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Original Research

SLEEP MEDICINE

Sleep-Disordered Breathing and Uric Acid in Overweight and Obese Children and Adolescents*

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Objective: **The aim of this study was to determine whether the severity of sleep-disordered breathing (SDB) was associated with increased levels of uric acid (UA), both in serum and in urine, as a marker of tissue hypoxia, in a sample of overweight and obese subjects, irrespective of indexes of adiposity.**

Methods: **Consecutive subjects underwent polysomnography, fasting blood sampling, and 24-h urine collection. Outcome parameters were serum UA, UA excretion ([24-h urinary UA × serum creatinine]/urine creatinine) and urinary UA/creatinine ratio.**

Results: **A total of 93 subjects were included (44% boys; mean [± SD] age = 11.1 ± 2.5; 73% obese). A fasting measurement of serum UA levels was available for 62 patients. The respiratory disturbance index was a significant covariate ($\beta = 0.09 \pm 0.03$; $p = 0.01$) in the regression model for serum UA, controlling for sex ($\beta = 0.32 \pm 0.29$; $p = 0.3$), puberty ($\beta = 0.87 \pm 0.34$; $p = 0.01$), and waist circumference ($\beta = 0.04 \pm 0.01$; $p = 0.005$). The percentage of total sleep time with arterial oxygen saturation ≤ 89% ($\beta = 0.94 \pm 0.45$; $p = 0.04$) was also significantly associated with serum UA level, controlling for sex ($\beta = 0.22 \pm 0.30$; $p = 0.5$), puberty ($\beta = 0.83 \pm 0.35$; $p = 0.02$), and waist circumference ($\beta = 0.04 \pm 0.02$; $p = 0.02$). None of the SDB variables correlated with UA excretion or with urinary UA/creatinine ratio.**

Conclusion: **This study in overweight children and adolescents demonstrated a relationship between the severity of sleep apnea and increased levels of serum UA, independent of abdominal adiposity. In view of the known associations between UA and cardiovascular risk, this finding may contribute to the mechanisms linking SDB with cardiovascular morbidity.**

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Key words: adolescence; childhood; obesity; sleep-disordered breathing; uric acid

Abbreviations: BMI = body mass index; OSAS = obstructive sleep apnea syndrome; RDI = respiratory disturbance index; Sa_{O_2} = arterial oxygen saturation; SDB = sleep-disordered breathing; UA = uric acid

Overweight and obese children and adolescents have a higher risk of sleep-disordered breathing (SDB).[1–4] Sleep apnea in obese children is often associated with oxygen desaturation, and this is proportional to the degree of obesity.[2] This could hypothetically result in tissue hypoxia. Tissue hypoxia is commonly defined as inadequate oxygen supply against oxygen demand in the integrity of cellular metabolic processes. This results in an impaired

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formation of adenosine triphosphate from adenosine diphosphate and in a net degradation of adenosine triphosphate to adenosine diphosphate and monophosphate. This leads to the release of purine intermediates and the purine catabolic end product, uric acid (UA).[5] Previous studies[6–8] have shown that elevated levels of these degradation products provide good indexes of tissue hypoxia in, for instance, infants with respiratory distress syndrome.[6–8]

Furthermore, increased urinary UA excretion has been shown in adult patients with obstructive sleep apnea syndrome (OSAS) with normalization following continuous positive airway pressure treatment.[9] To the best of our knowledge, there have been no reports in children or adolescents with SDB that have attempted to examine tissue hypoxia by studying UA metabolism.

An increased level of UA can thus be viewed as a marker of oxidative stress. Only a single study[10] evaluated the presence of oxidative stress, by determining urinary F2-isoprostane metabolites, in children with SDB, but found no relation between these metabolites and SDB. Since oxidative stress-related mechanisms are probably one of the most important contributors to cardiovascular morbidity in adult subjects with SDB,[11,12] it is therefore important to further investigate whether sleep apnea could lead to hypoxic stress in children and adolescents.

The aim of this study was therefore to examine whether the severity of SDB was associated with increased UA excretion both in serum and in urine, as a biological marker of tissue hypoxia and of oxidative stress, in a sample of overweight and obese subjects, irrespective of indexes of adiposity.

Materials and Methods

Patient Characteristics

We recruited children and adolescents who were 6 to 17 years of age who presented as overweight or obese between January 2001 and June 2006 at the Pediatric Obesity Clinic of the Antwerp University Hospital. Children were not included when they had any chronic medical condition, or any genetic, neuromuscular or craniofacial syndromes. Patients were classified as prepubertal or pubertal.[4] All subjects underwent all measurements as part of their routine clinical evaluation. This case study was approved by the Ethics Committee of the Antwerp University Hospital.

Anthropometry

Height, weight, waist circumference, and waist/hip ratio were measured by standardized techniques.[13] Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters and was further analyzed as z-score. Children were classified as overweight or obese according to the definitions of the International Obesity Task Force.[14]

UA Measurements and Analysis

Fasting blood samples were obtained from the subjects on the morning of the day of hospital admission with the use of an indwelling venous line for measurements of UA and creatinine levels. Urine collection was performed throughout a 24-h period, starting on the morning of the day of hospital admission. The calculation of UA excretion per deciliter of creatinine clearance has been proposed as the preferred means of determining UA excretion both in children and in adults, and is calculated as the product of urinary UA and serum creatinine concentrations divided by urine creatinine concentration (all in milligrams per deciliter).[15] UA excretion of < 0.56 mg/dL was considered to be normal.[15,16] The urinary UA/creatinine ratio was also calculated.

Polysomnography

A detailed description of the standard polysomnography procedure was described previously.[4] Obstructive apnea was defined as the presence of chest and/or abdominal wall motion associated with a cessation of airflow. Central apnea was defined as the absence of chest and/or abdominal wall motion associated with a cessation of airflow, lasting ≥ 10 s or of any length but associated with $\geq 4\%$ desaturation. Hypopnea was defined as a $\geq 50\%$ decrease in the amplitude of the airflow signal followed by $\geq 4\%$ desaturation. Respiratory disturbance index (RDI) was defined as the total number of apneas and hypopneas, as defined above, per hour of sleep. All desaturations defined as decreases of $\geq 4\%$ from baseline arterial oxygen saturation (Sa_{O_2}) were quantified (oxygen desaturation index). Measurements associated with poor pulse tracings or following movement, were excluded. For each child, the mean Sa_{O_2}, the Sa_{O_2} nadir, and the total duration of desaturation, expressed as a percentage of total sleep time, were recorded.

Statistical Analysis

The statistical analysis was performed with a statistical software package (Statistica, version 7.0; StatSoft; Tulsa, OK). All data are summarized as the mean $\pm$ SD. The Kolmogorov-Smirnov test was used to test normality. To illustrate the various degrees of SDB severity in our cohort, we compared polysomnographic characteristics among three groups, based on more recent published normative data in children,[17,18] as follows: RDI < 2; RDI ≥ 2 and < 5; and RDI ≥ 5. Comparisons among these three groups were performed with one-way analysis of variance or with the Jonckheere-Terpstra test as a nonparametric alternative.

To examine whether SDB was associated with increased UA excretion, we used the following outcome variables: serum UA; UA excretion; and urinary UA/creatinine ratio. First, the Pearson correlation coefficient was calculated between the latter outcome variables and the variables reflecting SDB severity (*ie*, RDI, oxygen desaturation index, mean Sa_{O_2}, Sa_{O_2} nadir, or the percentage of total sleep time spent with $Sa_{O_2} \leq 89\%$). In case of a significant correlation, we proceeded with multiple linear regression analysis to determine whether the correlation persisted after controlling for sex, puberty, and adiposity. Controlling for adiposity was done by the inclusion of one measure of adiposity with the highest univariate correlation coefficient with the respective outcome (*ie*, BMI z-score, waist circumference, or waist/hip ratio). Sex and puberty were included as dummy variables (1 for female patients; 1 for pubertal). In the case of multiple significant univariate correlations between SDB and UA variables, the SDB variables were introduced separately into the model, because of possible multicollinearity. Residual analysis was performed for each regression model to test the validity of model assumptions. For all analyses, $p < 0.05$ was considered to be statistically significant.

Table 1—*Polysomnographic Characteristics of Subjects With and Without SDB

Variables	RDI < 2 (n = 53)	RDI ≥ 2 and < 5 (n = 32)	RDI ≥ 5 (n = 8)	p Value
Total sleep time, min	455.0 ± 49.1	465.4 ± 41.0	460.2 ± 40.8	0.6†
RDI	0.8 ± 0.5	3.0 ± 0.9	13.1 ± 8.9	< 0.0001‡
Sa_{O_2}, %	97.0 ± 0.7	96.7 ± 0.6	96.1 ± 1.1	0.005‡
Sa_{O_2} nadir, %	91.7 ± 3.0	87.2 ± 3.8	83.9 ± 4.7	< 0.0001‡
Total sleep time, %				
$Sa_{O_2} \geq 95\%$	98.7 ± 2.2	97.1 ± 2.8	82.2 ± 23.7	< 0.0001‡
$Sa_{O_2} > 89$ to < 95%	1.3 ± 2.2	2.8 ± 2.7	17.1 ± 23.0	< 0.0001‡
$Sa_{O_2} \leq 89\%$	0.0 ± 0.1	0.1 ± 0.1	0.6 ± 0.8	< 0.0001‡
Oxygen desaturation index	0.6 ± 0.5	2.4 ± 1.1	12.4 ± 8.3	< 0.0001‡

*Values are given as the mean ± SD, unless otherwise indicated.
†One-way analysis of variance.
‡Jonckheere-Terpstra test.

Results

Patient and Polysomnographic Characteristics

A total of 94 children and adolescents were initially included in the study; afterward, 1 subject was excluded because of an abnormal serum creatinine value of 1.5 mg/dL. Of those subjects, 44% were boys, 58% were prepubertal (mean age, 11.1 ± 2.5 years; age range, 6.3 to 16.3 years). The mean BMI z-score was 2.31 ± 0.50 (range, 1.32 to 3.83); and 25 subjects (27%) were classified as overweight, and 68 subjects (73%) as obese. All subjects were nondiabetic.

All children had a normal UA excretion rate (mean rate, 0.33 ± 0.06 mg/dL; range, 0.20 to 0.47 mg/dL); and the mean urinary UA/creatinine ratio was 0.58 ± 0.13 (range, 0.31 to 0.85). There were 15 subjects (16%) with a total urinary creatinine concentration of < 500 mg/d, possibly suggesting an unreliable 24-h urinary collection. Excluding these 15 subjects did not result in significant changes in any of the subsequent analyses. A fasting measurement of serum UA was available for 62 patients (67%). Mean serum UA was 4.8 ± 1.4 (range, 1.5 to 8.8). The polysomnographic data of the subjects with or without SDB are presented in Table 1. There was no difference in age, sex, pubertal stage distribution, and anthropometric variables between these three groups.

Relation Between the Severity of SDB and UA Metabolism

RDI, oxygen desaturation index, and percentage of total sleep time with $Sa_{O_2} \leq 89\%$ correlated significantly with serum UA levels. None of the SDB variables were correlated with UA excretion or with urinary UA/creatinine ratio (Table 2). RDI and oxygen desaturation index were almost perfectly correlated ($r = 0.99$; $p < 0.001$); therefore, oxygen desaturation index was not used in the regression analysis. RDI and the percentage of total sleep time with $Sa_{O_2} \leq 89\%$ remained significant in their respective multiple regression models for serum UA, controlling for sex, puberty, and waist circumference (Tables 3, 4).

Discussion

This is the first study to assess the influence of SDB on UA metabolism in overweight children and adolescents. This study demonstrates is that the severity of sleep apnea was associated with higher serum UA levels after controlling for gender, puberty, and adiposity.

UA metabolism and renal handling in children differ from those in adults. From childhood to adolescence, a child's serum UA level increases linearly; the urinary UA/creatinine ratio is higher in

Table 2—*Correlation Analysis Between the Severity of SDB and UA Metabolism*

Variables	RDI	Oxygen Desaturation Index	Mean Sa_{O_2}	Sa_{O_2} Nadir	Percentage of Total Sleep Time With $Sa_{O_2} \leq 89\%$
Serum UA	0.26*	0.29*	−0.07	−0.18	0.39†
UA excretion	−0.06	−0.03	−0.03	0.06	−0.16
Urinary UA/creatinine ratio	−0.04	−0.03	0.01	−0.10	−0.14

*$p < 0.05$.
†$p < 0.01$.

Table 3—*Multiple Linear Regression Analysis With Serum UA as Outcome Variable (Adjusted R^2 = 0.40) and RDI as Predictor Variable, Controlling for Sex, Puberty, and Waist Circumference*

Variables	β ± SE	Partial Correlation Coefficient	p Value
Intercept	0.46 ± 1.18		0.7
Sex	0.32 ± 0.29	0.14	0.3
Puberty	0.87 ± 0.34	0.32	0.01
Waist circumference	0.04 ± 0.01	0.36	0.005
RDI	0.09 ± 0.03	0.32	0.01

young children and declines to adult levels during early childhood.[15] It is, therefore, necessary to control for sex and pubertal stage when studying UA metabolism in children and adolescents, which was done in the present study.

The independent relationship between both RDI and percentage of total sleep time with $Sao_2 \leq 89\%$ and serum UA in our study suggests that sleep apnea in these overweight subjects is severe enough to cause tissue hypoxia, which is marked by increased levels of serum UA. RDI was almost perfectly associated with the oxygen desaturation index, which is considered to be one of the most important markers of intermittent hypoxia. It is, therefore, reasonable to assume that the repetitive apneas and hypopneas encountered during sleep are associated with intermittent hypoxia, which, together with the total duration of desaturation (*ie*, the percentage of total sleep time spent with an $Sao_2 \leq 89\%$), is responsible for increased serum UA levels. It was not possible in the statistical analysis to separate the contribution of RDI independent of the duration of desaturation, because of multicollinearity between both variables.

A study[19] in 85 adult patients referred for suspected SDB, also found a significant correlation between serum UA levels and the apnea-hypopnea index. The authors[19] also pointed out multicollinearities of UA with markers of obesity and adiposity. Similar correlations were also present in this study. Abdominal adiposity correlated with serum UA levels and inversely with urinary UA/creatinine ratio (results not shown). To control for these confounding factors, the relation between SDB and UA metabolism was examined using multiple regression analysis. It is, however, still possible that the regression analysis only partially adjusted for this confounding effect. This finding needs thus to be confirmed by interventional studies that will examine the effect of the treatment of SDB on serum UA levels. We also recommend further studies in nonoverweight children with sleep apnea to examine the direct contribution of SDB on UA metabolism.

Table 4—*Multiple Linear Regression Analysis With Serum UA as Outcome Variable (Adjusted R^2 = 0.39) and % of Total Sleep Time With $Sao_2 \leq 89\%$ as Predictor Variable, Controlling for Sex, Puberty, and Waist Circumference*

Variables	β ± SE	Partial Correlation Coefficient	p Value
Intercept	1.05 ± 1.27		0.4
Sex	0.22 ± 0.30	0.10	0.5
Puberty	0.83 ± 0.35	0.30	0.02
Waist circumference	0.04 ± 0.02	0.31	0.02
Percentage of total sleep time with $Sao_2 \leq 89\%$	0.94 ± 0.45	0.28	0.04

Several studies[9,20–22] in adults with OSAS have also shown an overnight increase in urinary UA/creatinine ratio compared to control subjects and/or a decline of this ratio after treatment with continuous positive airway pressure. Saito et al[22] also demonstrated, despite the absence of a correlation between the severity of sleep apnea and the overnight change in urinary UA/creatinine ratio, a significant correlation between this ratio and serum levels of adenosine, which is considered to be another marker of tissue hypoxia in patients with OSAS.[23] Contrary to the results of studies in adults, we could not demonstrate a relation between the severity of sleep apnea and urinary UA metabolism. This might be due to our urine collection procedure, which has to be considered as a study limitation. The urinary indexes in our study were calculated from one 24-h collection. In most adult studies, two collections were performed to calculate an overnight increase in urinary UA excretion, which is probably a more sensitive technique for checking for an influence of sleep apnea on UA excretion. In future studies, we will have to confirm this hypothesis by performing two urine collections, one daytime collection and one collection of the first morning voiding.

The relevance of our main finding, the relation between the severity of SDB and increased serum UA levels, is twofold. First, the relationship between sleep and UA level could merely reflect the presence of oxidative stress. As already noted, oxidative stress is one of the most important mediators linking SDB with increased cardiovascular morbidity in adults.[11,12] Second, increased serum UA level is also an independent risk factor of cardiovascular disease in high-risk individuals.[24] Furthermore, it may also play a direct causal role by mechanisms such as the development of hypertension, platelet dysfunction, increased oxidation of biomolecules, increasing inflammation, and vascular smooth muscle cell proliferation.[24] UA is also already associated with certain cardiovascular risk factors in

children.[25–27] In this view, increased levels of UA could be another one of the mechanisms linking sleep apnea with cardiovascular morbidity.

In conclusion, this is the first study in overweight children and adolescents that has demonstrated a relationship between the severity of sleep apnea and increased levels of serum UA, independent of abdominal adiposity. This finding could indicate that sleep apnea results in tissue hypoxia in our subjects, which needs to be confirmed by interventional studies. In view of the well-known associations between UA and cardiovascular morbidity, this may be one of the mechanisms linking sleep apnea and an increased cardiovascular risk profile.

Finally, we could not document a relation between SDB and urinary UA metabolism. However, this could be due to our collection procedure. To confirm this, future research has to be performed with a separate collection of the first morning voiding.

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