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The Shifting Relationship Between Weight and Pediatric Obstructive Sleep Apnea: A Historical Review

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Objectives: For more than a century, pediatric obstructive sleep apnea (OSA) was associated with failure to thrive. However, that association has faded over the last few decades. A 21st century child with OSA is much more likely to be overweight than underweight. This raises the question: Has pediatric OSA changed over time, or has the rise of childhood obesity in the United States created a new, separate disease? This literature review explores the historical shift in the relationship between weight and OSA, and the associated changes in treatment.

Results: We demonstrate a clear transition in the prevalence of failure to thrive and obesity in the OSA literature in the mid-2000s. What is less clear is whether these two clinical phenotypes should be considered two distinct diseases, or whether subtle differences in one set of pathophysiologic pathways—adentonsillar hypertrophy, altered inflammation, and increased energy expenditure—can lead to divergent metabolic outcomes. More research is needed to fully elucidate the pathophysiology of OSA in children with obesity.

Conclusions: We may need new and different treatments for obesity-associated OSA as adenotonsillectomy—which is effective at reversing failure to thrive in OSA—is not as effective at treating OSA in children with obesity. One option is drug-induced sleep endoscopy, which could personalize and improve surgical treatment of OSA. There is some evidence that therapies used for OSA in adults (e.g., weight loss and positive airway pressure) are also helpful for overweight/obese children with OSA.

Key Words: Obstructive sleep apnea, obesity, failure to thrive, weight loss, positive airway pressure, adenotonsillectomy, drug-induced sleep endoscopy.

INTRODUCTION

Although obesity is by far the strongest risk factor for developing obstructive sleep apnea (OSA) in adults, the relationship between weight and OSA has not been well characterized in children. OSA in children classically results from adenotonsillar hypertrophy and has been associated with impaired growth and weight gain. This can present as failure to thrive (FTT) in the most severe cases. However, the pediatric population has not been spared from the obesity epidemic; over the past 20 years, children with OSA have increasingly resembled their adult counterparts—overweight or obese rather than underweight.

It is challenging to define the pathophysiology of OSA when the same condition can lead to such radically different metabolic derangements. Could there be two distinct pathophysiologic states of OSA in children? Some studies have even proposed dividing pediatric OSA into type I and II, analogous with type I and type II diabetes. This question has been debated since at least 2005, with no consensus reached in the literature yet. This question has a great deal of practical significance, as obese children may have more severe OSA than nonobese children, and may not respond as well to traditional treatment, namely adenotonsillectomy (T&A).

In this review of the literature we explore the history of OSA in children, specifically focusing on when obesity began playing a larger role. We also investigate the pathophysiology of these two phenotypes of OSA. Lastly, we discuss implications these differences have on treatment, namely whether we must search for more efficacious options for obese children.

RELATIONSHIP BETWEEN FAILURE TO THRIVE AND OSA

Although there are many definitions of FTT, weight under the 5th percentile is the most agreed-upon indicator. Many studies have suggested a causal relationship between adenotonsillar hypertrophy and FTT by demonstrating that children gain weight following T&A, often achieving normal growth. Several mechanisms have been proposed to explain the link between OSA and FTT, including low calorie
intake due to dysphagia, increased energy expenditure due to work of breathing at night, and interrupted nocturnal growth hormone secretion. However, a 1994 study found no change in caloric intake pre- and postoperatively, casting doubt on the role of dysphagia. The same study found that children's sleep energy expenditure was significantly decreased post-T&A, accompanied by weight gain. However, another study found no difference in sleep energy expenditure between 24 children with and without OSA, and no correlation between energy expenditure and severity of OSA. In a related study, Bland et al. found no significant difference in total energy expenditure between 11 children with OSA and controls before or after surgery.

The theory of interrupted nocturnal growth hormone has received the greatest attention. Growth hormone is secreted in a pulsatile, circadian rhythm that peaks at night. When secreted it stimulates insulin-like growth factor (IGF-1), the major mediator of somatic growth. IGF-1 increases significantly with postoperative OSA resolution. A meta-analysis of 20 studies found significant increases in weight and IGF-1 levels postoperatively. Tarasiuk et al. studied rodents with upper airway obstruction, which demonstrated interrupted sleep, and decreased secretion of growth hormone–releasing hormone and impaired growth.

### Timeline of Shift in BMI Associated with OSA

The first documented case of improved growth after T&A in a child with FTT was in 1893. Thus, it is possible obese OSA (manifesting as FTT) was treated with T&A as early as the 1800s. Although T&A was performed throughout the 20th century to promote weight gain (which later became problematic with the obesity epidemic), it was not until 1976 that pediatric OSA was formally recognized. The relationship between OSA and FTT was further explored in the 1980s by Guillemaintal et al., who studied 50 children with OSA, half of whom had FTT. A 1982 case study noted that relief of airway obstruction resulted in rapid catch-up growth. Similarly, another case study in 1987 found two children resumed normal growth velocities after T&A. Yet, although the focus of research at this time was on children with FTT, even then there were rare cases of obese children with OSA.

Throughout the 1990s children with OSA were still largely underweight. A 1992 study found that of 34 patients with OSA, only four were obese, whereas 15 weighed under the 10th percentile. Bonuck et al. reviewed seven studies of children presenting for T&A and one study of children presenting for overnight polysomnography from 1982 to 2003, and found that the incidence of FTT was two times higher than expected in six out of eight studies. In 2006, Bonuck et al. also conducted their own pilot study of 28 patients presenting for T&A, and found that 18% met either weight or height criteria for FTT, with 7% meeting both criteria. Of note, 32% of their study were obese.

In the mid-2000s the evidence regarding the relationship between body mass index (BMI) and OSA became mixed. One 2006 study examined 400 children referred for overnight polysomnography and found no correlation between obesity and OSA. However, in 2007, Mitchell and Kelly demonstrated that apnea-hypopnea index (AHI) scores were higher in obese children compared to normal-weight children. A large 2008 review found that although more obese children were referred for snoring or polysomnography, there was no relationship between weight and incidence of OSA, suggesting a possible referral bias based on the adult phenotype. They found a great deal of inconsistency among the 27 studies, with around half of the studies reporting a significant relationship between obesity and sleep-disordered breathing. This relationship was more prevalent in older children. Another 2008 review of 14 studies found significant methodologic issues in studies examining the relationship between weight and OSA. For instance, several studies used patient- or parent-reported measurements, which can be inaccurate, and several studies failed to normalize BMI for age and sex. They found that eight studies reported a positive, and possibly direct, relationship between weight and OSA severity. However, four of these studies had relatively narrow and high age ranges, potentially limiting the generalizability of their findings.

After the mid-2000s, however, the relationship between OSA and obesity in children became consistent in the literature. A 2012 study evaluated OSA severity in 197 children divided into four groups: underweight, normal weight, overweight, or obese. Obese children had the highest AHI scores. However, underweight children had the second highest. The NANOS (Prevalence of Sleep Apnea/Hypopnea Syndrome in Obese Children) study was the first prospective study of obese children in a community-based population. Among 248 obese children, the prevalence of OSA was 39.5%, establishing pediatric obesity as a major risk factor for developing OSA.

It is also around this time that the discussion of FTT as a consequence of OSA largely disappears from the literature, apart from mentions for its historical significance. The only recent study to more directly address FTT is a 2014 study examining anthropometric changes after tonsillectomy. They found only 14 of 464 children had FTT at baseline. It is possible that as OSA became recognized as a potential cause of FTT, interventions could be made before children progressed to FTT.

### Relationship Between Obesity and OSA

Although there is higher prevalence of OSA in children with obesity, the relationship is not straightforward. There is inconsistent evidence linking the degree of obesity or fat distribution and the severity of OSA indicating other factors at play. The picture is further complicated by overlap between the pathophysiology of OSA in children with obesity and FTT. For instance, obstruction due to adenotonsilar hypertrophy is common to both. Among 495 children both obese and not, there was a positive correlation between tonsil grade and

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interleukin-8, were significantly increased in obese children compared to nonobese children.31 However, there is conflicting literature on the interaction between obesity and adenotonsillar hypertrophy. A 2009 study found that although adenotonsillar hypertrophy is correlated with severity of OSA in nonobese children, this trend was not present for obese children.28 Furthermore, they found less adenotonsillar hypertrophy in obese children at any given level of AHI compared to nonobese children.28 However, Mallampati scores, which estimate airway crowding, were higher in obese children, indicating sources of obstruction beyond adenotonsillar hypertrophy. Arens et al. used magnetic resonance imaging to compare the airway structure and body fat composition between obese children with or without OSA.27 They found that children with OSA had larger adenoids, tonsils, and retrophyaryngeal nodes, with a resulting 28% decrease in oropharynx size. Whereas the size of upper airway lymphoid tissues was significantly correlated with the severity of OSA, BMI was not correlated to the size of these tissues, suggesting lymphoid proliferation in OSA may be independent of obesity.

Another way in which the pathophysiologies overlap is inflammation. Several studies have proposed that OSA in both adults and children is a disease of inflammation.32–35 Intermittent airway obstruction places mechanical stress on mucosa that promotes local airway inflammation, as well as systemic overexpression of proinflammatory cytokines.36 Adenotonsillar tissues in children with OSA have increased concentration of inflammatory cells and cytokines compared to children who had T&A for tonsillitis.33 As obesity is also a systemic inflammatory disease,32 it may exacerbate this process. In adults, the airway concentration of inflammatory markers, such as intercellular adhesion molecule 1 and interleukin-8, were significantly increased in obese patients with and without OSA, compared to nonobese patients with OSA.35 There was a positive correlation between BMI and these markers. A 2010 review in children found that OSA and obesity are independently associated with high levels of various inflammatory markers; this was further increased in children with both OSA and obesity.32

Another question being asked is whether there is a reciprocal relationship between obesity and OSA. The TuCASA (Tucson Children’s Assessment of Sleep Apnea Study) study, a large longitudinal cohort study, demonstrated that children with persistent OSA were at greater risk for developing obesity.37 This appears to contradict the previously discussed theories and evidence that OSA causes increased energy expenditure and hormonal changes leading to FTT. However, one thought is that in some, the increased energy expenditure in sleep may trigger overly compensatory hormonal changes to increase hunger and energy intake. A recent systematic review of energy balance in adults with OSA found both increased resting metabolic rate, as well as high leptin resistance and ghrelin levels that would be expected to cause decreased satiety and increased hunger.38 However, there are little data on children. One 2010 study found that obese children with OSA had higher ghrelin levels and unhealthier diets and physical activity, compared to nonobese children with OSA and obese children without OSA.39 A 2014 study found that OSA, independent of weight, leads to impaired exercise tolerance due to cardiovascular dysfunction, which could further contribute to obesity.40

In obese adults there is evidence that fat deposition at specific sites contributes to the development of OSA. This can lead to increased collapsibility of the upper airways, as well as decreased chest compliance and functional residual capacity.41 However, at this time there are no data on children.

**TREATMENT OF OSA IN OBESE CHILDREN**

In recent years, the effectiveness of surgical treatment for obese children with OSA has been scrutinized. Despite initial improvements in AHI, several studies have discovered persistent symptoms in obese children after T&A.42,43 There are several possible explanations for this. Although weight gain after T&A was once celebrated when children were underweight, it has become problematic now that children with OSA are increasingly obese. Though tonsillectomy does not increase the odds of being overweight or obese,44 children who were overweight or obese before surgery still often gain weight, or at least fail to lose weight, after surgery.7,45 Thus, T&A does not address the obesity component of OSA when present. Additionally, although T&A improves the AHI scores in obese children, it does not decrease C-reactive protein levels, which suggests it may not reduce the underlying chronic inflammation.46 Thus, there has been a recent push to address these underlying mechanisms over traditional surgical interventions.47 Although several studies have shown efficacy of anti-inflammatory agents like montelukast and budesonide in short-term treatment of OSA, no studies have looked at their efficacy in obese children or over longer periods of time.48–50

T&A may be less effective in children with obesity; however, it can be curative and improve comorbidities in some.45,51 Thus, there may be a role for more individualized surgical treatment. One way to optimize surgical success may be through drug-induced sleep endoscopy (DISE). DISE, first introduced in the 1990s by Croft and Pringle, offers direct visualization of upper airway obstruction in conditions similar to natural sleep.52 DISE can provide crucial diagnostic information about a child’s unique phenotype of disease. A recent study examining DISE findings in children with persistent OSA post-T&A found obese/overweight children were more likely to have obstruction at the tongue base, and adenoid regrowth than normal/underweight children.53 Gazzaz et al. found 76% of obese children had pharyngeal collapse during DISE.54 These data can have important implications for surgical management. In 2014, Boudewyns et al. found
DISE changed management in 24% of patients, and identified alternate sites of obstruction in 57%. They reported a 91% success rate of OSA resolution post-T&A.\(^5\) Similarly, a 2017 study found DISE changed the surgical plan in 35% of patients and revealed an alternate diagnosis in 54%; however, they did not report their success rate.\(^5\) He et al. reported mean AHI and oxygen saturation nadir improved after DISE surgery in children with persistent OSA post-T&A.\(^5\)

Though DISE has great potential, several limitations need to be addressed. The first challenge is defining the optimal candidates and timing of DISE. Some common indications for DISE include obesity, severe OSA, Down syndrome, OSA without tonsillar hypertrophy, and craniofacial anomalies.\(^5\) Currently, the most agreed-upon use of DISE is in a child with residual OSA after T&A.\(^5\)

However, some institutions perform DISE immediately pre-T&A to minimize the cost and inconvenience of general anesthesia, and to potentially identify other obstructions and procedures to perform.\(^5\) On the other hand, some argue that T&A changes airway dynamics, and thus, preoperative DISE results may not be applicable postoperatively. Additionally, there is no universal pediatric DISE scoring system in place, limiting the consistency of reported findings and the subsequent management decisions made based upon DISE results.\(^5\)\(^5\) Currently, the VOTE system (velum, oropharynx, tongue base, epiglottis) is most commonly used and involves qualitative evaluation of these four sites on a scale from no obstruction to total collapse. However, there are other proposed systems that include parameters, such as evaluation of the nasopharynx and subglottis, overall severity, and whether an obstruction is fixed or dynamic.\(^5\)

Continuous positive airway pressure (CPAP) has been used to treat residual OSA in children after T&A since 1986.\(^5\) CPAP has been shown to effectively reduce AHI in children,\(^5\) and treat some of the morbidities associated with OSA in obese children, such as hypertension and hyperlipidemia.\(^6\)\(^6\)\(^1\) Additionally, a randomized sham-controlled trial found that 12 weeks of CPAP usage in adults significantly increased IGF-1, and pulsatile and total growth hormone levels.\(^6\)\(^6\)\(^1\) However, CPAP usage in children is limited by adherence.\(^6\) Children often suffer from a suboptimal mask fit as a result of their rapid growth.\(^6\) Common complaints include nasal congestion or rhinorrhea, eye irritation, skin ulceration, and discoloration.\(^6\)\(^6\)\(^1\) More concerning is the risk of altered facial growth.\(^6\)\(^6\)\(^1\) Thus, further research is needed to determine safe and effective ways to implement CPAP as a treatment for pediatric OSA.

Another possible option for children who cannot tolerate CPAP is the nasal insufflation (NI), which delivers warm humidified air via the nasal cannula. The first evidence comes from a 2015 study of five children with OSA who did not tolerate CPAP.\(^6\) All children, including four with severe symptoms (AHI > 15/hr), experienced significant improvement in AHI after treatment with NI.\(^6\) These results were confirmed by a small study in 2017 of 10 overweight/obese children with OSA who were CPAP intolerant.\(^5\) All children tolerated NI, and two children had complete resolution of their OSA, whereas the others experienced a significant decrease in AHI.\(^5\)

Finally, we ask whether the obesity component of OSA can be reversed through weight loss. There are relatively few studies, and the majority have been on surgical weight loss in adolescents with class III obesity (BMI > 40). These results have been impressive. A retrospective review of 19 obese adolescents demonstrated an average reduction in AHI from 20.5/hr ± 6.9/hr to 1.9/hr ± 0.6/hr at 1 year.\(^6\)\(^7\) A small study of seven obese adolescents found rapid improvement of AHI, with a decrease by 9.2 events/hr in 3 weeks.\(^6\)\(^8\) There has been one study that looked at surgical weight loss in prepubertal children (ages 5–12 years).\(^6\)\(^9\) They found improved OSA symptoms as measured by the Pediatric Sleep Questionnaire responses, that was sustained at 3 years postoperatively.\(^6\)\(^9\) One 2009 study looked at sleep-disordered breathing in a diet- and exercise-based weight loss program.\(^7\) Of the 21 participants who had a follow-up sleep study, 62% had reduction of symptoms.

**CONCLUSION**

It is both interesting and challenging to conceptualize how the manifestation of OSA has changed so drastically over a relatively short time. No data tell us exactly when, but within the past 10 years there has been a clear swing in the conversation about the metabolic consequences of OSA. After this point, FTT fades from the literature, and the link between OSA and obesity is no longer debated. As a result, we now have to delve deeper into the pathophysiology of OSA. Although OSA in children is still a result of airway obstruction, disturbed inflammation, and hormonal imbalance, there are details missing.

We also have to critically examine the one-size-fits-all T&A approach to treating OSA, and be clear with patients and their families regarding their expectations and the possibility of further care after surgery. Though traditional treatments may be less effective, we may be able to adapt them using cutting-edge diagnostic tests like DISE. Because this phenotype of pediatric OSA resembles OSA in adults, it is intuitive that physicians have turned toward the mainstays of treatments in the adult population: weight loss and CPAP. Although data are limited, there appears to be promising evidence, particularly for weight loss. Therefore, there is a need for a concerted multidisciplinary approach to pediatric OSA involving nutrition and exercise counseling. As the story of pediatric OSA involves more than just obstruction from the adenoids and tonsils, we need to consider a more
holistic approach to treat the whole child. With the obesity epidemic showing no signs of slowing down, it is clear that the treatment of pediatric OSA must continue to adapt.

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