocyte expression of genes involved in hepatic lipogenesis, including sterol regulatory binding proteins 1 (SREBP-1c) and peroxisome proliferator activated receptor-gamma (PPAR-gamma) and a decrease in genes involved in mitochondrial beta oxidation, including PPAR-alpha and carnitine palmitoyltransferase-1 (CPT-1)(40). These animal studies support the hypothesis that nighttime hypoxemia triggers pathways that may induce steatosis and oxidative stress, leading to more advanced liver disease in obese patients. Generated reactive oxygen species may further amplify liver injury by activating hypoxia inducible factor-1 (HIF-1), a transcriptional activator and master regulator of oxygen homeostasis during hypoxia and by up-regulating NFkB, with subsequent downstream induction of inflammatory pathways (41–44). Thus, nocturnal hypoxemia may be an important factor causing progression from isolated steatosis to NASH. Future studies in larger cohorts of patients are necessary to validate these novel findings.

Limitations of this study include the cross sectional study design, which precludes us from definitively establishing causality between OSA/hypoxemia and the severity of NAFLD. The small sample size of this study raises the possibility of type 2 errors in detecting relationships between OSA, hypoxia and severity of NAFLD. Although this largely Hispanic male cohort of subjects reflects the demographics of pediatric NAFLD in the United States, these findings may not be generalizable to other populations. In addition, our sample may be biased towards more severe liver disease as all enrolled subjects underwent liver biopsy for clinical indications that included chronic elevation of aminotransferases.

Future longitudinal studies will be needed to determine the effect of treatment of nocturnal hypoxemia on the severity of NAFLD.

In conclusion, our study demonstrates that OSA/hypoxemia is common in pediatric patients with liver biopsy proven NAFLD and is associated with more advanced liver injury and histologic disease. Further investigation into the impact that prevention or treatment of hypoxia may have on NAFLD patients is indicated.

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Abbreviations

NAFLD	Non-Alcoholic Fatty Liver Disease
OSA	Obstructive Sleep Apnea
NASH	Non-Alcoholic Steatohepatitis
NAS	NAFLD Activity Score
SaO₂	O ₂ saturation
HOMA-IR	homeostasis model assessment of insulin resistance
BMI	Body Mass Index

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Figure 1.
A CONSORT diagram of subject enrollment into the study.

Figure 2a.

Figure 2b.

Figure 2.

A, NAFLD inflammation grade was similar between subjects with and without OSA/hypoxemia. B, Subjects with OSA/hypoxemia had significantly more severe hepatic fibrosis than those without OSA/hypoxemia.

Figure 3.

Correlations between key polysomnographic parameters and AST, ALT, and liver histology in subjects with NAFLD. A, Lower oxygen saturation nadir correlated with higher AST. B, Lower oxygen saturation nadir trended to correlate with higher ALT. C, Greater time with SaO₂ < 90% correlated with higher AST. D, Greater time with SaO₂ < 90% correlated with higher ALT. E, Lower oxygen saturation nadir correlated with higher fibrosis stage. F, Greater time with SaO₂ < 90% correlated with higher inflammation grade. G, Greater time with SaO₂ < 90% correlated with higher degree of steatosis. H, Greater time with SaO₂ < 90% correlated with a more severe NAFLD Activity Score. Regression lines were calculated by arcsine-root transformation.

Table 1

Clinical, laboratory and polysomnographic findings in patients with NAFLD, with and without OSA/hypoxemia.

Clinical Parameter	OSA/hypoxemia (n=15)	No OSA/hypoxemia (n=10)	p value
Mean Age	12.6 ± 1.7	13.3 ± 2.2	0.36
Male sex	73%	60%	0.48
Hispanic Ethnicity	87%	90%	0.24
BMI (±SD)	33.9 ± 6.2	31.5 ± 5.0	0.28
BMI Z score (±SD)	2.4 ± 0.3	2.2 ± 0.3	0.11
Waist to Hip Ratio (±SD)	1.03 ± 0.06	0.98 ± 0.05	NS
Acanthosis Nigricans			
Neck	73%	90%	0.59
Axilla	60%	70%	0.37
Tonsillar Hypertrophy	83%	50%	0.24
History of Diabetes	0%	0%	1.0
History of Hypertension	7%	20%	0.54
ALT (IU/L)	121 ± 101	95 ± 61	0.49
AST (IU/L)	73 ± 51	60 ± 25	0.41
CRP (mg/dL)	2.8 ± 3.7	2.1 ± 1.3	0.46
Uric Acid (mg/dL)	7.0 ± 1.6	5.7 ± 1.5	0.08
Cholesterol (mg/dL)	156 ± 39	120 ± 40	0.03
Triglyceride mg/dL)	147 ± 80	135 ± 59	0.67
HDL (mg/dL)	38.5 ± 8.4	34.7 ± 7.5	0.26
Glucose (mg/dL)	89 ± 7	93 ± 10	0.36
HOMA-IR	9.6 ± 6.4	7.9 ± 9.1	0.59
Adiponectin (ug/mL)	5.8 ± 3.0	6.7 ± 2.8	0.45
Leptin (ng/mL)	31.8 ± 12.2	30.1 ± 11.7	0.76
Sleep Disordered Breathing Symptoms (% of subjects)	87%	50%	0.045
Snoring	47%	33%	0.68
Apnea/Gasping for Air	60%	56%	0.83
Restorative Sleep	53%	44%	0.67

Clinical Parameter	OSA/hypoxemia (n=15)	No OSA/hypoxemia (n=10)	p value
Pediatric Daytime Sleepiness Scale	13.9 ± 5.7	13.0 ± 7.1	0.75
Total Sleep Time (minutes)	385 ± 89	409 ± 55	0.45
% REM Sleep	20.9 ± 8.9	19.3 ± 4.4	0.62
Apnea Hypopnea Index (AHI)	9.7 ± 7.8	1.02 ± 0.74	0.0007
Oxygen Nadir	81.7 ± 5.1	88.3 ± 3.4	0.002
% Time SaO₂ <90%	3.3 ± 4.4	0.4 ± 0.8	0.03
Oxygen Desaturation Index	19.4 ± 29.9	3.1 ± 4.2	0.06
Arousal Index	7.1 ± 4.8	5.4 ± 2.6	0.34
End Tidal CO₂ >50 mm Hg	1.7 ± 5.5	0.13 ± 0.29	0.32

OSA: Obstructive Sleep Apnea; BMI: Body Mass Index; REM: Rapid Eye Movements; OSA: Obstructive Sleep Apnea.

The normal values for laboratory measurements are ALT: 10–45 IU/L; AST: 15–40 IU/L; CRP: <0.5 mg/dL; Uric Acid: 2.3–5.4 mg/dL; Cholesterol: 170 mg/dL; Triglycerides: 150 mg/dL; HDL <35 mg/dL; Glucose: 60–105 mg/dL; HOMA-IR: <2.60; Adiponectin: 3.5–14 ug/mL; Leptin: 2.0–5.6 ng/mL (41) (42).