Treating Obstructive Sleep Apnea and Chronic Intermittent Hypoxia Improves the Severity of Nonalcoholic Fatty Liver Disease in Children

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Objective To determine the effects of treating obstructive sleep apnea/nocturnal hypoxia on pediatric nonalcoholic fatty liver disease (NAFLD) severity and oxidative stress.

Study design Biopsy proven participants (n = 9) with NAFLD and obstructive sleep apnea/hypoxia were studied before and after treatment with continuous positive airway pressure (CPAP) for sleep disordered breathing, including laboratory testing and markers of oxidative stress, urine F(2)-isoprostanes.

Results Adolescents (age 11.5 ± 1.2 years; body mass index, 29.5 ± 3.8 kg/m^2) with significant NAFLD (mean histologic necroinflammation grade, 2.3 ± 0.9; fibrosis stage, 1.4 ± 1.3; NAFLD Activity Score summary, 4.8 ± 1.6) had obstructive sleep apnea/hypoxia by polysomnography. At baseline, they had severe obstructive sleep apnea/hypoxia, elevated aminotransferases, the metabolic syndrome, and significant oxidative stress (high F(2)-isoprostanes). Obstructive sleep apnea/hypoxia was treated with home CPAP for a mean 89 ± 62 days. Although body mass index increased, obstructive sleep apnea/hypoxia severity improved on CPAP and was accompanied by reduced alanine aminotransferase, metabolic syndrome markers, and F(2)-isoprostanes.

Conclusions This study provides strong evidence that treatment of obstructive sleep apnea/nocturnal hypoxia with CPAP in children with NAFLD may reverse parameters of liver injury and reduce oxidative stress. These data also suggest CPAP as a new therapy to prevent progression of NAFLD in those children with obesity found to have obstructive sleep apnea/nocturnal hypoxia. *(J Pediatr 2018;■■:■■-■■).*

Nonalcoholic fatty liver disease (NAFLD), characterized by excessive lipid deposition in hepatocytes in the absence of significant alcohol intake, is the most common liver disease affecting children and adults, paralleling the obesity epidemic.[1] NAFLD affects up to 10% of all children and 38% of children with obesity across a spectrum of disease, including isolated hepatic steatosis, nonalcoholic steatohepatitis (NASH; defined as steatosis, hepatocyte ballooning, and inflammation), and cirrhosis.[1,2] Although isolated hepatic steatosis may have no apparent consequences, NASH progresses to liver fibrosis and cirrhosis in about 20% of cases and is associated with hepatocellular carcinoma in adults.[1,3] Moreover, NASH is poised to surpass viral hepatitis as the leading indication for liver transplantation in adults.

Emerging evidence demonstrates that obesity-related obstructive sleep apnea and intermittent nocturnal hypoxia are associated with NAFLD disease severity and progression. Patients with obstructive sleep apnea experience repeated episodes of nocturnal hypoxia alternating with normoxia (chronic intermittent hypoxia), resembling the pathophysiology of ischemia/reperfusion injury.[4,5] Obese mice with diet-induced hepatic steatosis exposed to chronic intermittent hypoxia develop significant alanine aminotransferase (ALT) elevations and histologic evidence of hepatic inflammation and fibrosis.[6,7] Adult patients with NAFLD with obstructive sleep apnea have an increased prevalence of NASH and fibrosis, with the severity of sleep apnea associated with the severity of advanced fibrosis.[8] Furthermore, morbidly obese adults with moderate to severe obstructive sleep apnea and hypoxia have more severe hepatic inflammation than those without hypoxia.[9] Recently, pediatric patients with NAFLD and obstructive sleep apnea/hypoxia have also been shown to have

AHI	Apnea/hypopnea index
ALT	Alanine aminotransferase
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BMI	Body mass index
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
ΔAHI	Change in AHI after CPAP compared with baseline
HDL	High-density lipoprotein cholesterol
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic steatohepatitis
PDSS	Pediatric Daytime Sleepiness Scale
SaO_2	O_2 saturation

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more advanced liver disease and fibrosis than those without obstructive sleep apnea/hypoxia.[10,11] Obstructive sleep apnea/nocturnal hypoxia-induced oxidative stress, propagated through reactive oxygen species generation, promotes this progression of NAFLD in pediatric patients.[12]

The clinical signs and symptoms of obstructive sleep apnea/hypoxia include snoring, apnea, daytime sleepiness, tonsillar hypertrophy, and poor school performance. In children with suspected obstructive sleep apnea/hypoxia, an objective assessment with polysomnography is recommended to establish a definitive diagnosis.[13,14] Continuous positive airway pressure (CPAP) therapy is an effective therapy for obstructive sleep apnea because it treats upper airway collapse.[15] Given the increasingly recognized association between obstructive sleep apnea and progression of NAFLD, CPAP may offer a potential therapeutic option for patients with NAFLD. Although several observational studies of adults with NAFLD treated with CPAP for ≥3 months demonstrated a significant decrease in aminotransferases, 2 small prospective randomized controlled trials of CPAP for a short duration in adults with NAFLD did not demonstrate a benefit.[16-19] These contradictory studies suggest the need for additional studies to clarify the potential usefulness of CPAP for NAFLD treatment. Moreover, CPAP therapeutic trials in children with NAFLD and obstructive sleep apnea/hypoxia have not been reported.

This pilot study was conducted to determine the therapeutic effect of treating obstructive sleep apnea/nocturnal hypoxia with CPAP on disease severity in pediatric patients with NAFLD and the accompanying oxidative stress. We hypothesized that reversing obstructive sleep apnea and nocturnal hypoxia would improve biomarkers of NAFLD disease severity and decrease systemic reactive oxygen species generation.

Methods

We have previously characterized and published findings from a prospective cohort of children with biopsy-proven NAFLD and obstructive sleep apnea and/or chronic intermittent hypoxia.[10,12] Participants in this cohort were ages 8-18 years, Tanner stage 2-4 (to minimize variations in insulin sensitivity), and cared for at Children's Hospital Colorado between August 2009 and October 2015. They were excluded from the study if they had Wilson's disease, alpha-1-antitrypsin deficiency, viral hepatitis, autoimmune hepatitis, other known chronic liver disease or cholelithiasis, or use of anticonvulsants, sedatives, corticosteroids, drugs that promote or reduce insulin resistance (including insulin sensitizers, thiazolidinediones, and metformin), or other treatments known to induce hepatic steatosis (amiodarone or parenteral nutrition) in the past 2 weeks. Additional exclusion criteria included regular tobacco or alcohol use, insulin-dependent diabetes, neuromuscular disorders, and genetic or craniofacial abnormalities. In the current study, we report on a subpopulation of these children with liver biopsy–proven NAFLD and obstructive sleep apnea and/or chronic intermittent hypoxia who were treated with CPAP therapy. This study was approved by the Colorado Multiple Institutional Review Board and informed written consent was obtained from parents/guardians and written assent from all participants.

Demographic and medical history data, including results of clinical testing for autoimmune hepatitis, alpha-1-antitrypsin deficiency, Wilson's disease, and viral hepatitis, were obtained. Height and weight were measured and body mass index (BMI) was calculated. BMI z-scores were determined based on age and sex data from the Centers for Disease Control and Prevention.[20]

Each participant had undergone a liver biopsy performed for clinical indications by standard percutaneous technique before enrollment. Liver histology (hematoxylin and eosin, and Masson's trichrome stains) was reviewed and scored by a single pediatric pathologist blinded to participant information to confirm the presence of NAFLD (defined as ≥5% of hepatocytes containing macrovesicular fat) and assign a grade of necroinflammation (0-3) and a stage of fibrosis (0-4) based on the histologic criteria of Brunt et al.[21] Biopsy samples 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%], or grade 3 [(>66%]); lobular inflammation (grade 0 [no foci of inflammation], grade 1 [<2 foci per high-powered field], grade 2 [2-4 foci per high-powered field], or grade 3 [>4 foci per high-powered field]); ballooning degeneration (grade 0 [none], grade 1 [few balloon cells], or grade 2 [many/prominent balloon cells]. A NAFLD Activity Score (NAS) was then calculated by summing the scores for steatosis, lobular inflammation and ballooning degeneration.[22] Hepatic fibrosis was scored as stage 0 (none), stage 1 (mild to moderate perisinusoidal or portal/periportal fibrosis only), stage 2 (zone 3 and periportal fibrosis), stage 3 (bridging fibrosis), or stage 4 (cirrhosis).[22]

Participants were admitted to the Clinical Translational Research Center at Children's Hospital Colorado and underwent a standard multichannel sleep study (polysomnogram), performed by a registered polysomnographic technologist in accordance with our center's standard clinical practice. We used an Xltek headbox (Natus Medical, Inc, Pleasanton, California) and had 6 electroencephalograms, 2 electrooculograms, 3 chin electromyelograms, 2 lower extremity electromyelograms, and 2 electrocardiogram leads. Nasal pressure (BiNAPS, Salter Labs, Lake Forest, Illinois), oronasal flow (Airflow Sensor, Dymedix Diagnostics, Inc, Shoreview, Minnesota), abdominal and chest effort (SleepSense, Salter Labs, Lake Forest, Illinois), pulse oximetry (SET Pulse Oximeter, Masimo, Inc, Irvine, California), transcutaneous CO_2 (TCM TOSCA Monitor, Radiometer Medical, Carlsbad, California), end-tidal CO_2 (Capnocheck Sleep, Smiths Medical, Dublin, Ohio), snore microphone, and video were also recorded as part of our center's standard clinical practice for polymnography.

The following data were analyzed by a single sleep medicine physician who was blinded to liver biopsy results: total sleep time, percent rapid eye movement sleep, apnea/hypopnea index (AHI), oxygen nadir, and percent of time O_2 saturation (SaO_2) of ≤90%. The presence of obstructive sleep apnea was defined as an AHI of >2.0, indicating total apneas and

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