Cardiometabolic risk profile in non-obese children with obstructive Sleep Apnea Syndrome

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Abstract

Obstructive sleep apnea syndrome (OSAS) in childhood is a complex disease primarily due both to adenotonsillar hypertrophy and pediatric obesity. Notably, inflammation has been recognized as one of the most important shared pathogenic factor between obesity and OSAS resulting in an increased cardiometabolic risk for these patients. To date, evidence is still limited in non-obese population with OSAS.

We aimed to evaluate the cardiometabolic risk profile of a pediatric population of non-obese subjects affected by OSAS. A total of 128 school-aged children (mean age 9.70 ± 3.43) diagnosed with OSAS and 213 non-OSAS children (mean age 9.52 ± 3.35) as control group were enrolled. All subjects underwent a complete clinical and biochemical assessment (including white blood cell count (WBC), platelet count (PLT), mean platelet volume (MPV),% of neutrophils (NEU%), C- reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), uric acid, fasting insulin, iron, ferritin, and transferrin levels) .

A significant association between inflammation markers (including WBC, PLT, MPV, NEU%, ferritin, CPR, and ESR) and OSAS was found (all $p < 0.001$). Children with OSAS also showed increased transaminase, glucose, uric acid, and insulin levels (all $p < 0.001$) compared to healthy controls.

Conclusion: Taken together, these findings suggested a worse cardiometabolic profile in non-obese children with OSAS. Given the pivotal pathogenic role of inflammation both for hypoxiemia and metabolic derangements, therapeutic strategies for OSAS might also counteract the increased cardiometabolic risk of these patients, by improving their long-term quality of life.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) in childhood represents a complex disease mainly linked both to adenotonsillar hypertrophy and obesity epidemic at this age, particularly in the Southern of Italy[1]. Several impairments have been related to OSAS in children including neurocognitive [2] and behavioral disorders [3], growth hormone deficiency [4], enuresis [5], systemic inflammation, cardiovascular disease [6], and imbalance in lipid homeostasis [7].

Particularly, an inflammatory state has been largely accepted as one of the major pathophysiological mechanisms underlying both obesity and OSAS. Over the last decades, several studies have focused on the role of potential biomarkers of pediatric OSAS[8], but no specific determinants in this field have been currently identified, likely due to the overlap of various comorbidities potentially acting as confounding factors[9,10]. Noteworthy, evidence has linked sleep duration to different cardiometabolic markers in a pediatric cohort[11]. More, changes in sleep duration and quality have been related to rapid serum increase of C-reactive protein (CRP) [12–14] insulin [15,16] and lipids[17].

Adipose tissue is one of the main sources of inflammatory cytokines (including IL-6). CRP is produced by the liver in response to raising levels of IL-6,derived from adipose tissue and closely related to fat mass[18].

Moreover, some studies have also suggested that OSAS might be associated with body fat deposition in specific areas, directly linked to the severity of clinical features and to visceral fat deposits, in turn closely related to metabolic derangements than subcutaneous fat[18].

Of note, a significant association has been highlighted between increased CRP levels in children with OSAS and both severity disease and treatment administration (e.g. CPAP)[19–21]. Indeed, CRP might be considered as a predictor of cardiovascular morbidity [22], with a direct effect on the atheromatic lesions development by reducing nitric oxide synthesis inducing adhesion molecule expression in endothelial cells [23,24]. Given that, children with high CRP levels may be considered at greater risk of developing long-term cardiovascular complications. Interestingly, vascular injury markers and endothelial activation factors such as adhesion molecules, fat-binding protein and circulating molecules, have been shown to be increased in children with OSAS, and associated with endothelial dysfunction[25–28]. In addition, the major role of obesity as cardiovascular risk factor has been studied already in childhood[29].

In this perspective, pediatric OSAS represents a tangled disease with multiple interrelated pathogenic factors. Besides, the shared inflammatory pathway between OSAS and obesity could make this latter as a confounder for sleep breathing problems.

Despite a large amount of studies evaluating OSAS in subjects with obesity [4,9,14,17], evidence in non-obese children is still scarce[16,31].

To fill this gap, we aimed to investigate the cardiometabolic risk profile in a population of non-obese children affected by OSAS.

2. Materials And Methods

2.1. Ethical approval study design

The present study was conducted according to the Declaration of Helsinki [32] and all parents of the enrolled children (both OSAS and Control group) gave their informed consent for participating to study. The Departmental Ethic Committee of our Institution approved the study.

2.2. Study population

We enrolled 128 school-aged children (mean age 9.70 ± 3.43) diagnosed with OSAS consecutively attending the Sleep Laboratory for Pediatric Age at Child and Adolescent Neuropsychiatry Clinic of our University between September 1th 2015 and November 30th 2017.

OSAS was diagnosed by overnight nocturnal polysomnographic examination according to the diagnostic ICSD-3 criteria[33].

Exclusion criteria were considered as follows: overweight (BMI-SDS > 85° percentile) and/or obesity (BMI-SDS > 95° percentile), neurological disorders (i.e. primary headaches, epilepsy, cerebral palsy), craniofacial genetic syndromes associated with sleep-related breathing disorders (e.g. Down, Prader-Willi, Crouzon, Pierre-Robin, velocardiofacial syndrome), psychiatric illness (e.g. mood disorders, anxiety disorders, attention deficit hyperactivity disorder (ADHD), psychosis), and psychoactive drugs treatment.

As control group, 213 healthy children (mean age 9.52 ± 3.35) without OSAS (AHI < 1.0-1.2 event/hour) at the same University Clinic.

All subjects underwent blood tests for the detection of the following parameters: white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), platelet count (PLT), mean platelet volume (MPV),% of neutrophils (NEU%),% of lymphocytes (LINF%),% of Monocytes (MON%),% of eosinophils (EOS%),% of Basophils (BASO%), albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), Sodium (Na), Potassium (K), Chlorine (Cl), Phosphorus (P), Calcium (Ca), iron (Fe), ferritin, transferrin, uric acid, alkaline phosphatase, lactate dehydrogenase (LDH), transferrin, CRP, erythrocyte sedimentation rate (ESR), fasting glucose, and insulin.

2.3. Polysomnography data collected selection

In order to establish the presence of OSAS in the experimental group, all the polysomnography (PSG) data collected from inpatients children between September 1th 2015 and November 30th 2017 were reviewed and analyzed.

OSAS severity was determined according to the current guidelines specified by the American Academy of Sleep Medicine (AASM): mild OSAS was defined by an obstructive apnea/hypopnea index (AHI) of 1 to < 5 events per hour; moderate OSAS was defined as ≥ 5 to < 10 events/hour, and severe OSAS as ≥ 10 events/hour.

2.4. Statistical analysis

Data were expressed as mean ± standard deviation. Kolmogorov-Smirnov test was used to examine normal distribution of the population. Differences for continuous variables were analyzed using ANOVA if normally distributed, or the Kruskal-Wallis test if non-normally distributed. Not-normally distributed variables were log-transformed before the analysis, but raw means are shown. Considering the relatively limited number of our sample and in order to rule out possible type II errors, the effect sizes using Cohen's d value was calculated. Cohen's d is defined as the difference between two means divided by their pooled standard deviation. According to Cohen, 0.2 is indicative of a small effect, 0.5 of a medium effect size and 0.8 of a large effect size.

Statistical analyses were performed using the STATISTICA software (data analysis software system, version 6, StatSoft, Inc. (2001).

The effect size was calculated with the online software Social Science Statistics (https://www.socscistatistics.com/effectsize/default3.aspx). P-values < 0.05 were considered statistically significant.

3. Results

The main features of the OSAS and non-OSAS group were showed in Table 1. No differences were found for age (p = 0.63), gender (p = 0.78) and z-score BMI (p=0.462) (Table 1).

As expected, in children with OSAS all the parameters evaluated by PSG (AHI, ODI, SpO_2% and mean desaturation O_2) were significantly lower than controls (p<0.001) (Table 1).

Inflammation markers levels (including WBC, PLT, MPV, NEU%, CRP, ESR, and ferritin) were significantly higher in the OSAS group compared to non OSAS group (all p< 0.001) (Table 2).

More, subjects suffering from OSAS showed increased serum glucose, insulin, uric acid, ALT, and AST levels than healthy controls (all p <0.001) (Table 2).

According to the effect size calculation, the Cohen's d appeared to be with large effect for the following parameters: WBC, MCV, PLT, MPV, NEU%, BASO%, AST, ALT, GGT, iron, serum uric acid, LDH, transferrin, CRP, and insulin (Table 2).

4. Discussion

In our study, we provided intriguing evidence for a worse cardiometabolic profile in a cohort of non-obese children with OSAS.

Sleep-Related Breathing Disorders (SRDB) are common in children and adolescents [39–41], with a different severity ranging from primary snoring to OSAS[39]. OSAS is a complex disease in which several risk factors (e.g. inflammation, obesity, etc.) are interrelated[42,43]. To date, available scientific findings in this field are still conflicting and mainly focused on subjects with obesity. Given the well-recognized role of obesity as major cardiometabolic risk factor[36–38], studies examining OSAS subjects with obesity might suffer from some limitations due to the potential pathophysiological overlap between these diseases.

In this perspective, findings from our non-obese population allow to expand knowledge in this research area. In fact, it could be supposed that gas exchange abnormalities and sleep disturbance characterizing OSAS promote inflammatory responses, as supported by the increased CRP levels observed in our cohort.

The association between SRDB and cardiovascular disease in pediatric age has been well documented, particularly in children with endothelial function impairment[39–41]. More, these patients experienced recurrent episodes of hypoxiemia leading to an increase in sympathetic activity, oxidative stress, and inflammation (mainly expressed as elevated serum C-reactive protein levels) that enhanced endothelial dysfunction[39,40].

Evidence also supported a close relationship between the night-time breathing habits and non-specific biochemical markers of inflammation with particular reference to the findings of neutrophilia in OSAS children [44–47]. In this regard, results from our study not only confirmed these findings but provided further evidence in a non-obese pediatric cohort, by underscoring the pivotal pathogenic role of the inflammation also in a such selected population.

As previously reported, both metabolic (including metabolic syndrome, insulin-resistance (IR), and non-alcoholic fatty liver disease(NAFLD)) and cardiovascular derangements have been closely linked to OSAS patients with obesity[48,49].

Interestingly, our data seem to draw a worse cardiometabolic profile also in non-obese children with OSAS. According to previous findings [50,51], pediatric OSAS also showed a close relationship with fatty liver independently of the presence of a metabolic dysfunction as obesity status.

In addition to the pathogenic role of inflammation, dysregulation of other metabolic pathways involving insulin signaling and hepatic homeostasis might be supposed as further harmful players in the tangled puzzle of OSAS pathophysiology[52].

Considering the design of the study (including a selected population such as non-obese children with OSAS and a control group), our results might add to the existing knowledge on the pediatric OSAS development. Therefore, a careful management of these patients by taking into account also the impact of the hypoxemia correction on the metabolic impairments is highly recommended.

However, our study has some limitations that deserve mention. Firstly, our population, although well-characterized, is limited. The lack of a more comprehensive metabolic evaluation (e.g. lipid profile, glucose metabolism assessment) did not allow to provide evidence for a wider cardiometabolic risk in these patients. On the other hand, the presence of a control group enhances the strength of our findings.

In conclusion, a worse cardiometabolic profile has been found also in non-obese children with OSAS. In light of this, therapeutic strategies for hypoxiemia correction might also pay the way for a better cardiometabolic management, by improving the long-term quality of life of non-obese children with OSAS[42,53]. Further studies are needed to provide a better characterization of these selected patients.

Declarations

Funding: No funding was received for conducting this study.

Conflicts of Interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

Code availability: STATISTICA software (data analysis software system, version 6, StatSoft, Inc. (2001).

Author Contributions: Conceptualization, ADS, GM, MC; Data curation, IB, CF, MC; Formal analysis, ADS; Investigation, MC; Methodology, ADS, MC; Project administration, GF; Supervision, AV; Writing – original draft, ADS, MC.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Campania (Protocol code 13887 , approval date 09/03/2015; EudraCT number 2015-001164-19).

Consent to participate: Written informed consent was obtained from the parents of all the enrolled children.

Consent for publication: not applicable

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Tables

Table 1. Main features of the OSAS and non OSAS group.

	OSAS (n=128)	**Non-OSAS (n=213)**	**P**
Age	9.70 ± 3.43	9.52±3.35	0.638
Sex (male),%	61.7	59.6	0.788
BMI-SDS	0.49 ± 0.13	0.59 ± 0.29	0.462
Apnea/hypopnea index (AHI)	8.99 ± 6.14	0.58 ± 0.31	<0.001
Oxygen desaturation index (ODI)	2.26 ± 2.07	0.29± 0.10	<0.001
Mean Oxygen Saturation,%	97.26 ± 1.37	98.13 ± 0.51	<0.001
Nadir Oxygen saturation	96.59 ± 0.83	94.32 ± 1.89	<0.001
Mean Oxygen Desaturation,%	3.93 ± 1.94	0.89 ± 0.63	<0.001

AHI, apnea/hypopnea index; BMI-SDS, Body Mass Index Standard Deviation Score; ODI, oxygen desaturation index.

Table 2. Main biochemical parameters in OSAS and non-OSAS group.

	OSAS (n=128)	Non-OSAS (n=213)	p	*Cohen's d*
WBC,10^3/µl	12.05 ± 3.09	6.48 ± 2.08	<0.001	2.11
RBC, 10^6/µl	6.01 ± 1.36	5.82 ± 1.14	NS	-
HGB, g/dl	13.97 ± 1.42	14.07 ± 1.35	NS	-
HCT, %	46.92 ± 5.91	47.73 ± 5.33	NS	-
MCV, fl	88.15 ± 9.03	89.8 ± 8.17	NS	-
PLT, 10^3/µl	386.92 ± 74.12	204.11 ± 56.92	<0.001	2.76
MPV, fl	10.95 ± 2.69	8.19 ± 1.78	<0.001	1.21
NEU%	5.87 ± 1.33	2.66 ± 1.15	<0.001	2.58
LINF%	2.86 ± 1.48	2.98 ± 1.03	NS	-
MONO%	0.37 ± 0.21	0.41 ± 0.18	NS	-
EOS%	0.26 ± 0.14	0.23 ± 0.16	NS	-
BASO%	0.21 ± 0.11	0.19 ± 0.14	NS	-
Glucose, mg/dl	98.19 ± 9.04	84.19 ± 12.7	<0.001	1.27
Albumin, g/dl	4.06 ± 0.58	4.15 ± 0.31	NS	-
AST, U/L	35.18 ± 6.14	8.57 ± 3.36	<0.001	5.37
ALT, U/L	34.97 ± 7.03	9.83 ± 4.19	<0.001	4.34
GGT, U/L	47.19 ± 5.69	10.23 ± 1.18	<0.001	8.99
Na, mEq/l	140.64 ± 1.09	140.72 ± 1.06	NS	-
K, mEq/l	3.87 ± 0.52	3.91 ± 0.47	NS	-
Cl, mEq/l	103.71± 1.33	103.94 ± 1.26	NS	-
P, mg/dl	4.76 ± 1.91	4.81 ± 1.93	NS	-
Ca, mg/dl	9.52 ± 1.09	9.73 ± 1.01	0.072	-
Iron, µg/dl	65.92 ± 11.04	80.14 ± 7.36	<0.001	1.51
Uric Acid, mg/dl	5.03 ± 1.18	3.49 ± 0.34	<0.001	1.77
Alkaline phosphatase, U/L	76.29 ± 32.66	78.44 ± 21.19	NS	-
LDH, U/L	396.17 ± 62.33	302.91 ± 58.33	<0.001	1.54

Ferritin, ng/ml	109.45 ± 26.09	98.65 ± 17.02	<0.001	0.49
Transferrin, mg/dl	139.02 ± 46.14	219.77 ± 21.05	<0.001	2.25
CRP, mg/dl	0.32 ± 0.11	0.12 ± 0.07	<0.001	2.16
ESR, mmh	2.17 ± 1.35	1.32 ± 0.43	<0.001	0.84
Insulin, IU/ml	19.55 ± 7.01	8.36 ± 2.99	<0.001	2.07

White blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), platelet count (PLT), mean platelet volume (MPV),% of neutrophils (NEU%),% of lymphocytes (LINF%), % of Monocytes (MONO%),% of eosinophils (EOS%),% of Basophils (BASO%), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), Sodium (Na), Potassium (K), Chlorine (Cl), Phosphorus (P), Calcium (Ca), iron (Fe), lactate dehydrogenase (LDH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).