**INTRODUCTION**

Pediatric obesity (BMI >95th %) is an ongoing growing epidemic in the United States. Prevalence rates continue to rise, with most recent data highlighting that 26% of children in the US are affected [1]. For US teens between the ages of 16 - 19, 41.5% have obesity and 4.5% fall into Class III obesity (BMI >140th %) [1]. These children with severe obesity are at increased risk for many related comorbid conditions, including diabetes, hyperlipidemia, non-alcoholic fatty liver disease (NAFLD) and sleep related disorders such as obstructive sleep apnea (OSA) [2, 3]. Studies dating from 2002 outline the intricate relationship between sleep dysfunction and obesity. Recent research illustrates that sleep disruption leads to dysregulation of appetite, glucose intolerance, insulin resistance and elevation in blood pressure [4-10]. One model suggests this particular relationship is bidirectional [5, 7, 9] and that disruption in hormonal signals that control appetite and feeding behavior also result in sleep disturbance. Supportive data exists which outlines the association between OSA and obesity; a high prevalence of OSA is often found in patients with obesity, as well as the presence of obesity in many with OSA [7, 11]. Because patients with obesity are at increased risk for sleep disorders [5], addressing sleep-related concerns and improvement of sleep-related diagnoses can positively impact overall weight loss efforts. In this short case review, we highlight the importance of screening for sleep disturbances in a pediatric patient with obesity, conduct further evaluation to confirm the presence of pathology, and as OSA presents, consider how treating this comorbidity impacts the diagnosis of obesity.

**CASE PRESENTATION**

A 14 year old teenage boy initially presented to our weight management clinic with a BMI of 41 kg/m² (160th BMI%, Class 3 obesity).

Birth History: Maternal history was positive for gestational diabetes without insulin therapy. Birth weight was 8 pounds. The patient was formula fed with solids starting at age 6 months.

Weight History: Concerns regarding weight began between 5-7 years of age when his BMI percentile was noted to be 120%. The BMI percentile increased to the 160% at the time of presentation over a seven-year time frame with highest weight upon initial evaluation at our weight management clinic. Parents reported no hyperphagia at an early age; however they did note hunger and decreased satiety on a daily basis.

Sleep History: A thorough sleep history revealed a history of snoring and some daytime sleepiness. A sleep study was performed at age 7 years for snoring but negative for obstructive sleep apnea (OSA); tonsillectomy and adenoidectomy were performed at that time despite a negative sleep study. The patient went to bed at 10 pm and awakened at 6:30 am for school. There were no red flags on history in regards to night eating syndrome, sleep walking, or other mal-adaptive sleeping patterns.

Nutrition and Physical Activity History: The patient reported he ate when bored and had mild binging symptoms as measured on the Binge Eating Disorder scale. Large portion sizes (equivalent to 2 adults) were ingested with grazing on snacks.
The patient was in the 8th grade and an average student. He had several friends and liked fall sports. He lived with his parents and had 3 older siblings who were no longer living at home. There was a history of bullying when he was younger, though none presently.

Physical Examination: Physical examination revealed normal blood pressure and heart rate measurements as per gender and height. Initial weight was 252 pounds, height 66 inches with a waist circumference of 114 centimeters. BMI percentile was above the 95th percentile and had reached 160% by presentation. Pertinent findings on physical examination included nonsymetric facial appearance, central adiposity, and mild acanthosis nigricans.

Laboratory Findings: The patient had normal complete blood count and comprehensive metabolic panels, vitamin D-25-hydroxy level of 20 ng/mL with a mildly elevated fasting insulin level (26 uU/mL), normal blood sugar (93 mg/dL), Hemoglobin A1c (5.4%) and elevated triglycerides (163 mg/dL).

Assessment: This was a fourteen year old teenage boy with a history of tonsillectomy/adenoidectomy during childhood related to snoring (prior negative sleep study) presenting with worsening Class 3 severe obesity (initial BMI 160%) and early onset obesity-related comorbidities such as insulin resistance.

Plan: Initial intensive lifestyle therapy (ILT) goals focused on reducing added sugars and replacing sugar sweetened beverages with water or zero sugar flavored water; goals were successfully attained. Minimal change though was noted in BMI percentile after 6 months. A trial of a lowcarbohydrate (CHO) dietary pattern was implemented led by the clinic’s dietitian; leading to a BMI reduction of 39 (decrease in BMI percentile to the 155th percentile). Despite initial success, BMI returned to baseline. Three months later, a 50 gram low carbohydrate dietary plan was agreed upon with supportive handouts and guides provided. At this point, the patient faced his maximum weight of 274 pounds, height now 67 inches, BMI 43 kg/m² and waist circumference 120 centimeters.

At the two month follow up, the patient showed a positive response to this plan, with BMI down to 39 kg/m². During the review of systems at this appointment, our patient reported feeling tired and getting to bed later. Sleep hygiene was reviewed again with a low threshold for sleep study. However, during next few months the patient continued with sleep issues. Symptoms included daytime fatigue, falling asleep during car rides, yawning throughout visits, and difficulty staying awake during classes with screen in bedroom. A repeat sleep study was thus attained and it showed an apnea hypopnea index (AHI) of 4.5 events/hour indicating moderate to severe sleep apnea. Continuous positive airway pressure (CPAP) was recommended and begun; patient reported waking after titration feeling rested – which he stated he had not felt in many years.

Three weeks after starting CPAP, weight decreased down to 15.4 lbs., dropping his BMI to 38 (140%). Two months later with continued CPAP, weight decreased an additional 9lbs, BMI 36.2 (130%), Class 2 obesity. During subsequent follow-up, our patient continued to report improved energy, focus and attention since using CPAP with improved body composition (increased fat free mass [FFM] and decreased percent body fat). Repeat labs showed normalization of fasting insulin (8 uU/mL), fasting blood sugar (86 mg/dL), hemoglobin A1c (5.3%), and lowering of triglycerides. To date, the patient always demonstrated compliance with his CPAP machine if sleeping away from home; engagement and openness during visits were notably improved. At his most recent visit, the patient had lost an additional 23 pounds with a current weight of 231 pounds, height 68 inches, BMI 35.2, 122%BMI % and waist circumference 99 cm (decrease from 110 cm) with a waist/height ratio of 0.57. Figure 1 depicts his BMI chart over time.

**DISCUSSION**

Obesity continues at epidemic proportions, impacting more than 23 million children and adolescents [1]. Obesity, along with its many related comorbidities, negatively impacts the health and wellbeing of our youth. Along with treating obesity, awareness of obesity related comorbidities with their screening and treatment can improve outcomes.

The management and treatment of pediatric obesity is particularly challenging. Understanding of the disease process and underlying etiology of weight gain is highly relevant in clinical practice and cannot be overstated. The above case highlights a novel approach to weight management in children where in addition to nutrition and physical activity, sleep and stressors are assessed and repair of altered sleep patterns led to significant weight loss and improvement in overall quality of life and medical comorbidities, independent of other factors. In our case presented here, we continued to work on foundational ILT goals, providing a modified dietary pattern implementing a low CHO plan. With these measures in place, we did see some improvement in the patient’s BMI percentile. We also continued to screen for related health concerns. Recurrence of obesity-related medical comorbidities can recur despite negative testing in the past. In the above case, the patient already had a negative polysomnogram during childhood with a surgical tonsillectomy and adenoidectomy. However, this diagnostic testing was done several years ago and more thorough screening and attention to details on history coupled with poor to modest response to initial weight loss efforts alerted the clinical team on likely missed obstructive sleep apnea and persistence of symptoms in the absence of treatment.

Obstructive sleep apnea (OSA) is defined as repeated periods of prolonged upper airway obstruction during sleep with continued or increased respiratory effort which can result in hypoxia, hypercapnia and fragmented sleep [7, 12]. Patients
with obesity are at increased risk for OSA. The gold standard for diagnosis of OSA remains nocturnal polysomnography (sleep study). The American Academy of Pediatrics (AAP), the American Academy of Sleep Medicine (AASM) and the American Academy of Otolaryngology-Head and Neck Surgery provide further guidelines on treatment and management [7, 13, 14]. In adults, a sleep study is positive if the AHI (apnea hypopnea index) is > 5 events/hour. In pediatric patients (defined as children and adolescents < 15 years of age), the criteria are more stringent. In this population, AHI >1 event/hour is considered abnormal. AHI is further classified as mild (AHI 1-1.5 events/hour), moderate (AHI1.5-5 events/hour) and severe (AHI >5 events/hour) [7].

Multiple mechanisms have been described to explain the increased risk of OSA in patients with obesity. Of interest in this case review is the relationship between the obesity, hunger and satiety cues, and insulin resistance coupled with sleep disturbance. Obesity is characterized by dysregulation of the appetite regulating hormones that influence central processing centers in the brain signaling fat storage, increases in insulin and leptin resistance. A disruption in the system, such as sleep disturbance, is manifested behaviorally (increase in hunger or decrease in satiety) though it is biologically and physiologically driven. These changes may contribute to the persistence and development of OSA and vice versa. Some data postulates that OSA itself creates a state of increased insulin resistance, dyslipidemia, hypertension, and inflammation [7, 15-19]. In the case, the patient’s hunger and satiety cues improved and binging symptoms abated when CPAP treatment was initiated.

Data suggests that intermittent hypoxemia and sleep fragmentation of OSA contributes to the obesogenic state [7, 16, 17]. Additional studies in adults highlight that OSA impairs insulin sensitivity; in children, this association is stronger in patients with coexisting obesity. Treatment of OSA in adults with CPAP has been shown to improve insulin sensitivity [15, 20, 21]. The chronic intermittent hypoxia (CIH) impacts the autonomic nervous system, end organs (liver, pancreas, muscle, and adipocytes) as well as the impact of inflammation on the immune system with resultant complex perturbations in these pathways. These changes on visceral white adipose tissue (vWAT) are referred to as the “hypoxia theory” [15, 22]. Chronic intermittent hypoxia [CIH] also reduces adiponectin, a protein secreted by adipocytes, which increases basal and insulin-stimulated glucose uptake and increases fatty acid uptake and oxidation, as well as increases mitochondrial mass and oxidative capacity. Low adiponectin is associated with obesity, increased risk of non-alcoholic fatty liver disease, atherosclerosis, hypertension, and endothelial dysfunction [22, 23]. This is additive to CIH on pancreatic beta cell function – where this hypoxia causes beta cell apoptosis and diminished beta -3 adrenergic receptor mediated insulin secretion [15, 24].

Additionally, human studies considering sleep fragmentation and appetite regulation outline that in adults and children with OSA, OSA alters food preferences towards fat and carbohydrates and reduced satiety. This suggests OSA changes leptin signaling that results in reduced satiety, increased cravings for high-energy foods [15, 25-27]. Overall, we see over-activation of the
sympathetic system in favor of insulin resistance [28]. In mice models, chronic sleep fragmentation contributes to hyperphagic behaviors in the awake phase and increase in fat mass and obesity. These data define that these perturbations are mediated by increased endoplasmic reticulum stress in the hypothalamus and tyrosine-protein phosphatase non-receptor type-1 mediated resistance to the hypothalamic leptin receptor, with decreased leptin signaling inspite of elevated leptin levels [15, 29, 30]. This is consistent in obesity where both insulin and leptin resistance are present.

For our patient, reviewing the past negative polysomnogram and history of adenotonsillectomy did present a challenge to repeating the study. As highlighted in Narang et al., up to 50% of patients with obesity and OSA will continue to have OSA status post adenotonsillectomy [7, 31, 32]. Additionally, obtaining prior authorization from the patient’s insurance did require diligence and work on the part of our clinical coordinator. Frequently, not only are we faced with the challenge of access to and coverage for these studies, but also, compliance with the treatment, CPAP, itself. This requires dedicated time to fully review these points with patients and families openly and in a supportive manner. In our case, our patient responded well, particularly due to the improved sleep he experienced for himself during his titration study.

Of importance is the fact that our patient lost considerable weight with significant improvement in BMI percentile when CPAP treatment was begun. Addressing and understanding the etiology of obesity, and in this context its relation to sleep disruption, can successfully increase weight loss efforts [7, 15, 33]. Since the presence of obesity and its interrelated maladaptive sleep hygiene patterns lead to inflammation, weight gain, and metabolic derangements, treatment of both simultaneously can result in weight loss and improvement in metabolism through an additive and synergistic manner. In children, OSA has also been linked to endothelial dysfunction that is an early marker of atherosclerosis [34, 35] and hence treatment might potentially reverse this phenomenon. Guidelines outlined in Pediatrics for management of OSA [14] suggest weight loss as a treatment; furthermore, prompt initiation of CPAP is indicated while weight loss efforts are implemented and continued.

In conclusion, we have highlighted that treating the co-existing sleep disorder, OSA, may in fact aid in weight loss efforts. Though adjunctive intensive lifestyle therapy to treat pediatric obesity showed modest stabilization in weight gain for the patient, we noted significant improvements in BMI percentile once the actual etiology of obesity, sleep disruption, was addressed. Complex hormonal physiology affects the energy regulatory system and hormonal changes occur when dysregulated sleep improves once the initial disruption is addressed. Finally, because children with severe pediatric obesity are afflicted with early-onset related comorbidities, rigorous screening and prudent attention to details on history for missed diagnoses and recurrence or persistent pathological symptoms are warranted at any stage of treatment.

REFERENCES

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