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C-reactive protein and obstructive sleep apnea syndrome in children

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1. ABSTRACT

Obesity has emerged as one of the most important epidemics in the Western hemisphere, and as its prevalence continues to increase in children, the associated risk for cardiovascular and metabolic complications follows parallel increases in prevalence, and reflects activation of underlying inflammatory pathways. The obstructive sleep apnea syndrome (OSAS) is a frequent condition in children associated with intermittent upper airway obstruction during sleep, its prevalence is markedly increased in the presence of obesity, and is associated with activation of similar inflammatory mechanisms as those activated by obesity, suggesting that the 2 disorders may reciprocally contribute to their adverse consequences. C-reactive protein (CRP) is a prototypic marker of inflammation that has repeatedly shown promise as a potentially reliable biomarker of cardiovascular morbidity. In addition, under certain circumstances CRP may enhance inflammation, oxidative stress, and pro-coagulant activity and thus promote atherogenesis. In this paper, we will critically review the available evidence linking OSAS to systemic inflammation in children using CRP levels as the reporter biomarker.

2. INTRODUCTION

The incidence of obstructive sleep apnea syndrome (OSAS) in children has remarkably increased in recent years, and is estimated to affect 2-3% of all children, reaching a peak prevalence between 2 to 8 years of age. (1-8) Although the mechanisms leading to OSAS in children certainly involve multifactorial components, adenotonsillar hypertrophy is clearly the principal contributor to this condition.

OSAS consists of the occurrence of repeated episodes of increased upper airway resistance culminating in partial or complete obstruction of the upper airway during sleep, accompanied by loud intermittent snoring, repetitive decreases in oxygen saturation followed by rapid re-oxygenation, episodic hypercapnia, repeated arousals, and fragmented sleep. Further, occlusion of the upper airway leads to large swings in intrathoracic pressure, which may induce or potentiate the activation of sympathetic nervous system activity elicited by the gas exchange abnormalities and disrupted sleep.

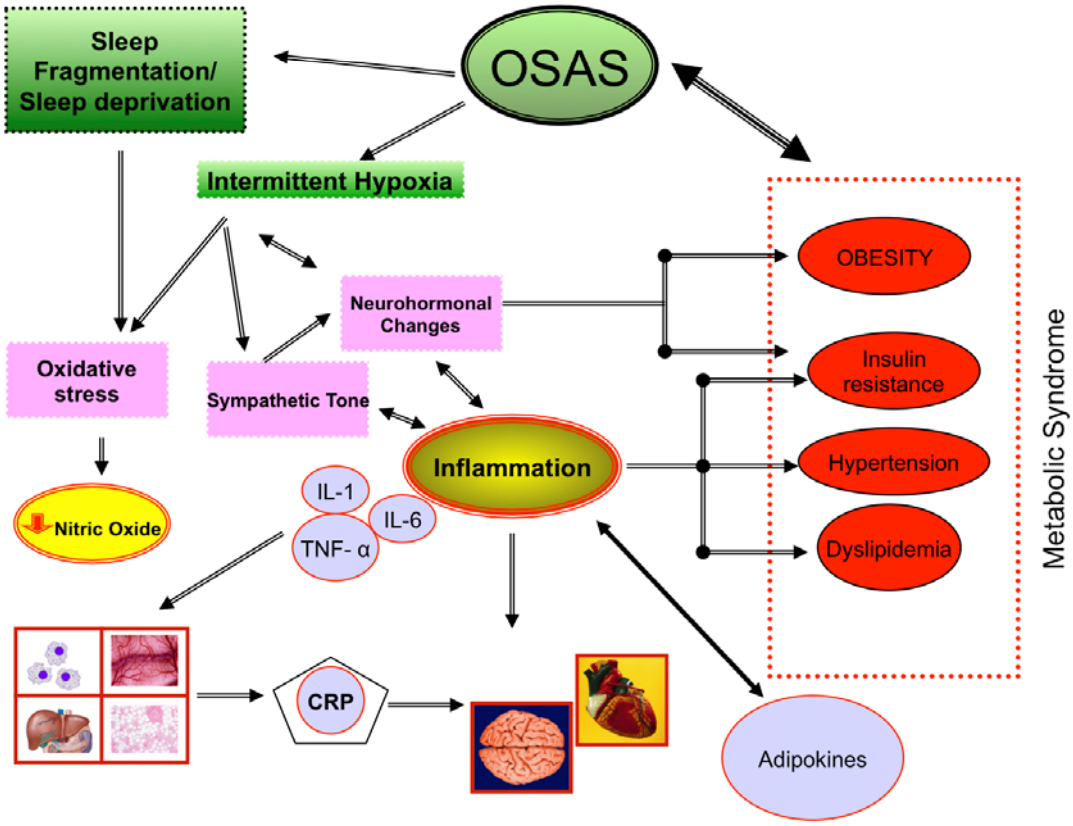

Figure 1. Schematic diagram outlining potential inflammatory pathways linking between obesity and obstructive sleep apnea syndrome in children. CRP – C-reactive protein; IL-1 – interleukin-1; IL-6 – interleukin-6; TNF-a - tumor necrosis factor alpha

Conclusive evidence has emerged in the last 2 decades to indicate that OSAS is associated with an increased risk for neurocognitive and behavioral disturbances, (9-15) and that delays in the treatment of pediatric OSAS may lead to persistent declines in cognitive function, as illustrated by reduced or failing academic performance. (16) Cardiovascular morbidity has also now been conclusively reported in children with OSAS, (17) with several studies showing the presence of increased sympathetic activity and reactivity, (18-20) endothelial dysfunction, (21) systemic hypertension, (22-25) pulmonary hypertension, (26, 27) and myocardial left ventricular remodeling. (22, 27) On the metabolic front, the presence of alterations in serum lipids and insulin receptor sensitivity in children with OSAS, i.e., metabolic syndrome, have further brought attention to the similarity and overlap between OSAS-associated morbidities and those of obesity.

While the precise mechanisms underlying the induction of cardiovascular, neurocognitive, and metabolic morbidity in the context of childhood OSAS remain to be fully delineated, it has become apparent that several pathways are operational, (28) and that the presence of OSAS induces activation of several inflammatory cascades, which are central to the initiation and progression of disease morbidity. One of the prototypic biomarkers of systemic inflammation is C-reactive protein (CRP), an ubiquitous protein that can be generated in multiple cell types, and that in addition to its effects on endothelial function and integrity, appears to be a reliable reporter of cardiovascular and metabolic risk, even if such role has been more recently challenged. (29-31) Indeed, Cao and colleagues have reported only modest predictive value for hsCRP levels and only when atherosclerosis was detectable.(32) In this paper, we will review the evidence that supports childhood OSAS as a distinctive systemic inflammatory condition in children using CRP as the reporter, and will critically assess the potential interactions between OSAS and obesity (Figure 1), since the latter not only greatly increases the risk for OSAS and its severity, but is also a well characterized inflammatory condition. (33)

3. PATHOPHYSIOLOGY OF OSAS IN CHILDREN – CONTRIBUTION OF ADENOTONSILLAR HYPERTROPHY

The cardinal abnormality associated with an increased likelihood of OSAS in children is the presence of adenotonsillar hypertrophy (ATH). Enlargement of upper airway lymphoid tissues in the upper airway increases in an exponential pharyngeal resistance in an exponential fashion that will promote the occurrence of episodic airway collapse during sleep, a characteristic feature of OSAS. (34, 35) However, the isolated presence of enlarged tonsils and

adenoids will not reliably predict the likelihood of OSAS in children, (36) since children without ATH may suffer form OSAS, and conversely children with marked and severe ATH may have no symptoms or evidence of OSAS. Thus, other factors such as obesity, craniofacial features, and neuromuscular elements may all independently contribute to the risk of OSAS in children, by altering the balance between upper airway dilators, constrictors, and pharyngeal tissue force vectors, thereby promoting increases in the intrinsic collapsibility of the upper airway. Of note, adenotonsillar tissues per se could further contribute to the changes in upper airway collapsibility. Indeed, increases in the proliferation of resident or migratory inflammatory cells, and increased expression of pro-inflammatory cytokines and other inflammatory mediators (e.g., TNF-a, IL-6 and IL-1a) are apparent in adenotonsillar tissues removed in the context of treatment of children with OSAS, and could alter the dynamic behavior of the airway.(37) Both exhaled breath condensate(38) and induced sputum(39) in children with OSAS reveal the presence of increased inflammatory processes in upper airway tissues, and these processes could not only contribute to the disruption of the mechanical properties of the airway, but could also propagate to the systemic circulation and contribute there as well.

4. PATHOPHYSIOLOGY OF OSAS IN CHILDREN – CONTRIBUTION OF OBESITY

As mentioned above, the presence of obesity significantly increases the risk of OSAS in children. (40-43) The epidemic of obesity in childhood is now undisputable, (44) and prevalence rates ranging from 7-22% of children in various Western countries have been reported. (45, 46) The prevalence of OSAS in children has substantially increased in tandem with the increases in obesity. (47) In fact, for every increase of 1 kg/m2 of BMI above the mean in children, the risk of OSAS has been shown to increase by 12%. (48) Surgical removal of ATH, which is the standard initial therapeutic approach for pediatric OSAS, is fraught with a markedly greater risk for residual OSAS in obese children. (49) This is not surprising considering that at any given level of OSAS severity, the degree of ATH required is lesser in obese children. (50) A review on the pathophysiological contributions of obesity to the risk of OSAS has been recently published. (51) We should also mention that the concurrent presence of both OSAS and obesity is likely to amplify the individual morbidities of either disease, suggesting the presence of interactive processes, as evidenced by the differential phenotypic presentations of OSAS in the context of ATH alone or ATH and obesity. (52)

5. C-REACTIVE PROTEIN

CRP is a highly soluble member of the pentraxin family, consisting of a discoid configuration of 5 identically non-covalently bound globular subunits organized in a cyclic pentameric symmetry. The protomers are arranged around a central pore and the 206 amino acids are folded in a “lectin fold” topology. (53) Pentameric CRP (pCRP) is primarily synthesized in the liver, and 50% of the individual variance in baseline pCRP concentration is genetic(54) and accounted for non-coding polymorphisms in the pCRP gene, (55) which is located on the short arm of chromosome 1. (56) However, recent evidence has challenged the dogma that CRP is exclusively produced by the liver, and cells within the kidney, atherosclerotic lesions, as well as neurons and tissue resident macrophages (adipose tissue, lung) have all demonstrated *in situ* pCRP production. (57-62) Transcriptional induction is predominantly regulated by the cytokine interleukin 6 (IL-6) and, to a lesser degree, by IL-β and tumor necrosis factor α. (63)

Another frequent misconception involves the biological activity of pCRP, whereby a pro-inflammatory activity has been assigned to this protein. In fact, many of the discrepant findings may be explained by the concurrent presence of pentameric and monomeric CRP. Indeed, uncontaminated pCRP was shown to effectively attenuate inflammatory response by inhibiting neutrophil activation, adherence and trafficking into tissues. (64) Incubation of human coronary artery endothelial cells with pCRP for a short time failed to induce cytokine release and adhesion molecule expression such as intercellular adhesion molecule-1 (ICAM-1), E-Selectin, and vascular adhesion molecule-1 (VCAM-1). (65, 66) In contrast, monomeric CRP (mCRP), rather than pCRP, accumulates in atherosclerotic lesions, (67) prolongs neutrophil survival and induces key regulators of leukocyte recruitment, such as monocyte chemoattractant protein-1 (MCP-1) and IL-8. (68) In endothelial cells, mCRP but not pCRP directly facilitates the expression of intercellular adhesion molecule-1 (ICAM-1), E-Selectin, and vascular adhesion molecule-1 (VCAM-1). (65) Taken together, increased serum levels of pCRP should be viewed as an increased expression of this acute-phase reactant, whereby increased production of various proinflammatory cytokines, such as IL-6, TNF-α, and IL-1 derived from inflammatory cells, vascular endothelium and adipose tissue, will stimulate its formation. Indeed, the release of IL-6 from macrophages via increased oxidative stress and infection may be the original insult that initiates this process. Notwithstanding, CRP, particularly mCRP or structurally modified CRP rather than pCRP may promote uptake of low-density lipoproteins by macrophages and contribute to atherogenesis by tilting the balance of endovascular health through reduction of the synthesis and biological activity of nitric oxide, upregulation of endothelin-1, and activation of cell adhesion molecules. (69) In addition, monomeric CRP appears to be detrimental to endothelial progenitor function and fate. (70) CRP has been shown to facilitate the transformation of monocytes to m1 macrophages while inhibiting the m2 phenotype (71), a finding that would suggest an adverse effect tilting it towards a pro-inflammatory balance. CRP also appears to be detrimental to the biophysical properties of the endothelium. (72) Furthermore, in 2 recent studies, CRP was identified as a specific ligand for oxidized LDL receptor LOX1, thereby linking the potential functional implications of CRP on endothelial function via lipid-dependent biological pathways. (73, 74) However, in a meta-analysis of 83 published studies, Hemingway and colleagues explored the

Table 1. Factors Affecting Circulating CRP Levels

Increase in CRP levels	Decrease in CRP levels
Overweight and central obesity	Hypocaloric diet and intentional weight loss
Sedentary lifestyle	Regular physical activity (particularly aerobic exercise)
Acute infections	Lipid-lowering (statin) therapy
Major trauma	Use of aspirin
Inflammatory disorders (Inflammatory bowel disease, arthritis, asthma)	
Hyperglycemia, acute and chronic	
OSAS	
Asthma	

association between CRP levels and cardiovascular events in known patients with heart disease. There were multiple methodological flaws in most of the published studies, and although patients with a CRP level in the top third of the distribution were nearly twice as likely to have a cardiovascular event when compared with patients whose CRP levels were in the bottom third of the distribution (RR: 1.97), adjustment for publication bias reduced the risk associated with high CRP levels to 1.19 (29). An additional recent review of the evidence showed that hsCRP meets four of the six American Heart Association statement criteria for use as a cardiovascular risk marker (i.e., proof of concept, prospective validation, incremental value beyond risk factors, and clinical utility), but also concluded that there is a clear shortage of evidence on the impact of clinical outcomes, cost effectiveness of reclassification, and on routine measurement of hs-CRP. (75).Therefore, further studies will be needed to evaluate the overall reporter ability and cost-effectiveness of hsCRP as a risk-related biomarker for cardiovascular disease. Such epidemiologically-based skepticism regarding the deleterious role of CRP on the vasculature has also started to emerge from data generated using several murine-based models. For example, Teupser and colleagues showed that atherosclerosis progression rate or severity were not affected by the absence of the CRP gene. (76) Similarly, Kovacs *et al* suggested that CRP was beneficial and slowed the rate of atherosclerosis in a murine model (77), and overexpressin of human CRP was not atherogenic. (78) Taken together, the specific biological, biomarker, and epidemiological roles of CRP remain unclear, and will require much more extensive exploration.

6. CRP AND OBESITY IN CHILDREN

Emerging evidence has shown that obesity is best characterized as a multi-systemic disease. In addition to cardiovascular and metabolic complications, obesity in children also imposes an elevated risk of psychological disturbances including depression, (79, 80) suicidality, (81) and poor peer relationships. (82) In addition, the gastrointestinal morbidities secondary to obesity in children include gastroesophageal reflux disease, (83) hepatic disease including nonalcoholic steatohepatitis (NASH) (84, 85) and irritable bowel syndrome. (86) Similarly, associations between asthma and obesity and ADHD and obesity have also started to emerge. (87-93)

The association between obesity and inflammation as epitomized by serum CRP levels was initially reported in children by Cook and collaborators, who showed markedly increased CRP levels among children in the top quintile of BMI when compared with those in the lower BMI quintile. (94) These findings were subsequently confirmed in multiple studies, whereby 3-4-fold increases in the odds of high CRP levels were found among overweight children. (95, 96), The associations between CRP levels and obesity in children have now been extended to very young children, and confirmed among several ethnic groups, with children from non-Caucasian backgrounds (African-American and Asian) having higher CRP levels than Caucasians. (97-102) Accordingly, the large number of studies in children that have thus far examined the changes in inflammatory mediators including CRP in the context of obesity, (95, 103-113) provide a rather compelling body of evidence strongly supporting the concept that obesity increases the risk for increased expression of inflammatory mediators, many of which have demonstrated roles in the pathophysiology of cardiovascular and endothelial dysfunction, and the emergence of insulin resistance and diabetes. However, although CRP has been proposed as a reliable and consistent marker for the early diagnosis of metabolic syndrome and cardiovascular risk in obese children and adolescents, the value of measuring CRP levels in routine clinical practice will need further prospective studies, particularly when considering the large number of factors potentially affecting the circulating levels of CRP (Table 1).

The metabolic syndrome or insulin-resistance syndrome affects approximately 4% of the general population of adolescents, but prevalence as high as 30% to 50% have been reported in overweight/obese children, (114, 115) with parallel and significant increases in the prevalence of childhood type 2 diabetes mellitus secondary to obesity.(116) As a consequence of such increases in obesity rates, the Bogalusa longitudinal study (117, 118) and the Muscatine study (119, 120) have shown that obesity during childhood underlies marked increase in the risk for hypertension, left ventricular hypertrophy, dyslipidemia and atherosclerosis. Taken together, the consequences of obesity manifest as several co-morbidities, including OSAS, and it is expected that the accumulation of these morbidities will result in increased risk of mortality and morbidity.(121)

In this context, we will critically review the impact of OSAS in obese children with a proposition that physiological aberrations induced by both obesity and OSAS in children likely combine resulting in further accentuation of systemic inflammation thereby elevating the risk of early onset cardiovascular disease (Figure 1).

7. CRP IN OSAS IN CHILDREN

As mentioned in previous sections, CRP levels have been extensively assessed as an independent marker of future cardiovascular events, (122-125) and have also been shown to be increased in the presence of obesity. (126) However, the effects of OSAS on circulating CRP levels have only been explored in recent years.

In adults, the cumulative evidence is supportive of a strong association between OSAS and hsCRP levels that is independent of other well established risk factors. Indeed, since the initial association was reported by Shamsuzzaman and colleagues (127), many other investigators have confirmed that OSAS induces elevations in hsCRP, particularly during daytime hours, and that such increases in hsCRP are reduced following effective treatment of the underlying sleep-disordered breathing. (128-143) However, not all studies have been able to confirm these findings, even if some of these negative reports have noted improvements in hsCRP levels with treatment, suggesting that potential interactions between OSAS and other confounding factors may be operationally pertinent and contribute to hsCRP circulating concentrations. (144-149) Of note, the strength of the association between the degree of OSAS severity and hsCRP serum concentrations varies substantially between studies and appears to manifest stronger linkage with the levels of nocturnal hypoxemia than with the more traditionally used apnea-hypopnea index.

In the initial study in children on this issue published in 2004, Tauman and colleagues(150) studied 81 children (mean age: 9.3 ±3.7 years) who underwent polysomnographic evaluation for OSAS and CRP levels and lipid profile determinations were performed the next morning in a fasting state. Significant associations between log CRP levels and AHI, arousal index, and the lowest nocturnal arterial oxygen saturation emerged, and remained significant after adjusting for BMI. (150) Moreover, 94% of the children with elevated log CRP levels reported excessive daytime sleepiness and/or learning problems, compared with 62% of the children with normal CRP levels.(150) Similar findings were also reported by Larkin *et al.* in an adolescent cohort, (151) while a subsequent report by Kaditis and collaborators on a cohort of Greek children with OSAS did not find evidence for this association. (152) To further elucidate this issue, we initially examined 20 non-obese children with OSAS and found significant decreases in CRP levels after effective resolution of OSAS; thereby providing evidence that OSAS induces elevations in CRP independent of obesity in children.(153) Furthermore, when IL-6 and CRP levels were assessed in relation to sleep measures in the context of pediatric OSAS, similar associations emerged even among non-obese children, thereby confirming the biological plausibility of this association. In a subsequent study aiming to examine the metabolic implications of OSAS in children, we found that CRP levels were increased in both non-obese untreated OSAS (n=25) and in obese untreated OSAS children (n=37). Furthermore, CRP levels were decreased after treatment in both non-obese (4.0 ±0.9 to 1.1 ±0.2 μg/ml, $p<0.0001$) and in obese children (6.1± 1.0 to 2.4±0.6 μg/ml; $p<0.001$)(154). The link between CRP and OSAS in children has been further corroborated in recent studies. (155-158) Furthermore, while no dose-dependent relationship could be found between hsCRP and OSAS severity in a cohort of Greek children, those children with OSAS exhibited higher hsCRP serum concentrations when compared to snoring children without OSAS. (159) It is however important to emphasize that both genetic and environmental demographical factors may still account for some, if not a substantial proportion of the discrepancies among these studies, and it will definitely be important to explore the implications of specific CRP gene polymorphisms on these associations. In this context, a recent study in adults has pointed out the relevance of these polymorphisms in the population. (160) There is no doubt that the clinical relevance of elevated CRP in childhood OSAS and the risk of cardiovascular disease are currently undefined, and clearly merit prospective studies. Of note, we have shown that CRP may serve as a useful biomarker of OSAS-mediated cognitive morbidity in children. (10)

8. SUMMARY

In children, both obesity and OSAS share common pathways that lead to the induction of chronic low-grade inflammation, as epitomized by increases in CRP serum concentrations. The latter may not only accelerate the occurrence of endothelial dysfunction and promote atherogenesis, ultimately leading to cardiovascular disease, but may also induce favorable conditions for cognitive and behavioral susceptibility, sleepiness and depression, as well as ultimately accelerate obesogenic behaviors and the occurrence of diabetes. The coincident pathways leading to the existence of a pro-inflammatory state further support the conceptual framework whereby OSAS and obesity, either separately or in tandem will initiate and propagate cardiovascular or metabolic disease, even during early childhood. Thus, major efforts should be directed at establishing the value of routine CRP monitoring, as a potentially viable and valuable biomarker in the context of conditions such as OSAS or obesity, the latter serving as a prompt for great concern among pediatricians. Thus, early recognition and treatment of both obesity and OSAS will be of paramount importance for the immediate and future prevention of cardiometabolic and cognitive morbidities. In this context, it will be also important to identify potential interactions between environmental and lifestyle elements, as well as recognize genetically dependent effects afforded by gene-gene interactions and gene polymorphisms. Finally, research efforts focused on the use of combinatorial biomarkers for identification and stratification of morbidity risks in children with OSAS will be critical, since it is highly unlikely that a single biomarker, even as putatively robust as hsCRP, will become the sole indicator of prognosis and outcomes in affected children.

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