The Role of Obesity and Inflammation in Pediatric Sleep-Disordered Breathing

CATHERINE KIER, MD
Professor of Clinical Pediatrics
Division Chief, Pediatric Pulmonology, and Cystic Fibrosis Center
Director, Pediatric Sleep Disorders Center
SUNY Stony Brook
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Objectives:

- At the end of this session, the participant would be able to:
  1. Explain the interaction of obesity and pediatric sleep disordered breathing in activating the inflammatory pathway
  2. Identify the metabolic alterations and complications stemming from this shared inflammatory pathway
Obstructive sleep apnea in children

- Incidence of 2–3% of all children
- Peak prevalence between 2 and 8 years
"If you grow up to be half the man your father is, that will be plenty."
Obesity in children

- 17% (or 12.7 million) of children and adolescents aged 2 to 19 years
- Racial and age disparities in obesity prevalence
- 2011-2012
  - Higher among Hispanics (22.4%) and non-Hispanic black youth (20.2%)
  - Non-Hispanic white youth (14.1%)
  - Non-Hispanic Asian youth (8.6%)
Obstructive sleep apnea in children
Fight and flight

- an interruption of normal sleep architecture
- alterations in physiologic gas exchange
  - repetitive decreases in oxygen saturation followed by rapid re-oxygenation
  - episodic hypercapnia
- occlusion of the upper airway
  - large fluxes in intrathoracic pressure
  - recurrent brain arousals
- induces potent and sustained activation of sympathetic nervous system
What happens when your sympathetic nervous system is activated?
Stress hormones during sleep!!!
Liabilities

- Neurocognitive and behavioral disturbances
  - delays in the treatment may lead to persistent declines in cognitive function (reduced or failing academic performance - Gozal, 2001)

- Cardiovascular morbidity
  - Endothelial dysfunction (a marker of subclinical cardiovascular disease)
  - Systemic hypertension
  - Pulmonary hypertension
  - Myocardial left ventricular remodeling

Pediatrics 2001;107:1394–1399;
short-term and long-term implications of OSAS could be amplified by the concurrent presence of obesity
Sleep fragmentation

- Associated with neurohormonal changes
- Results in altered pro-inflammatory pathways and higher levels of plasma adipokines
- A key determinant in the development of neurocognitive dysfunction associated with OSAS may be the magnitude of this inflammatory response

Cognitive function

- High-sensitivity C-reactive protein (hsCRP) levels are higher in children with OSA, and particularly in those who develop neurocognitive deficits.

- Recent study: 278 children, 5 to 7 years
  - Both snoring and non-snoring children
  - Overnight polysomnography, neurocognitive testing and a blood draw the next morning

Cognitive function and CRP

Sample of 278 children

Snoring → Non-snoring

Non-OSA

Mean hsCRP = 0.19+/-0.07 mg/dl

Non-OSA

> 2 abnormal cognitive subtests

Mean hsCRP = 0.48+/-0.12 mg/dl

OSA

Mean hsCRP = 0.36+/-0.11 mg/dl

(normal cognitive scores)

Mean hsCRP = 0.21+/-0.08 mg/dl

(p<0.01)

(p<0.002)

Obesity and Obstructive sleep apnea syndrome (OSAS)

- share common chronic inflammatory pathways
Fig. 1. Hypothetical interaction of obstructive sleep apnea syndrome and obesity in activating pathways leading to metabolic disease. TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; CRP, C-reactive protein.
Pathophysiology of OSA

- In children: adenotonsillar hypertrophy
  - reduce the anatomical patency of the airway
  - lead to exponential increases in pharyngeal resistance
  - result in episodic airway collapse
- several other risk factors such as obesity, craniofacial and neuromuscular elements may all independently contribute to the risk of OSA
Interesting...

- Adenotonsillar tissues from OSA
  - Increases in inflammatory cell proliferation
  - Increased expression of pro-inflammatory cytokines and other inflammatory mediators (e.g., TNF-α, IL-6, and IL-1α)
- When compared to adenotonsillar tissues removed in children with recurrent tonsillitis

recurrent vibration in the upper airway will promote localized inflammation
- subsequent mucosal swelling and overexpression of inflammatory cytokines such as TNF-alpha (animal models)
exhaled breath condensate and induced sputum in children with OSA
- upregulation of localized inflammatory processes in upper airway tissues
Emerging epidemic of obesity

- Prevalence rates of 7% to 22% of children in Western countries
- Each increase of 1 kg/m² of BMI above the mean in children, the risk of OSAS increases by 12%

Phenotype of OSA in children is also changing

• With the epidemic of obesity, emergence of a phenotypic variant of OSA in children and adolescents
  • closely resembles that of adults with the disease

• defines two types of OSA in children
  • divided into types I and II pediatric OSA
    • Type I – adenotonsillar hypertrophy
    • Type II – obese children and adolescents
  • analogy with type I and type II diabetes
OSA and obesity studies

- The risk for residual OSAS is markedly greater in obese children.
- Children with persistent OSAS after 5 years are at an elevated risk of developing obesity.
- The degree of adenotonsillar hypertrophy required is lesser in obese children.
- Obesity-induced OSAS behaves differently from the OSAS phenotype that is exclusively induced by adenotonsillar (similar to adult phenotype).
Obesity in children

- a multisystemic disease
- elevated risk of psychological disturbances
  - Depression, suicidality, poor peer relationships
- gastrointestinal complications (GERD, hepatic disease, irritable bowel syndrome)
- Metabolic syndrome or insulin-resistance syndrome (4% of adolescents) but the prevalence of 30–50% in overweight/obese children
 Obesity (continued)

- significant increase in the prevalence of childhood type 2 diabetes mellitus
- subsequent increases in early onset cardiovascular disease and cardiovascular risk factors (hypertension, left ventricular hypertrophy, dyslipidemia, and atherosclerosis)
Obesity as chronic state of low-grade systemic inflammation

National Health and Nutrition Examination Survey
BMI was the best predictor of elevated C-reactive protein (CRP)
Lipid and metabolic profiles

- the effect of OSAS treatment on lipid and metabolic profiles
  - 62 children (37 obese and 25 non-obese) with sleep studies

- significant associations between sleep-disordered breathing parameters and serum insulin/glucose ratios, low-density lipoprotein (LDL) levels, high-density lipoprotein (HDL) levels, LDL/HDL ratio, and apolipoprotein B (ApoB)

Effect of treatment of OSA

- resulted in significant reductions of LDL and ApoB and reciprocal increases in HDL in both obese and non-obese
- insulin sensitivity improved in obese children
- pathogenic role for OSAS in lipid homeostasis, and effective treatment of OSAS result in marked improvements in metabolic control
Leptin and ghrelin
Leptin and ghrelin

- Leptin
  - a mediator of long-term regulation of energy balance, suppressing food intake and thereby inducing weight loss
- Ghrelin
  - fast-acting hormone, role in meal initiation
- obese subjects
  - hormone leptin is increased - anorexigenic
  - hormone ghrelin is decreased - orexigenic
  - now established-obese patients are leptin-resistant
Sleep duration and weight gain

- Epidemic of obesity with parallel growth in chronic sleep deprivation
- Society: demands and diet
  - Influence on leptin and ghrelin secretion and functioning
- Potentials of leptin and ghrelin as drug targets

Systemic inflammation and leptin

- White adipose tissue produce over 50 molecules termed adipokines with various functions (specific inflammatory and metabolic regulation)

- Leptin, a cytokine
  - Regulation of body adiposity through promotion of satiety
  - Important immunomodulatory role
Leptin (continued)

- stimulates production of pro-inflammatory cytokines including IL-6 and TNF-a (which are independently induced by OSAS)
- typically elevated in obesity
  (leptin is the “bad guy”)
  - systemic inflammation provoked by obesity is related to elevated circulating leptin
- independent risk factor for cardiovascular disease
In adults

- OSAS leads to elevated circulating levels of leptin
- Effective resolution of OSAS will reduce leptin levels particularly in adults who are non-obese
In children

- 130 children with sleep studies:
  - Plasma adipokine concentrations
  - Association between the degree of obesity and circulating leptin levels
  - Accentuated in the presence of co-morbid OSAS
- Increase in circulating leptin levels induced by OSAS remained significant even after adjusting for the degree of obesity

TNF-alpha

- Tumor necrosis factor-alpha
- pro-inflammatory cytokine
- promotes expression of cellular adhesion molecules (leukocytes with the vascular endothelium)
- stimulating the onset and propagation of atheromatous plaque formation
- correlate with severity of daytime sleepiness and degree of hypoxia induced by OSAS
SDB, inflammation, and Uric Acid

- A study was done measuring effects of SDB on inflammation and oxidative stress in childhood obesity, showing that weight loss is an effective treatment in obese SDB cases.
- It was found that there is a link between SDB and inflammation.
- UA was shown to be a good reflector of oxidative stress, decreasing in concentration as SDB improved.
Adenotonsillectomy in Obese Children

- A study was done to analyze the effects of adenotonsillectomy (removal of adenoids and tonsils) on plasma-based inflammatory biomarkers.

- Overall, significant decreases of biomarkers such as IL-6, IL-18, PAI-1, MCP-1, among others were found providing evidence that interactive pro-inflammatory effects of sleep disorders contribute to downstream end-organ morbidities.
SDB and C-reactive protein

- Elevated C-reactive protein (CRP) is a risk factor for cardiovascular disease and is independently correlated with obstructive sleep apnea syndrome (OSAS) in adults.
- Unlike adults, CRP levels are not influenced by SDB in children despite being correlated with obesity.
In children

- TNF-alpha
- Recent study:
  - Children with sleep studies
  - Morning plasma samples:
    - TNF-a levels significantly correlated with the degree of respiratory-induced sleep fragmentation in children with OSAS
  - Presence or absence of gene polymorphisms on the gene encoding for TNF-alpha

Sleep 2010;33:319–325.
Summary

shared inflammatory pathways with obesity and obstructive sleep apnea syndrome
Message

- great concern to all pediatricians
  - onset of cardiovascular disease in the context of obesity, OSAS, or both begins to develop at a very early stage of life (during childhood)
  - the true impact of such inflammatory and atherogenic alterations will only become apparent during adulthood
- The recognition and treatment of both obesity and OSAS is of paramount importance and urgency in children
Complexity of interactions...

- between obesity, OSAS, and activated inflammatory pathways
- recognition of additional potential interactions
- between environmental and lifestyle elements, as well as the modulatory effects of gene polymorphisms
Have to be integrated...

- into a single multifactorial model
- if we wish to develop predictive and reliable algorithms that will identify the risks for short-term and long-term morbidity in children with obesity and OSAS
References


References (2)


References (3)
