HIGHLIGHTED TOPIC  |  Pulmonary Physiology and Pathophysiology in Obesity

Childhood obesity and obstructive sleep apnea syndrome

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Arens R, Muzumdar H. Childhood obesity and obstructive sleep apnea syndrome. J Appl Physiol 108: 436–444, 2010. First published October 29, 2009; doi:10.1152/japplphysiol.00689.2009.—The increasing prevalence of obesity in children seems to be associated with an increased prevalence of obstructive sleep apnea syndrome (OSAS) in children. Possible pathophysiological mechanisms contributing to this association include the following: adenotonsillar hypertrophy due to increased somatic growth, increased critical airway closing pressure, altered chest wall mechanics, and abnormalities of ventilatory control. However, the details of these mechanisms and their interactions have not been elucidated. In addition, obesity and OSAS are both associated with metabolic syndrome, which is a constellation of features such as hypertension, insulin resistance, dyslipidemia, abdominal obesity, and prothrombotic and proinflammatory states. There is some evidence that OSAS may contribute to the progression of metabolic syndrome with a potential for significant morbidity. The treatment of OSAS in obese children has not been standardized. Adenotonsillectomy is considered the primary intervention followed by continuous positive airway pressure treatment if OSAS persists. Other methods such as oral appliances, surgery, positional therapy, and weight loss may be beneficial for individual subjects. The present review discusses these issues and suggests an approach to the management of obese children with snoring and possible OSAS.

metabolic syndrome; sleep-disordered breathing

OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS) as a clinical entity in children was first described in the 1970s (44). The condition refers to a breathing disorder characterized by recurrent, partial, or complete episodes of upper airway obstruction, commonly associated with intermittent hypoxemia and sleep fragmentation (5). Since the original report, at least four clinical phenotypes associated with OSAS in children have been recognized. Although the pathophysiological mechanisms leading to each phenotype are not fully understood, it appears that anatomic factors restricting the upper airway and neuronal factors increasing the collapsibility of the upper airway are important mechanistic contributors and are distinctly different in each phenotype (13).

The first phenotype is associated with adenotonsillar hypertrophy (14). This phenotype has also been noted to be associated with increased upper airway collapsibility (62, 87). It affects ~2% of normal children between the ages of 2 and 8 yr (8, 104) and may lead to significant neurocognitive deficits and cardiovascular dysfunction if untreated (10, 41).

The second phenotype is associated with craniofacial malformations and syndromic conditions such as Down syndrome and Pierre-Robin syndrome. Children with this phenotype may present with OSAS soon after birth. The mechanism leading to this form of OSAS is primarily related to alterations in craniofacial skeletal size restricting the space for soft tissue growth and airway size. However, deficits in upper airway neuronal control may also contribute to the increased upper airway collapsibility in some syndromes. The prevalence of OSAS in these children varies and depends on the specific syndrome.

The third phenotype is associated with primary neuromuscular disorders such as Duchenne muscular dystrophy and spinal muscular atrophy. Although many of these children do have evidence of OSAS per se, others may have sleep-disordered breathing (SDB) in the form of hypoxemia and hypoventilation without frank obstructions (29). SDB in children with neuromuscular disorders is mostly related to decreased upper airway muscle tone and/or altered chest wall mechanics leading to hypoventilation, particularly during rapid eye movement sleep (29, 35). Children with neuromuscular disorders may present with SDB and/or OSAS at any time during childhood, according to the severity and progression of the disorder.

The fourth phenotype is associated with obesity (66). Previous reports have associated obesity from early infancy to late childhood obesity with OSAS (59, 81, 82, 106, 117), but the the emerging epidemic of obesity has refocused attention to this phenotype in children today. The prevalence of OSAS in obese children seems to exceed that of any other phenotype and may increase the risk by more than fourfold (104). However,
many questions remain unanswered regarding the pathophysiological mechanisms leading to OSAS in obesity and why only some of these children have OSAS while others do not. This review will focus on the obese phenotype of childhood OSAS.

THE EPIDEMIC OF OBESITY

The prevalence of obesity among children in the United States in the past 30 yr is continuously rising and has reached epidemic proportions. Obesity is a true threat to the individual and our society and has been described as a potential cause for the decline in life expectancy during the 21st century (94). Data from the National Health and Nutrition Examination Survey (1976–1980 and 2003–2006) (48, 92, 93) have shown that the prevalence of obesity in children between 2 and 5 yr increased from 5.0% to 12.4%, children between 6 and 11 yr increased from 6.5% to 17.0%, and children between 12 and 19 yr increased from 5.0% to 17.6%. Moreover, in some regions of the United States, the prevalence is much higher. In a recent survey from 2002–2003, 31% Hispanic and 23% African-American children in New York City were found to be obese (91a, 91b).

Even as the epidemic of childhood obesity becomes a global problem (131), its cause is not completely understood. Simple measurements of food intake and physical activity do not explain all of an individual’s risk for obesity (64). Thus, other putative mechanisms include the following: maternal gestational weight gain, breastfeeding duration, and short sleep duration in early childhood (31, 72). Obesity affects children in many ways and may induce psychological, neurological, endocrine, cardiovascular, respiratory, gastrointestinal, and orthopedic abnormalities (80). In recent years, “metabolic syndrome” has been shown to be an important manifestation of obesity in children. It encompasses a cluster of metabolic and cardiovascular abnormalities such as dyslipidemia, hypertension, insulin-resistant diabetes, and prothrombotic and inflammatory states and may play an independent role in the pathophysiology of OSAS in children as well (102).

OBESITY AS A RISK FOR CHILDHOOD OSAS

Guilleminault et al. (45) reported that 10% of children diagnosed with OSAS were obese. Marcus et al. (83) reported that 46% of unselected obese children undergoing polysomnography had OSAS, and Silvestri et al. (118) reported OSAS in 59% of obese children referred for the evaluation of SDB. Similarly, Kalra et al. (61) reported that 55% of morbidly obese children undergoing bariatric surgery had evidence of OSAS. Although the prevalence of OSAS in obese children seems to be very high, the true prevalence of the disorder in the general obese population cannot be ascertained from the above studies, which were performed on small and selected obese populations. However, a recent population-based study (104) involving 399 children between 2 and 18 yr of age found that obesity was the most significant risk factor for OSAS, with an odds ratio of 4.5. The reason for such a high prevalence of OSAS in obese children compared with the 2% reported in the general population remains unknown. However, it may be related to a different underlying phenotype distinguishing it from OSAS in nonobese children and/or an augmented effect on known causative factors resulting from the obese phenotype.

PATHOPHYSIOLOGY OF OSAS IN OBESE CHILDREN

Anatomic factors. Adenoid and tonsillar hypertrophy limiting upper airway size are a well-known cause of OSAS in nonobese children (14). Similarly, several investigators have emphasized the role of such hypertrophy in obese children with OSAS (19, 83, 120, 129, 136), and a recent study (34) has suggested that 45% of obese children with OSAS have evidence of adenotonsillar hypertrophy. In this regard, in 2002, the American Board of Pediatrics (4) suggested that adenotonsillectomy be the first line of treatment for obese children with OSAS. However, after adenotonsillectomy, residual OSAS persists in ~50% of obese children (90) compared with 10–20% in nonobese children (123, 124). Such a difference suggests that additional anatomic or functional factors may also contribute to OSAS in these children.

The frequency of adenotonsillar hypertrophy in obese children is striking. Therefore, mechanisms leading to such overgrowth should be investigated to evaluate their role in the pathogenesis of the disorder in this group. Putative causes leading to overgrowth of the adenoid and tonsils may include hormonal changes associated with somatic growth and local and systemic inflammatory changes noted with childhood obesity (37). Other soft tissues restricting upper airway size, such as the fat pads, soft palate, lateral pharyngeal wall, and tongue, have been previously identified in adults with obesity and OSAS (49, 108, 109). However, a critical analysis of the nasal and pharyngeal airway passages and soft tissues surrounding the upper airway has not been performed so far in obese children with OSAS.

Abnormal craniofacial structure is considered to be a major risk factor for pediatric OSAS because it sleep apnea is common and severe in children with the phenotype associated with distinct craniofacial abnormalities, such as Pierre Robin syndrome (1, 121) and Down syndrome (26, 86), and 2) cephalometrics have demonstrated more subtle structural abnormalities in children with OSAS who do not have these distinct craniofacial anomalies (2, 63, 115, 116). However, craniofacial structure has not been studied in obese children with OSAS, and more data are needed to evaluate if it plays a role in the pathophysiology of OSAS in children.

Functional factors. Despite the anatomic evidence of adenoid and tonsillar hypertrophy limiting upper airway size in a significant amount of obese children with OSAS, several arguments suggest that OSAS is caused by alterations in functional mechanisms that lead to increased airway collapsibility (neuromotor tone, tissue properties, increased resistance, etc.). Obese children with OSAS having large tonsils and adenoids do not obstruct during wakefulness (high motor tone), and removal of the adenoid and tonsils in obese children with OSAS does not cure or resolve OSAS in a significant number of those subjects.

Modeling of the upper airway as a Starling resistor has given some insight regarding the mechanical properties of the upper airway as a collapsible tube. By measuring changes in peak inspiratory flow during continuous external application of positive/negative pressure, the propensity for the upper airway to collapse can be measured. This measurement is known as the critical closing pressure of the pharynx (Pcrit) and is affected by both anatomic and nonanatomic mechanisms (55, 110–113, 119). Adult subjects with OSAS often have a posi-
tive $P_{\text{crit}}$, indicating that the airway would collapse during sleep due to even mild inspiratory negative pressure (33) if it were not “protected” by the action of dilator muscles. Similar results have been found in children (85, 87). A recent study (67) in obese adults with OSAS has suggested that obesity is associated with higher $P_{\text{crit}}$ values, explaining to some degree the propensity of these subjects to develop OSAS. Although not studied, it is plausible that a similar functional deficit in the upper airway exists in obese children as well.

**Chest wall mechanics.** Obesity is associated with significant alterations in body composition that could affect chest wall mechanics by weighting the chest wall and reducing lung compliance. In addition, functional residual capacity is diminished due to abdominal visceral fat impinging on the chest cavity (52, 75). Such a reduction in functional residual capacity and compliance increases the risk for SDB by mechanisms of hypoventilation, atelectasis, and ventilation perfusion mismatch and increases the work of breathing and fatigue. Moreover, hypoventilation in itself may reduce upper airway motor tone. In addition, reduced lung volumes decreases airway stiffness by reducing the tracheal tethering effect and may further increase the risk for airway collapse and OSAS in these subjects (127).

**Ventilatory drive.** The role of the ventilatory drive in the pathophysiology of OSAS in adults and children remains unclear. Modeling studies (77, 134) have suggested that adult patients with OSAS have a high loop gain ventilatory control system, resulting in ventilatory instability and, hence, apnea. There is strong evidence that altered ventilatory responses are present in adults with OSAS, although not in all cases (16, 70, 76, 95, 101). Studies focusing on obese adults have shown that morbidly obese subjects are more susceptible to decreased ventilatory responses to both hypoxia and hypercapnia (78, 139) compared with normal or mildly decreased ventilatory responses in less obese adults or when eucapnia was present (68, 69, 79, 107).

Although the overall rebreathing ventilatory responses in nonobese children with OSAS were shown to be normal (84), subtle abnormalities were identified (30, 36, 122). Thus, it is possible that obese children have altered ventilatory responses predisposing them to OSAS, as noted by some investigators in obese adults.

**INTERACTIONS BETWEEN OBESITY, OSAS, AND RISK FOR CARDIOVASCULAR DISEASES**

The association between obesity and OSAS in both adults (138) and children (104) is well recognized today. However, the association among obesity, OSAS, and risk for cardiovascular diseases is difficult to ascertain, since subjects with either of these disorders often share common risk factors for cardiovascular diseases. The Sleep Heart Health Study (114), which prospectively evaluated >6,400 adults between 40 and 65 yr of age found an increased association of OSAS with coronary artery disease, congestive heart failure, and stroke independently of individual’s demographic characteristics (i.e., age, sex, and race) or risk markers (i.e., smoking, alcohol, body mass index, diabetes, dyslipidemia, and hypertension).

The above cardiovascular morbidities are not detected in young children due to their younger age and duration of OSAS. However, when studying other markers of cardiovascular diseases such as the regulation of blood pressure, cardiac function, autonomic function, and endothelial function, it becomes apparent that OSAS in obese children is strongly and independently associated with such morbidities, as in adults (10, 11, 37, 38, 128).

Some of the proposed mechanisms that can lead to the above cardiovascular effects include sleep fragmentation, sustained sympathetic activation, intermittent hypoxia, and oxidative stress. In addition, specific increases in proinflammatory vascular mediators leading to endothelial dysfunction and platelet activation, promoting cardiovascular morbidity, have been found in obese children with OSAS (Fig. 1) (38, 40, 126).

**Reversibility of cardiovascular morbidities with treatment of OSAS.** Additional confirmation for the direct association between OSAS and cardiovascular diseases comes from studies showing reversal in markers of cardiovascular diseases with the treatment of OSAS. The primary modality of treatment of OSAS in adults is continuous positive airway pressure (CPAP). Thus, CPAP treatment in adults with OSAS reduces systolic blood pressure and improves systemic circulation and ventricular function (3, 54, 96). In children, studies on CPAP effects on cardiovascular morbidities are not available at this time. However, the treatment of choice for OSAS in children is adenotonsillectomy. Two recent studies (9, 57) on the long-term effects of adenotonsillectomy on cardiovascular outcomes have demonstrated a decrease in diastolic blood pressure after adenotonsillectomy in children in the short term (up to 6 mo). However, at 1 yr of age, children with residual or recurrent OSAS had an increase in systolic and diastolic blood pressure; it is still not clear if this is related to the underlying obesity, persistent weight gain, or residual OSAS (9).

**INTERACTIONS AMONG OBESITY, OSAS, AND METABOLIC SYNDROME**

Metabolic syndrome is an important manifestation of obesity in children and includes elements of hypertriglyceridemia, reduced HDL-cholesterol, fasting hyperglycemia, insulin resistance, diabetes mellitus (DM), abdominal obesity, hypertension, and the presence of prothrombotic and proinflammatory state (25, 43, 50). Metabolic syndrome was initially defined with an emphasis on insulin resistance as the most important link in this above cluster of metabolic abnormalities. However, today, insulin resistance is considered an important component and not the sole mediator of the syndrome. Insulin resistance is a precursor to DM, but this progression is thought to occur only in a subset of individuals who have an inherent predisposition to DM (60). Insulin resistance is usually estimated by the homeostasis assessment model (HOMA) or by the “gold standard” euglycemic clamp method. HOMA is easily estimated from fasting plasma insulin and glucose levels, whereas the clamp test is more cumbersome, requiring the infusion of glucose with a standardized insulin infusion (130). The prevalence of metabolic syndrome increases with the severity of obesity and may reach 50% in severely obese children (133).

Obesity is closely associated with OSAS (103, 138) and with metabolic syndrome (133). Therefore, an association between obesity/metabolic syndrome and OSAS is intuitive (Fig. 1). More intriguing, however, is the possible association of OSAS as a cause of obesity/metabolic syndrome (Fig. 1). Studies in recent years have suggested that OSAS is indeed an important
mediator of insulin resistance, dyslipidemia, hypertension, and inflammation via mechanisms such as sympathetic discharge, intermittent hypoxemia, sleep fragmentation, and insufficient sleep. Many of these interactions may be seen in childhood and have the potential for greater morbidity secondary to the longer duration of these processes starting earlier in life.

OSAS has been implicated in the development of insulin resistance in adults (53, 99, 105). Analysis of data from the Wisconsin Sleep cohort revealed that subjects with moderate OSAS [apnea-hyponea index (AHI)/h] were 2.3 times more likely to be diagnosed with DM than subjects without OSAS after adjusting for age, sex, and abdominal girth (105). While obesity is a major determinant of insulin resistance, moderate OSAS is associated independently with insulin resistance (53). In a study of nondiabetic subjects, moderate to severe OSAS was reported to be associated with reduced insulin sensitivity and reduced glucose disposition after correcting for age, sex, race, and adiposity (99). In addition, treatment with CPAP may reduce insulin resistance in patients with OSAS (47).

What is the evidence in children? Redline et al. (102) reported increased levels of insulin with OSAS, indicative of insulin resistance, in a community-based cohort of adolescents. This association was independent of the body mass index percentile and sex (102). Data in prepubertal children have also suggested an association between insulin sensitivity and OSAS in obese children, with the correction of OSAS in obese children being associated with an improvement in measures of insulin sensitivity (37, 132). In nonobese children, or in children with mild OSAS, the association between OSAS and insulin resistance is not seen (12, 37), suggesting that OSAS might contribute to the exacerbation of insulin resistance but may not be causing insulin resistance independently (12, 37). Studies in adults have linked oxygen desaturation, including levels of desaturation between 2% and 4% associated with hypopneas, with insulin resistance. Higher insulin levels were associated with a higher respiratory disturbance index in adolescents (102) and with the arousal index, in addition, in prepubertal children (37).

Insulin resistance is thought to be causally associated with dyslipidemia, which is an integral part of metabolic syndrome and may manifest as high triglyceride levels, high total cholesterol, LDL-cholesterol levels, or low HDL levels (100). One of the pathogenic mechanisms may be through increased levels of free fatty acids because of the reduced inhibition of lipoprotein lipase in adipocytes seen in insulin resistance (89). Several studies in adults and children have shown increased levels of triglycerides and LDL-cholesterol and low HDL levels that were independently associated with OSAS, but others have not found this link (22, 23, 27, 37, 91, 135).

The presence of hypertension as a criterion for metabolic syndrome captures endothelial dysfunction and systemic inflammation in metabolic syndrome (50). OSAS by itself has been implicated in the genesis of endothelial dysfunction in adult and pediatric studies (39, 54) via reduced levels of nitric oxide and increased levels of endothelin-1, endothelial cell apoptosis, and plasma aldosterone levels (28, 32, 56, 97, 98). The nature of the interaction between obesity and OSAS in the
genesis of endothelial dysfunction is not yet clear. In addition, increased levels of C-reactive protein have been associated with OSAS and with correlation to indexes of hypoxemia or arousals (65, 73, 125). However, these associations have not been reported in all studies (58).

Reversibility of features of metabolic syndrome with treatment of OSAS. The efficacy of CPAP in mitigating manifestations of metabolic syndrome has not been consistent across studies in adult subjects. Greater stability and lower mean levels of glucose with improved β-cell function, insulin sensitivity, and fasting glucose have been reported (23, 24, 27). However, these studies have not reported a change in HbA1c levels. Harsch and colleagues (46, 47) reported improved insulin sensitivity with clamp studies in nonobese subjects with OSAS within 2 days of CPAP therapy and improved insulin sensitivity in nonobese and obese subjects with OSAS after 3 mo of treatment with CPAP. They speculated that reduced sympathetic activity with CPAP may contribute to the early improvement in insulin sensitivity with the longer-term improvement being related to improved oxygenation. In contrast to these studies, improvements in insulin sensitivity, lipid profile, or inflammatory marker status have not been reported in two well-designed studies with a control sham CPAP arm and a small pediatric study (22, 91, 135). The two adult studies did have evidence of CPAP efficacy in the form of improved sleepiness, and one of these studies also reported an ∼5-mmHg drop in systolic and diastolic blood pressures. Many other studies in adults have reported modest improvements in blood pressure after treatment with CPAP (15, 27).

In children, adenotonsillectomy may completely reverse OSAS and presents a relatively clean model to examine the effects of reversing sleep apnea. In this setting, improvements in lipid profile, insulin sensitivity, and inflammatory markers have been reported (37, 132). As with adult studies, these findings are not consistent (12). Adenotonsillectomy has been reported more consistently to lower diastolic blood pressure in children with OSAS, but children who gained significant weight after surgery have been reported to have increases in systolic pressure 1 yr after surgery (9, 12, 57). This change in systolic blood pressure may reflect an increase secondary to obesity that overwhelms changes related to the reduction in OSAS.

The many variables that may contribute to difficulty in interpretation of these studies include the presence of obesity, age of subjects, insulin resistance (prediabetes) versus established diabetes, degree of sleep apnea, amount of CPAP usage, and effects of CPAP itself on various parameters. In addition, the validity of the parameters such as HOMA, HbA1c, glucose tolerance test, and lipid profile in predicting the actual outcomes of interest (morbidity and mortality) is not clear. However, these parameters are important considerations in the development of appropriate therapeutic trials. Overall, the changes in insulin resistance with treatment of OSAS seem to be modest and are much smaller than those seen with insulin-sensitizing medications (135).

**APPROACH TO THE OBESE CHILD WITH POSSIBLE OSAS**

Children with obesity are at risk for OSAS and should be screened at routine clinic visits for the presence of habitual snoring and possible OSAS (Fig. 2). Currently, polysomnography is considered the gold standard for the diagnosis of OSAS (4). Clinical questionnaires are not accurate enough, and other methods, such as nocturnal pulse oximetry or daytime nap polysomnography, are specific but need confirmation by polysomnography if the results are negative (4). Other methods...
such as audio taping, videotaping, and home polysomnography are not yet considered standard of care (4).

The recommended approach to treat the obese child with OSAS and with adenotonsillar hypertrophy is adenotonsillectomy with a followup for the persistence of OSAS (4). Adenotonsillectomy is reported to improve the AHI and oxygenation nadir significantly in obese children with OSAS, but ~50% of children continue to have >5 AH/h (21). CPAP is recommended if adenotonsillectomy is not adequate or not appropriate in obese children (88). Other modalities of treatment for OSAS include oral appliances, uvulopalatopharyngoplasty, positional therapy, and weight loss.

Oral appliances help to expand the upper airway and are effective in the management of milder cases of OSAS in adults who do not tolerate CPAP or are not appropriate for CPAP (71). The efficacy of oral appliances in children has not been established (17), and these are more appropriate for older children with adequate development of dentition.

Positional therapy uses devices such as shirts, pillows, and belts that promote sleeping in a lateral, prone, or upright position, which reduces obstructive sleep apnea in a subset of patients. These techniques have not been adequately explored and may be effective in children with demonstrated positional sleep apnea (18).

Uvulopalatopharyngoplasty is a procedure in which the lateral pharyngeal pillars are trimmed and the uvula and posterior palate are excised to enlarge the airway. This option may be relevant in the management of OSAS in older children who cannot use CPAP. Uvulopalatopharyngoplasty has been reported to improve mild to moderate OSA by ~40–50% but may result in significant complications such as velopharyngeal insufficiency, stenosis, and dysphagia (137).

Weight loss, particularly the greater degrees of weight loss seen with bariatric surgery, is associated with a significant reduction in sleep apnea, but most patients have residual OSAS, albeit with likely lower CPAP requirements (42, 61, 74). The benefits of bariatric surgery in maintaining the quality of life after 10 yr are less clear (20). Bariatric surgery in children is considered reasonable when children with OSAS are morbidly obese, are more skeletally mature, and have failed organized attempts at weight loss (51).

In summary, the management of OSAS in obese children can be difficult and often requires a comprehensive and longitudinal evaluation from a team with expertise in sleep, otolaryngology, nutrition, pulmonary and cardiovascular disease, and behavioral science.

SUMMARY

The pathophysiology of OSAS in obese children has not been sufficiently studied and is not well understood. It may have similarities to those noted in obese adults (alterations in anatomy and function as well as inflammation). The interactions among obesity, OSAS, and metabolic syndrome are complex and yet to be understood. However, OSAS seems to be an independent factor that may induce metabolic effects that can potentiate metabolic syndrome and its end-organ effects. Care for the obese child with OSAS requires an expert team with capabilities to monitor and adopt a wide range of treatments that are available today to the specific needs of the child.

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