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, CRP, 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 hypoxemia 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.

What is Known:
- Pediatric OSAS has shown a close relationship with obesity and its cardiometabolic comorbidities.
- Inflammation represents the hallmark of both obesity and OSAS.

What is New:
- Non obese children with OSAS presented with a worse cardiometabolic risk profile.
- OSAS treatment might serve as an effective approach also for the increased cardiometabolic risk of these children.

Keywords OSAS · Inflammation · Cardiometabolic risk · Non-obese · Children

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| AHI          | Apnea/hypopnea index |
| ALT          | Alanine aminotransferase |
| AST          | Aspartate aminotransferase |
| BASO%        | % Of Basophils |
| BMI-SDS      | Body Mass Index Standard Deviation Score |
| Ca           | Calcium |
| Cl           | Chlorine |
| CRP          | C reactive protein |
| EOS%         | % Of eosinophils |
| ESR          | Erythrocyte sedimentation rate |
| Fe           | Iron |
| GGT          | Gamma-glutamyl transpeptidase |
| HGB          | Hemoglobin |

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Introduction

Pediatric obstructive sleep apnea syndrome (OSAS) represents a complex disease mainly linked to both adenotonsillar hypertrophy and childhood obesity epidemic, particularly in the Southern of Italy [1]. Several impairments have been related to OSAS in children including neurocognitive [2, 3] and behavioral disorders [4], growth hormone deficiency [5], enuresis [6], systemic inflammation, rhinitis [7], cardiovascular disease [8], and imbalance in lipid homeostasis [9].

From a pathophysiological perspective, inflammation has been largely accepted as one of the major pathogenic mechanisms underlying both obesity and OSAS. Over the last decades, several studies have focused on the role of potential biomarkers of pediatric OSAS [10–13], but no specific determinants in this field have been currently identified, likely due to the overlap of various comorbidities potentially acting as confounding factors [14, 15]. Noteworthy, evidence has linked sleep duration to different cardiometabolic markers in a pediatric cohort [16]. Moreover, changes in sleep duration and quality have been related to rapid serum increase of C-reactive protein (CRP) [17–19] insulin [20, 21] and lipids [22].

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 [23]. 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 [24].

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) [25–27]. Indeed, CRP might be considered as a predictor of cardiovascular morbidity [28], with a direct effect on the development of atheromatic plaques [29, 30]. 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 [30–32]. In addition, the major role of obesity as cardiovascular risk factor has been studied already in childhood [33, 34].

In light of this, pediatric OSAS represents a tangle 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 [5, 12, 18, 20], evidence in non-obese children is still scarce [20, 35, 36].

To fill this gap, we aimed to investigate the cardiometabolic risk profile (defined as a cluster of biomarkers such as serum glucose, insulin, acid uric, and transaminase) in a population of non-obese children affected by OSAS.

Materials and methods

Ethical approval study design

The present study was conducted according to the Declaration of Helsinki [37], 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.

Study population

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

OSAS was diagnosed by overnight nocturnal polysomnographic examination according to the diagnostic ICSD-3 criteria [38]. Non-obese children were diagnosed with OSAS because of the presence of nasal turbinate hypertrophy or non-genetic craniofacial alterations (e.g., retrognathia, prognathism).

Exclusion criteria were considered as follows: overweight (BMI-SDS > 85th percentile) and/or obesity (BMI-SDS > 95th percentile), preterm birth, 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 without OSAS (AHI < 1.0 event/h) were enrolled at the same university clinic. The control group was recruited among inpatient subjects (admitted for assessment of recurrent episodes of headache and abdominal pain) resulted negative for neuropsychiatric evaluation and pediatric screening during hospitalization in our 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.

**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 1, 2015, and November 30, 2017, were reviewed and analyzed.

An airflow cease for at least two breaths associated to paradoxical ribcage and abdominal movements identified obstructive apnea. The hypopnea index was defined as a nasal flow curve signal reduction > 50% associated to oxygen
desaturation or arousal. Central apnea was defined as airflow absence at both nose and mouth with no inspiratory effort within the duration of the event for 20 s or longer, or two missed breaths with an oxygen desaturation ≥ 3%, an arousal, or an awakening. The apnea–hypopnea index (AHI) was determined as the number of apneas and hypopneas per hour of sleep and the lowest oxygen saturation value, and the number of desaturation events ranging from 4 to 90% was computed. Moreover, the oxygen desaturation index (ODI), classified on the basis of events per hour, was calculated.

OSAS severity was determined according to the current guidelines specified by the American Academy of Sleep Medicine (AASM) [39]: mild OSAS was defined by an obstructive apnea/hypopnea index (AHI) of 1 to < 5 events/h; moderate OSAS was defined as ≥ 5 to < 10 events/h, and severe OSAS as ≥ 10 events/h.

**Statistical analysis**

Data were expressed as mean ± standard deviation. Kolmogorov–Smirnov test was used to examine normal distribution of the population. The independent t-test was used to compare the main parameters between patients with and without OSAS. Not-normally distributed variables were log-transformed before the analysis, but raw means are shown. Age, sex, and insulin used were as covariates, when appropriate.

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.

To reduce the chances of false–positive results (type I errors) when multiple pairwise tests were performed on a single set of data, Bonferroni corrections (Bonferroni type adjustment) were applied by dividing the p-value by the number of comparisons being made.

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.

**Results**

The main features of the OSAS (mean age 9.70 ± 3.43) and non-OSAS group (mean age 9.52 ± 3.35) were shown 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, SpO2%, and mean desaturation O2) were significantly lower than controls (p < 0.001) (Table 1).

Inflammation marker 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). These associations were confirmed even after adjustments (all p < 0.001).

Moreover, subjects suffering from OSAS showed increased serum glucose, insulin, uric acid, ALT, and AST levels than healthy controls, even after adjustments (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 (Cohen’s d 2.11), PLT (Cohen’s d 2.76), MPV (Cohen’s d 1.21), NEU% (Cohen’s d 2.58), AST (Cohen’s d 5.37), ALT (Cohen’s d 4.34), GGT (Cohen’s d 8.99), iron (Cohen’s d 1.51), serum uric acid (Cohen’s d 1.77), LDH (Cohen’s d 1.54), transferrin (Cohen’s d 2.25), CRP (Cohen’s d 2.16), and insulin (Cohen’s d 2.07) (Table 2).

| 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

*Adjusted p-values
Discussion

In our study, we provided intriguing evidence for a worse cardiometabolic profile in a cohort of non-obese children with OSAS. In fact, robust statistical data regarding the differences in the main cardiometabolic biomarkers (such as serum insulin, glucose, uric acid, and transaminase) between the two examined groups have been observed.

Sleep-related breathing disorders (SRBD) are common in children and adolescents [40–42], with a different severity ranging from primary snoring to OSAS [40]. OSAS is a complex disease in which several risk factors (e.g. inflammation, obesity) 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 [34, 35], 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.

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

| Parameter                  | OSAS (n = 128) | Non-OSAS (n = 213) | p*   | Cohen’s d |
|----------------------------|----------------|--------------------|------|-----------|
| WBC, 10³/µl                | 12.05 ± 3.09   | 6.48 ± 2.08        | < 0.001 | 2.11     |
| RBC, 10⁹/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, 10³/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     |

WBC white blood cell count, RBC red blood cell count, HGB hemoglobin, HCT hematocrit, MCV mean corpuscular volume, PLT platelet count, MPV mean platelet volume, NEU% % of neutrophils, LINF% % of lymphocytes, MONO% % of Monocytes, EOS% % of eosinophils, BASO% % of Basophils, AST aspartate aminotransferase, ALT alanine aminotransferase, GGT gamma-glutamyl transpeptidase, Na sodium, K potassium, Cl chloride, P phosphorus, Ca calcium, Fe iron, LDH lactate dehydrogenase, CRP C-reactive protein, ESR erythrocyte sedimentation rate

* Adjusted p-values
The association between SRDB and cardiovascular disease in pediatric age has been well documented, particularly in children with endothelial function impairment [44–46]. Moreover, these patients experienced recurrent episodes of hypoxemia leading to an increase in sympathetic activity, oxidative stress, and inflammation (mainly expressed as elevated serum C-reactive protein levels) that enhanced endothelial dysfunction [44–46].

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 [47–50], by suggesting also potential therapeutic options based on the pathogenic role of specific proinflammatory mediators [51, 52]. 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 [53–55].

Interestingly, our data seem to draw a worse cardiometabolic profile also in non-obese children with OSAS. According to previous findings [56–58], 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 [59].

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. Based on the current limited data on cardiometabolic outcomes in non-obese children diagnosed with OSAS, our findings might also have significant clinical implications. Indeed, these subjects may benefit from a wider management taking into account also the impact of the hypoxemia correction on the metabolic impairments. Moreover, lifestyle programs might also improve the overall quality of life of non-obese children with OSAS by reducing their cardiometabolic risk.

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 hypoxemia 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 [53, 56]. Further studies are needed to provide a better characterization of these selected patients.

Author's 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.

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).

Declarations

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.

Conflict of interest The authors declare no competing interests.

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