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Increased systemic inflammation overnight correlates with insulin resistance among children evaluated for obstructive sleep apnea

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Abstract

Purpose—Obstructive sleep apnea (OSA) in children is associated with obesity, insulin resistance, and elevated baseline inflammation as measured by high-sensitivity C-reactive protein (hsCRP). Our goal was to evaluate whether inflammation increases overnight among children suspected of having OSA and to determine whether worsened inflammation is associated with the degree of OSA severity, obesity, and/or insulin resistance.

Methods—Twenty-three children with clinical suspicion of OSA underwent a sleep study. Levels of hsCRP were tested the evening before and morning after the sleep study. Fasting insulin and glucose levels were measured from which the homeostasis model of insulin resistance (HOMA-IR) was calculated. Linear correlations were performed to evaluate relationships between

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hsCRP levels at baseline and change overnight (ΔhsCRP) vs. HOMA-IR, body mass index (BMI) *z*-score, and sleep study parameters related to O_2 saturation and the apnea-hypopnea index (AHI).

Results—Among children with OSA and the entire cohort, hsCRP values were correlated with HOMA-IR and BMI *z*-scores. HOMA-IR but not BMI *z*-score correlated with ΔhsCRP overnight in the entire cohort. Sleep study parameters, including AHI mean O_2 saturation overnight, REM O_2 nadir, and non-REM O_2 nadir were not correlated with hsCRP or ΔhsCRP overnight.

Conclusion—Among children being evaluated for OSA, degree of insulin resistance may be an important determinant of increased systemic inflammation overnight. Sleep study markers did not correlate with ΔhsCRP, leaving uncertain the role of OSA in increasing inflammation overnight. Further studies are needed to explore these associations and their potential mechanisms.

Keywords

Obstructive sleep apnea; Inflammation; hsCRP; Obesity; Insulin resistance; Oxygen desaturation; Adolescents

Introduction

Obstructive sleep apnea (OSA) consists of repetitive upper airway collapse during sleep, potentially causing oxygen desaturations and episodes of hypercapnia [1, 2]. OSA is strongly associated with obesity and insulin resistance and has been a problem of increasing importance in pediatrics in parallel with the epidemic of pediatric obesity [3]. However, while the prevalence of obesity in children has been closely followed [4], the prevalence of OSA in children is more difficult to estimate because the gold standard for assessment of OSA is an overnight sleep study. Sleep studies consist of multiple continuous measurements, including electroencephalogram, electromyogram, electrooculogram, electrocardiogram, plethysmograph, as well as oxygen saturation, end-tidal CO_2, and nasal/oral airflow measurements [1, 5]. The presence and severity of OSA are based on the apnea-hypopnea index (AHI, calculated as the number of apneic events per hour of total sleep time), as well as percentage of sleep time characterized by low oxygen saturations and elevated end-tidal CO_2 measurements. Using such studies, the prevalence of OSA in children is estimated to be between 2% and 12% [6–8].

In addition to its associations with increased risk of obesity and insulin resistance, obstructive sleep apnea is associated with underlying chronic inflammation [9, 10]. This is at least in part due to the intermittent hypoxic events in OSA that result in the production of nitric oxide (NO), the production of reactive oxygen species, and subsequent activation of monocytes [11, 12]. The relationship between OSA and inflammation has been demonstrated repeatedly in both adults [13–16] and children [17, 18]. However, it is not known if this level of inflammation changes in children overnight or if such a change could be associated with more severe findings of OSA. Also, it is important to note that underlying inflammation is itself associated with obesity and insulin resistance, which are also likely to contribute to further increases in inflammation [19, 20].

Given these associations between OSA, obesity, and underlying inflammation, our goal was to determine (1) whether the degree of systemic inflammation increases overnight among children with OSA and (2) whether change in inflammation correlated with the degree of severity of OSA, obesity, and insulin resistance.

Methods

Subjects

This study was approved by the UVa Institutional Review Board for Health Sciences Research. Children and adolescents were recruited from the pediatric sleep disorders clinic at the University of Virginia to sign an informed consent/assent prior to participation. Subjects were eligible to participate if they were aged 12–22 years old and were undergoing a sleep study for clinical indications. Exclusion criteria were known chronic inflammatory disease (cystic fibrosis, juvenile rheumatoid arthritis, lupus, and inflammatory bowel disease) or use of anti-inflammatory or antihypertensive medication within 12 h of arrival to the hospital for sleep study. A detailed history and physical examination was performed for each patient. Height, weight, and body mass index (BMI) were obtained.

Sleep study

Sleep studies were performed overnight from 9:00 P.M. to 7:00 A.M., according to standard protocol at the UVa sleep laboratory. Testing consisted of an electroencephalograph, electromyograph, electrooculograph, and electrocardiograph. Additional measurements included oxygen saturation by digital pulse oximetry, nasal/oral airflow by thermistor or nasal pressure cannula, end-tidal CO_2 by nasal cannula, and qualitative thoracic/abdominal movement by respiratory inductive plethysmography. Natural sleep was observed overnight. No sedation was administered. Central apneas, obstructive apneas, hypopneas, periodic breathing, the adequacy of gas exchange, and heart rate were recorded during sleep. Data were recorded on the SANDMAN (version 9.0) computerized polysomnography acquisition and storage system. No oxygen was used.

Sleep studies were all interpreted by the same sleep physician (PLY), who was blinded to other outcomes of the research study. The parameters used to diagnose sleep apnea were from clinical criteria recommended for use in children by the American Association of Sleep Medicine [21–23]: sleep efficiency (time spent asleep/total time in bed), sleep-onset latency (time to fall asleep after recording is begun), REM latency (time to first REM period after recording has begun), obstructive apneas (cessation of airflow for ≥2 breaths duration [22, 23], associated with a >90% fall in the signal amplitude for ≥90% of the entire respiratory event compared to the pre-event baseline amplitude, associated with continued or increased respiratory effort throughout the entire period of decreased airflow, the duration of the apnea is measured from the end of the last normal breath to the beginning of the first breath that achieves the pre-event baseline inspiratory excursion), hypopneas (associated with a ≥50% fall in the amplitude of the nasal pressure or alternative signal compared to the pre-event baseline excursion, lasts at least two missed breaths or the duration of two breaths as determined by the baseline breathing pattern from the end of the last normal breathing amplitude, the fall in the nasal pressure signal amplitude must last for ≥90% of the entire respiratory event compared to the signal amplitude preceding the event, the event is associated with an arousal, awakening, or ≥3% desaturation), and AHI (total number of apneas and hypopneas/h of sleep)[1, 5]. Subjects were considered to have OSA if the apnea index was greater than 1 (in the correct clinical context) or the hypopnea index was greater than 5 [22, 23]. Subjects were then classified as being OSA (+) or OSA (−).

Blood collection and assays for markers of inflammation

Venous blood samples were collected from each patient at 6:30 P.M. prior to each sleep study. The serum was isolated, immediately frozen in liquid nitrogen, and stored in a freezer at −80°C until processed. A boxed dinner was then given to each patient. After dinner, the patient was not allowed to eat or drink, with the exception of water, until after the morning

blood collection. The blood collection process was repeated at 7:30 A.M. after each sleep study.

Levels of high-sensitivity C-reactive protein (hsCRP) were measured in each plasma sample pre- and post-sleep study using the Immulite 2000 Automated Immunoassay Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL). High-sensitivity IL-6 (hsIL-6) and high-sensitivity TNF-α (hsTNF-α) were measured pre- and post-sleep study using standard ELISA kits (R & D Systems Inc., Minneapolis, MN). Fasting insulin and glucose were also measured post-sleep study, using the Immulite 2000. The intra- and inter-assay coefficients of variation were 1.6 and 3.3, respectively, for hsCRP, 3.0 and 5.6 for hsIL-6, 3.8 and 11.6 for hsTNF-α, and 3.5 and 5.6 for insulin. The sensitivities for hsCRP, hsIL-6, hsTNF-α, and insulin assays were 0.02–15 mg/dL, 0.312–10 pg/mL, 0.02–15 mg/dL, and 2–300 μIU/mL, respectively. For each assay, samples from all 23 patients were run simultaneously to minimize intra-assay variability.

Statistical analyses

BMI was expressed as a percentile adjusted for gender and age using growth charts by the Center of Disease Control (CDC) (http://www.cdc.gov/growthcharts/). A BMI percentile of 85–95 was classified as overweight and >95% was classified as obese. BMI *z*-scores (i.e., the number of standard deviations above/below the mean for age) were also calculated from CDC growth charts. Homeostasis model for insulin resistance (HOMA-IR) was calculated using the following formula: fasting insulin(μU/mL) × fasting plasma glucose(mmol/mL)/ 22:5 [24].

We compared differences in clinical and laboratory values between OSA (+) and OSA (−) subjects using *t* tests. Non-parametrically distributed variables were evaluated by Mann–Whitney tests, with significance considered at $p<0.05$. Additionally, we evaluated linear correlations between baseline hsCRP and ΔhsCRP as correlated with HOMA-IR, BMI *z*-score, AHI, mean O_2 saturation during sleep, O2 saturation during REM and non-REM (NREM) sleep to determine R^2 values. Because these correlation calculations involved related variables (evening and morning hsCRP, absolute, and percent ΔhsCRP), we used a Bonferroni adjustment to our threshold for significance, and significance was considered at $p<0.025$ for correlation calculation.

Results

We studied 23 children undergoing a sleep study for clinical indications; among them, nine were found to have OSA based on the results of their sleep study. Additional subject characteristics are shown in Table 1. There were no significant differences in age, BMI *z*-score, or HOMA-IR between groups. Subjects who were OSA (+) had a higher AHI than OSA (−) subjects. There were no other significant differences in sleep study parameters between groups.

With respect to markers of systemic inflammation, there were no significant differences in the levels of inflammatory markers or change in inflammatory markers overnight between subjects that were OSA (+) vs. OSA (−) (Table 1). Using paired *t* tests for individual subjects within each group, there was no significant change in hsCRP, hsIL-6, or hsTNF-α in either of the groups or in the groups combined (data not shown).

Linear relationships between hsCRP, dhsCRP and HOMA-IR, BMI, and inflammatory cytokines are shown in Table 2. Among subjects with OSA, HOMA-IR was significantly correlated with evening and morning levels of hsCRP while among the entire cohort HOMA-IR correlated with morning levels of hsCRP and ΔhsCRP reported as either the

absolute change or percent change. BMI *z*-score was associated with baseline levels of hsCRP but not ΔhsCRP.

Regarding measures of OSA severity (AHI, O_2 saturation during REM and non-REM nadir, and mean O_2 saturation), none of these measures were associated with baseline levels of inflammation or ΔhsCRP (Supplementary Table 1). None of the measures of OSA severity were correlated with HOMA-IR, either among the entire cohort or only those subjects with OSA (data not shown).

Discussion

Our study was unique in assessing for change in levels of inflammation overnight in a cohort of adolescents and in demonstrating that changes in inflammation overnight correlated with insulin resistance. The vast majority of prior studies on this topic have focused on baseline levels of inflammation and not on changes in inflammation overnight as their means of investigating interrelationships between inflammation, obesity, insulin resistance, and severity of OSA.

Many [13–18] but not all [25–28] prior studies evaluating these relationships have demonstrated a correlation between OSA severity (as measured by AHI) and baseline inflammation (usually assessed by levels of hsCRP). These relationships have been tested among large cohorts of adults [13–16] and children [17, 18] with OSA and the association has been further supported by data documenting that non-obese children have increased levels of inflammatory markers (hsCRP and IL-6) which return to control levels after tonsillectomy and adenoidectomy [8, 29].

The elevated degree of baseline inflammation in OSA has been postulated to occur as a result of multiple events related to hypoxemia and hypercapnia in OSA, including increase NO production overnight [30], increased oxidative stress [31], increased sympathetic activity [32], and activation of monocytes [11]. Because these pathophysiologic consequences of OSA occur overnight, it is reasonable to hypothesize that levels of inflammation may worsen overnight among individuals affected by OSA. Indeed, there appears to be a diurnal variation in hsCRP levels among individuals with OSA, with a trough at approximately 8:00 P.M. and a peak around noon [33]. No such diurnal variation in hsCRP has been noted in the general population [34].

In evaluating the change in inflammation overnight as related to the degree of OSA severity, we did not find correlations between sleep study parameters (AHI, mean O_2 saturation overnight, REM nadir, and non-REM nadir) and absolute ΔhsCRP overnight. Given that AHI and hsCRP have been previously shown to be correlated with hsCRP [13, 17, 18], we may have been underpowered to detect a true relationship between AHI, measures of oxygen saturation, and ΔhsCRP. Nevertheless, it must be noted that our R^2 values for these relationships were all close to 0, suggesting a lack of correlation. Additionally, our subjects with OSA had a mean AHI of 13.5 and were thus not as severely affected as other reports. It may be that these correlations are less apparent in a less affected population.

Among our subjects, the degree of insulin resistance (as measured by HOMA-IR) was the only factor significantly correlated with ΔhsCRP, expressed as both absolute and percent ΔhsCRP. HOMA-IR was also correlated with morning levels of hsCRP, as was BMI *z*-score. Along these same lines, it is notable that while OSA severity has been shown to be an independent predictor of baseline inflammation, the degree of obesity (as measured by BMI) has been found to be a better predictor. This is supported by R^2 values for BMI-hsCRP of 0.38–0.53 compared to R^2 values for AHI-hsCRP of 0.30–0.37 [13, 17, 18]. The strength of relationship between BMI and hsCRP thus suggests that influences related to obesity

predominate over influences of intermittent hypoxia itself. Obesity is thought to relate to underlying inflammation via the production dysfunction of hypertrophied adipocytes, including the release of inflammatory cytokines and chemoattractants that recruit macrophages to adipose tissue [20]. These underlying processes are more marked in the setting of insulin resistance and metabolic syndrome, which are both strongly associated with OSA [19]. While similar BMI-hsCRP correlations have frequently been shown among children [17, 18] and adults [13, 25], undergoing sleep studies and HOMA-IR-hsCRP or insulin-hsCRP correlations have been shown among children in other settings [35], we are not aware of HOMA-IR-hsCRP correlations being tested among children undergoing a sleep study. We are also unaware of other studies investigating associations with ΔhsCRP overnight among children undergoing a sleep study.

It is unclear why insulin resistance but not BMI would have effects on overnight changes in levels of hsCRP. It is possible that the increase in hsCRP was due to effects of intermittent hypoxia on monocytes in adipose tissue, as has been proposed [11]. Unfortunately, our data set was too small to evaluate for interactions that might have shed more light on relationships between the severity of OSA and insulin resistance. It is possible that insulin resistance potentiates the effects of intermittent hypoxia on underlying inflammation and that this effect is due more to the number and activity of adipocyte-associated monocytes among insulin-resistant individuals than to the severity of hypoxia in OSA [19, 20].

In addition to small sample size, a further limitation to our study was that we did not obtain baseline fasting insulin and glucose values prior to the sleep study, nor did we perform a more detailed evaluation for metabolic syndrome status of the subjects. Future studies will be needed to confirm our findings and further explore the relationship between the metabolic syndrome. We also did not evaluate the duration of subjects' clinical symptoms—either of OSA or of obesity. It is possible that a longer duration of disease could worsen the overnight inflammatory response.

In conclusion, among children and adolescents undergoing a sleep study, degree of insulin resistance correlated significantly with increased overnight increase in hsCRP, while measures of oxygen desaturation and AHI were not correlated. These data may extend previous investigations revealing that sequelae of adiposity have a stronger influence on systemic inflammation than does OSA itself. The effect of OSA on overnight changes in inflammation requires further investigations in larger cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Subject characteristics by OSA status

	OSA (+)	OSA (−)	*p* value
Number (males)	9 (4)	15 (10)	0.386
Age, mean (years)	14.2 (1.66)	14.6 (1.72)	0.577
Age, range (years)	12–17	12–18	
BMI *z*-score	1.30 (1.03)	1.44 (1.30)	0.785
Sleep study indices			
Apnea-hypopnea index	**13.5 (11.9)**	**0.78 (0.86)**	**<0.001**
AHI, range	5.9–40.4	0–2.5	
REM O_2 saturation nadir	93.5 (5.68)	95.8 (1.66)	0.154
Non-REM O_2 saturation nadir	92.9 (4.9)	93.9 (2.4)	0.520
Mean O_2 saturation	98. 5 (1.5)	98.5 (0.5)	0.880
Insulin resistance			
HOMA-IR	8.7 (3.9)	9.0 (7.0)	0.171
Insulin (fasting, IU/mL)	79.9 (122)	37.8 (39.2)	0.210
Glucose (fasting, mg/dL)	101.7 (3.6)	95.4 (9.7)	0.917
Systemic inflammation			
hsCRP (mg/L)			
Evening hsCRP	1.70 (2.68)	1.88 (2.10)	0.860
Morning hsCRP	1.69 (2.49)	2.03 (2.60)	0.882
Change hsCRP (absolute)	−0.002 (0.31)	0.15 (1.03)	0.343
Change hsCRP (percent)	12.7 (27.0)	4.0 (21.3)	0.140
hsIL-6 (pg/mL)			
Evening hsIL-6	1.84 (1.73)	2.29 (2.29)	0.643
Morning hsIL-6	1.69 (1.10)	1.61 (1.27)	0.882
Change hsIL-6 (absolute)	−0.15 (0.96)	−0.68 (1.41)	0.343
Change hsIL-6 (percent)	48.6 (126.3)	−8.8 (41.5)	0.140
hsTNF-a (pg/mL)			
Evening hsTNF-α	0.94 (0.46)	0.90 (0.48)	0.850
Morning hsTNF-α	0.99 (0.24)	0.98 (0.10)	0.968
Change hsTNF-α (absolute)	0.0.54 (0.10)	0.085 (0.10)	0.706
Change hsTNF-α (percent)	12.2 (30.2)	9.3 (10.0)	0.772

Mean values are listed with standard deviations in *parentheses*. Items in *bold* are statistically significant ($p<0.05$)

OSA obstructive sleep apnea, *BMI* body mass index, *AHI* apnea-hypopnea index, *REM* rapid eye movement, *HOMA-IR* homeostasis model for insulin resistance, *hsCRP* high-sensitivity C-reactive protein, *hsIL-6* high-sensitivity IL-6

Table 2

Linear correlations related to baseline hsCRP and ΔhsCRP

	Full cohort *N*=23		OSA subjects only *N*=9	
	R^2	*p* value	R^2	*p* value
Insulin resistance and body mass index				
HOMA-IR vs. evening hsCRP	0.00	0.858	**0.76**	**0.011**
HOMA-IR vs. morning hsCRP	**0.43**	**0.002**	**0.80**	**<0.001**
HOMA-IR vs. change hsCRP (absolute)	**0.25**	**0.025**	0.11	0.477
HOMA-IR vs. change hsCRP (%)	**0.31**	**0.011**	0.01	0.870
BMI *z*-score vs. evening hsCRP	**0.46**	**0.001**	0.51	0.031
BMI *z*-score vs. morning hsCRP	**0.41**	**0.001**	**0.57**	**0.019**
BMI *z*-score vs. change hsCRP (absolute)	0.00	0.789	0.01	0.771
BMI *z*-score vs. change hsCRP (%)	0.05	0.955	0.02	0.663
Inflammatory markers				
Evening hsCRP vs. evening hsIL-6	**0.68**	**<0.001**	**0.71**	**<0.001**
Morning hsCRP vs. morning hsIL-6	**0.8**	**<0.001**	**0.87**	**0.003**
Change hsCRP vs. change hsIL-6 (absolute)	0.19	0.047	0.22	0.207
Change hsCRP vs. change hsIL-6 (%)	**0.27**	**0.015**	**0.64**	**<0.001**
Evening hsCRP vs. evening hsTNF-α	0.01	0.713	0.15	0.385
Morning hsCRP vs. morning hsTNF-α	0.03	0.489	0.01	0.848
Change hsCRP (%) vs. change hsTNF-α (absolute)	0.06	0.323	0.74	0.028
Change hsCRP (%) vs. change hsTNF-α (%)	0.14	0.145	0.40	0.175

R^2 values for correlations. Items in *bold* are significant ($p<0.025$ after Bonferroni adjustment for multiple comparison)

HOMA-IR homeostasis model for insulin resistance, *hsCRP* high-sensitivity C-reactive protein, *BMI* body mass index, *hsIL-6* high-sensitivity IL-6, *hsTNF-α* high-sensitivity TNF-α