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Metabolic biomarkers in community obese children: effect of obstructive sleep apnea and its treatment

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Abstract

Objective: Obesity and obstructive sleep apnea in children have been associated with metabolic morbidities. The present study aimed to evaluate the presence of metabolic alterations among obese children recruited from the community, with and without obstructive sleep apnea syndrome (OSAS), and the impact of treatment of OSAS on metabolic profiles.

Methods: A cross-sectional, prospective, multicenter study of Spanish children aged 3-14 years with a body mass index (BMI) ≥95th percentile for age and sex were randomly selected in the first phase. Four groups emerged for follow-up: (1) no treatment; (2) dietary intervention; (3) surgical treatment of OSA; and (4) continuous positive airway pressure (CPAP) treatment of OSA. Fasting blood tests were performed at baseline (T0) and approximately 1 year after the intervention (T1).

Results: A total of 113 obese children with a mean age of 11.3±2.9 years completed T0 and T1 assessments. Their mean BMI *z*-score at T1 was 1.34±0.59, and mean Respiratory Disturbance Index was 8.6±13.0 at T0 and 3.3±4.0/hour total sleep time at T1. Only glucose fasting levels differed among metabolic parameters in obese children with OSAS and without OSAS at baseline (T0) (p=0.018). There were statistically significant diferences between surgically treated OSAS (p=0.002), and CPAP-treated OSAS (p=0.024) versus the non-OSAS group in the glucose levels between baseline (T0) and follow-up (T1) after controlling for age and change in BMI. Significant univariate associations between BMI and C-reactive protein, insulin, and homeostasis model assessment of insulin resistance emerged at both T0 and T1.

Conclusions: Concurrent obesity and OSAS could promote metabolic and inflammatory alterations, and the latter appeared to be sensitive to OSAS treatment outcomes.

Keywords:

Sleep apnea

Children

Obesity

Biomarkers

Metabolic alterations

Abbreviations

AASM	American Association of Sleep Medicine
AHI	Apnea-Hypopnea Index
BMI	Body Mass Index
OSAS	Obstructive Sleep Apnea Syndrome
CRP	C Reactive Protein
CPAP	Continuous Positive Airway Pressure
ECL	Electrochemiluminescence
FPI	Fasting Plasma Insulin
FPG	Fasting Plasma Glucose
HDL	High Density Lipoproteins
HOMA	Homeostasis Model Assessment of Insulin Resistance
LDL	Low Density Lipoproteins
NPSG	Overnight polysomnography
RDI	Respiratory Disturbance Index
SDB	Sleep disordered breathing
TG	Triglycerides
TST	Total Sleep Time
T & A	Tonsils and Adenoids

Introduction

The prevalence of childhood obesity has reached epidemic proportions worldwide, with rates ranging from 7-22% in various countries [1]. In Spain, the enKID study, a cross-sectional epidemiological study of a representative sample of the Spanish population aged 2-24 years, has clearly established a high frequency of obesity among 6-13 year-old children, as evidenced by the 15.6% and 12% rates in boys and girls, respectively [2]. Furthermore, the ALADINO study, a community-based cross-sectional study, the aim of which was to determine the prevalence of overweight and obese children in Spain, was conducted in children aged between 6-9.9 years; the prevalence of obesity was 20.9% in boys and 15.5% in girls [3].

In this context, pediatric obesity has been recognized as a major medical and public health problem because it affects nearly every major organ system [4]. Possible complications include insulin resistance, dyslipidemia, and cardiovascular morbidity [4-6]. 'Metabolic syndrome' is a known risk factor for cardiovascular disease in adults, and refers to the clustering of insulin resistance, dyslipidemia, hypertension, and obesity. Furthermore, when metabolic syndrome occurs during childhood and/or adolescence, it indicates a high risk for cardiovascular morbidity during early adulthood [7-9].

Sleep disordered breathing (SDB) is a large group of associated conditions that includes habitual snoring, upper airway resistance syndrome, hypoventilation, and obstructive sleep apnea syndrome (OSAS), all of which reflect different categories of respiratory alteration severity during sleep. Sleep disordered breathing – particularly OSAS – has been associated with a large spectrum of neurocognitive, behavioral, cardiovascular, and metabolic adverse consequences, the risk of which appears to be particularly exacerbated when concurrent obesity is present [10,11]. In recent years, it has become apparent that the risk and severity of OSAS are markedly increased by the concurrent presence of obesity [12]. Indeed, the prevalence of OSAS in a community-based cohort study in obese children was high, ranging from 21.5-39.5% depending on the cut-off and nature of the polysomnographically-derived respiratory disturbance measures used [13].

Although OSAS in adults has been associated for several decades with increased risk for cardiovascular morbidities, it is only more recently that nocturnal elevation of systemic blood pressure and sustained diurnal hypertension [14-16], severity-dependent changes in left ventricular geometry and function [17], and abnormal endothelial function [18] have emerged and been recognized in children with OSAS, along with exacerbated cardiovascular risk, when insulin resistance is concurrently present [19,20]. Thus, evaluation of the potential

cardiometabolic burden that is inherently assignable to OSAS in children, and improved understanding of its reversibility would be of clear importance, considering that such morbidity is primarily silent in children and usually manifests much later in life, possibly too late for corrective measures to be implemented. To better understand the potentially adverse contributions of obesity and OSAS to metabolic regulation in children, a prospective study of obese children with OSAS and without OSAS was conducted [13,21]. The following analyses were performed before and after treatment of OSAS: fasting levels of glucose (Glu), insulin (FPI), high sensitivity C-reactive protein (CRP), and plasma lipid profile concentrations.

Subjects and methods

A detailed description of the methods pertaining to this cross-sectional, prospective, multicenter study has been previously published [13]. Briefly: inclusion criteria were ages between 3-14 years, along with a body mass index (BMI) >95th percentile for age and sex, and informed consent from parents or legal caretakers (ClinicalTrials.gov Identifier: NCT01322763). Consent was routinely obtained from children aged >12 years. The local human subject committees of the institutions of the various participating cities in which pediatric sleep laboratories were available approved the study. To guarantee the confidentiality of the data, coding of all the data was performed, such that personal information was not available to the investigator-based network. Exclusion criteria were: failure to fulfill inclusion criteria, and presence of known genetic syndromes, or any other chronic debilitating diseases. All children were obese, and dietary advice and guidance were provded to all of them.

Decisions on the need for treatment of OSAS during the first phase of the study were reached by strictly adhering to the Spanish Consensus Criteria, which defined a respiratory disturbance index (RDI) ≥3/hour of total sleep time (TST) as the cut-off criterion for treatment of OSAS [8]. Based on the polysomnographic findings, four severity-defined groups emerged, and were used for follow-up:

Group 1: No polysomnographic evidence of OSAS (ie, children with RDI <3/hour TST) – no treatment was administered. A random sample of 52 children who had an RDI <3/hour TST was selected for the follow-up study.

Group 2: Mild OSAS: children with an RDI ≥3/hour TST but apnea-hypopnea index (AHI) <10/hour TST and/or presence of obstructive hypoventilation *without* significant adenotonsillar hypertrophy (0-2 grade of tonsillar hypertrophy and/or adenoid hypertrophy <25%). The treatment for this group consisted of supervised dietary modification by a clinical nutritionist.

Group 3: Moderate-severe OSAS: children with an RDI ≥3 and AHI ≥10/hour TST, and/or presence of obstructive hypoventilation *with* significant adenotonsillar hypertrophy (3-4 grade of tonsillar hypertrophy and/or adenoid hypertrophy >25%) as confirmed by nasopharyngoscopy. Treatment consisted of surgical removal of enlarged tonsils and adenoids (T&A).

Group 4: Moderate-severe OSAS: children with an RDI ≥3 and AHI ≥10/hour TST, and/or presence of obstructive hypoventilation *without* nasopharyngoscopic evidence of adenotonsillar hypertrophy. The treatment approach in these cases consisted of mask fitting sessions along with behavioral modification and application of continous positive airway pressure (CPAP) treatment after in-laboratory titration.

All participants underwent assessment of their medical and sleep history, and were subjected to a comprehensive physical examination that included craniofacial evaluation by visual inspection, as well as an otolaryngology assessment that also incorporated an awake nasopharyngoscopy under topical sedation. An overnight sleep study (NPSG) in the laboratory was then conducted using standard techniques in the presence of one of the caretakers throughout the study. Children arrived accompanied by one of their parents to the sleep laboratory at approximately 19:30-20:00, and a lights-off routine was implemented at 21:00, with discontinuation of the sleep recordings at 08:00 the next morning. After removal of movement and technical artifacts, the studies were scored according to standard criteria as defined by the by the American Academy of Sleep Medicine (AASM) [22]. The proportion of time spent in each sleep stage was expressed as percentage of total sleep time (%TST). The apnea index (AI) and the AHI were defined as the number of apnea and hypopneas per hour of TST. The AHI, obstructive AHI (OAHI), and the RDI were also calculated. The RDI was defined as the number of apnea, hypopneas and flow limitations per hour of TST. Furthermore, the flow limitation index was calculated based on all events in which flow limitation was identified [11,22].

Four of the 117 children who completed their designated treatment and follow-up protocol did not have blood sampes drawn at follow-up, and were therefore excluded from analyses. These four missing cases were evenly distributed across the various groups, and no apparent differences in age, sex, RDI, and BMI *z*-score were present between the missing cases and their diagnostic groups.

Metabolic assessments

Following the overnight PSG, participants underwent a fasting blood draw. Fasting plasma insulin (FPI) levels were measured by electrochemiluminescence (ECL) (Roche Cobas 8000 e602; Mannheim, Germany). This assay had a sensitivity of 0.2 uU/mL, linear range between 0.2-1000 uU/mL, and intra-assay CV ≤1.2%. Fasting plasma glucose (FPG)

was measured via an enzymatic method with hexokinase (Roche Cobas 8000 c702; Mannheim, Germany). This assay had a sensitivity of 2 mg/dL, exhibited a linear range between 2-750 mg/dL, and an intra-assay CV ≤1.5%. High-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol and triglycerides were measured via homogenous enzymatic colorimetric assays (Roche Cobas 8000 c702, Mannheim, Germany). The analytical measuring ranges and assay coefficients of variations (CV) were:

- Total cholesterol (TChol): range 3.86-800 mg/dL, CV ≤1.5%
- HDL cholesterol: range 3-121 mg/dL, CV ≤1.5%
- LDL cholesterol: range 3.87-5.49 mg/dL, CV ≤2%
- Triglycerides (TG): range 8.85-885 mg/dL, CV ≤1.5%

High-sensitivity CRP levels were determined using a turbidimetric immunoassay technique (Roche Cobas 8000 c702, Mannheim, Germany). This assay had a sensitivity of 0.3 mg/dL, linear range of 0.3-350 mg/L, and intra-assay CV ≤2%. In addition, the TChol/HDL, LDL/HDL and TG/HDL ratios were calculated. Higher values denoted greater cardiovascular risk [23]. The homeostasis model assessment of insulin resistance (HOMA) was calculated as a measure of insulin resistance: [FPI (μIU/mL) * fasting plasma glucose (FPG, mg/dL)]/405 [24]; abnormal HOMA values were >3 [25,26].

Data analysis

Data were reported as frequency distributions for qualitative variables and means±standard deviation for quantitative variables. Comparisons between groups at baseline (before treatment) were conducted with *t*-tests or analysis of variance for quantitative values. Comparisons of polysomnographic and demographic characteristics before and after treatment were conducted with paired sample *t*-tests, or analysis of variance for paired data followed by post hoc comparisons (or their corresponding non-parametric tests when the conditions of application were not fulfilled), with *p*-values adjusted for unequal variances, when appropriate, after assessment using the Levene's test for equality of variances, or Chi-squared analyses for paired data. Spearman´s correlation coefficients were used to examine associations between polysomnographic and anthropometric variables and metabolic measures of interest.

To analize the changes in metabolic parameters between baseline (T0) and follow-up after treatment (T1), general linear models for repeated measures were performed using treatment as an independent variable, and age and change in BMI (BMI1-BMI0) as co-variables, or change in percentile BMI or change in BMI *z*-score.

To examine potential predictors for incidence, persistence or residual OSAS (ie, RDI >3/hour TST at follow-up) a general lineal model and logistic regression analysis was performed. A two-tailed *p*-value <0.05 was considered as achieving statistical significance and 95% confidence intervals were calculated. All analyses were conducted with the use of SPSS software (version 22.0; SPPS Inc., Chicago, Ill.).

Results

A total of 113 obese children (58 boys, 55 girls) aged 10.3±2.9 and 11.3±2.9 years, respectively, at baseline (T0) and follow-up (T1) completed the initial and follow-up assessments, including the blood draws within 11.8±4.1 months. Their mean RDI was 8.6±13.0 at T0 and 3.3±4.0/hour TST at T1 (Wilcoxon test rank: $p<0.001$). Their mean BMI at follow-up was 27.6±4.7 kg/m^2, corresponding to a BMI *z*-score of 1.34±0.59 (Table 1).

Table 1. Anthropometric characteristics of the study cohort at initial assessment (T0; *n*= 113).

	Anthropometric measures		
Gender	Male: 58 (51.3%) Female: 55 (48.7%)		
	T0	T1	*p*
Age (years)	10.35±2.89	11.32±2.85	0.001
Weight (kg)	59.90±21.01	65.24±21.72	0.001
Height (m)	1.46±0.18	1.51±0.17	0.001
BMI (kg/m^2)	27.06±4.05	27.63±4.70	0.070
BMI percentile	96.84±0.54	95.26±6.73	0.012
BMI *z*-score	1.27±0.50	1.34±0.59	0.196
Neck circumference (cm)	33.82±3.72	33.82±3.42	0.974
Waist/hip circumference	0.90±0.07	0.88±0.07	0.067
Systolic BP (mmHg)	103.19±14.32	105.90±12.36	0.038
Diastolic BP (mmHg)	61.96±10.67	63.10±9.40	0.342

BMI, body mass index; BP, blood pressure; T0, baseline; T1, follow-up

When metabolic parameters between obese children with OSA and without OSAS were compared at baseline (T0), only fasting levels of glucose showed statistically significant differences (p=0.018) (Table 2).

Primary outcome

Using a general lineal model for repeated measures, there were no statistically significant differences between baseline T0 and follow-up (T1) in the metabolic parameters for the whole cohort, after controlling for age and change in BMI. However, there were statistically significant differences in the glucose values between surgically treated OSAS (magnitude of change: 5.728; p=0.002), CPAP-treated OSAS (magnitude of change: 6.589; p=0.024) when compared with the non-OSAS group. There were also statistically significant differences between the CPAP-treated OSAS versus non-OSAS group in: CRP (magnitude of change: 4.528 p=0.036), cholesterol/HDL cholesterol (magnitude of change: 0.917; p=0.008) and LDL cholesterol/HDL cholesterol ratios (magnitude of change: 0.824; p=0.004).

Table 2. Metabolic values at baseline (T0) in obese children with and without OSAS.

	OSAS (mean±SD) ***n*=62**	**Non OSAS (mean±SD)** ***n*=51**	***p***
Glucose (mg/dL)	87.77±9.45	83.68±8.33	0.018
Triglycerides mg/dL	87.41±43.53	79.74±33.61	0.310
Cholesterol mg/dL	162.34±38.24	168.10±36.68	0.423
HDL cholesterol mg/dL	47.85±11.56	52.04±11.93	0.064
LDL cholesterol mg/dL	98.75±29.60	97.98±32.80	0.896
Cholesterol total/HDL cholesterol	3.55±1.003	3.32±0.77	0.202
LDL cholesterol/HDL cholesterol	2.16±0.77	1.95±0.70	0.128
Triglycerides/HDL cholesterol	2.00±1.29	1.67±0.95	0.134
CRP mg/L	4.71±10.95	2.54±2.60	0.175
FPI insulin µU/mL	16.82±12.36	15.01±7.61	0.369
HOMA	3.63±3.006	3.13±1.56	0.300

CRP, C-reactive protein; FPI, fasting plasma insulin; HDL cholesterol, high-density lipoprotein; HOMA, homeostasis model assessment of insulin resistance; LDL cholesterol, low-density lipoprotein; OSAS, obstructive sleep apnea syndrome

Using RDI ≥3/hour TST on PSG at follow-up as the criterion for the presence of OSAS, the study found that in Group 1, 41 (78.8%) of the children remained with an RDI <3/hour TST at T1 (no OSAS), while 11 (21.2%) evolved into RDI ≥3/hour TST at T1 (incident cases). In Group 2, 18 (50%) subjects remained with an RDI ≥3/hour TST at T1 (persistent cases) and in the other 18 (50%), nutritional intervention resulted in a RDI <3/hour TST at T1 (remission cases). In Group 3, 10 (43.5%) children remained with an RDI ≥3/hour TST at T1 (residual cases), while 13 (56.5%) had an RDI <3/hour TST at T1 (resolved cases). In Group 4, one (16.6%) remained with an RDI ≥3/hour TST at T1 (residual case), while five (83.3%) had an RDI <3/hour TST at T1 (controlled cases). The findings for age, sex, RDI, AHI, BMI and BMI *z*-score of the eight groups at follow-up are shown in Table 3.

Table 3. Characteristics of the cohort at follow-up (T1) according to diagnosis at T0 (*n*=113).

		Sex M/F	Age	RDI	AHI	BMI	BMI1-BMI0	BM
	Non OSAS							
Non OSAS *n*=40	T0	21/19	10.2±2.7	1.4±0.8	0.5±0.5	25.8±3.2	0.4±2.4	–0.4
	T1		11.1±2.6	0.9±0.7	0.4±0.4	26.2±3.9		–0.2
Incident cases *n*=11	T0	7/4	10.8±2.8	1.8±0.9	0.8±0.8	27.9±4.1	0.4±2.1	–0.0
	T1		11.6±2.6	7.2±2.8	4.1±2.1	28.4±5.4		0.15
	Mild OSAS							
Remission cases *n*=17	T0	7/10	11.1±2.3	5.9±2.2	2.6±1.6	27.8±4.1	–0.3±2.8	–
	T1		12.2±2.4	1.7±0.9	0.6±0.6	27.5±5.0		0
Persistent cases *n*=18	T0	8/10	11.4±2.1	11.2±6.3	4.5±5.2	27.9±3.0	0.4±2.1	–
	T1		12.2±2.2	7.7±5.5	3.9±3.5	28.3±4.0		0
		Moderate-severe surgically treated OSAS						
Resolved cases *n*=12	T0	5/7	8.3±3.9	20.6±24.2	13.9±23.9	26.2±5.2	0.2±3.8	–0
	T1		9.6±3.7	1.2±0.9	0.4±0.5	26.4±3.1		–0
Residual cases *n*=9	T0	5/4	9.4±3.4	16.7±14.2	12.9±13.7	25.9±3.9	1.8±1.5	–0
	T1		10.4±3.6	6.7±3.2	2.6±3.2	27.7±4.9		–0
		Moderate-severe CPAP-treated OSAS						
Resolved cases *n*=5	T0	2/3	11.2±2.2	28.1±19.8	24.9±19.9	33.3±3.5	1.9±1.7	1.
	T1		11.8±2.2	0.4±0.2	0.1±0.2	35.2±3.9		1.
Residual cases *n*=1	T0	1/0	15.0±	40.0	39.8	40.1	–0.7±	2.
	T1		16.5±	14.7	11.8	39.4		2.

AHI, apnea-hypopnea index; BMI *z*-score, body mass index *z*-score; BMI, body mass index; F, female; M, male; RDI, respiratory disturbance index; T0, baseline; T1, follow-up

Changes in metabolic parameters according to sub-group categories at follow-up are shown in Table 4 and Table 5. In general, there were no significant changes in blood-based measures for the whole cohort. However, several significant changes occurred in the sub-group analyses after treatment. Indeed, among children undergoing T&A, HDL cholesterol was significantly higher, and triglycerides, total cholesterol/HDL, LDL/HDL, triglycerides/ HDL cholesterol ratios were all significantly lower at T1, indicating more favorable lipoprotein profiles in the group of children in whom T&A successfully normalized polysomnographically-recorded respiratory measures.

In the non-OSAS group, CRP levels decreased at T1, whereas the levels increased in the incident group. Similarly, CRP levels decreased in the remission group and increased in the persistent group. Regarding the surgically treated group, the children in the residual group presented higher plasma levels of CRP when compared with the surgically resolved group. The highest levels of CRP emerging among the group of children treated with CPAP with trend to decrease after treatment (Table 4 and Table 5).

Table 4. Metabolic values at baseline (T0) and follow-up (T1) in children initially included in Groups 1 and 2.

		Group 1 (non-OSAS) Mean±SD *n*=40	**Group 1 (non-OSAS) Incident Mean±SD *n*=11**	**Group 2 (mild OSAS: dietary treatment) Remission Mean±SD *n*=17**	**Group 2 (mild OSAS: dietary treatment) Persistent Mean±SD *n*=18**
Glucose mg/dL	**T0**	83.9±7.4	82.6±11.3	84.4±9.2	87.7±7.9
	T1	84.7±6.7	87.6±8.9	88.0±8.9	84.3±6.0*
Triglycerides mg/dL	**T0**	79.7±35.6	80.0±26.9	83.8±42.4	83.7±46.8
	T1	78.7±37.7	67.2±25.1*	79.4±34.7	85.2±50.8
Cholesterol mg/dL	**T0**	172.9±4	151.0±26.3	162.2±37.4	156.4±42.2
	T1	167.8±29.1	148.6±26.7	155.4±27.5	159.1±33.1
HDL cholesterol mg/dL	**T0**	53.5±11.8	46.8±11.3	46.1±10.4	49.9±11.5
	T1	53.6±12.9	49.4±12.6	45.5±9.5	45.5±10.4
LDL cholesterol mg/dL	**T0**	100.7±35.1	88.3±21.6	99.3±28.6	95.8±27.5
	T1	98.5±25.6	85.9±21.9	94.4±23.7	96.5±25.2
Cholesterol total/HDL cholesterol	**T0**	3.3±0.8	3.3±0.6	3.6±0.9	3.3±1.1
	T1	3.2±0.9	3.1±0.6	3.5±0.9	3.6±1.1
LDL cholesterol/ HDL cholesterol	**T0**	1.9±0.7	1.9±0.5	2.2±0.7	2.0±0.2
	T1	1.9±0.8	1.8±0.5	2.2±0.8	2.2±0.2
Triglycerides /HDL cholesterol	**T0**	1.6±0.9	1.9±1.1	1.9±1.1	1.8±0.3
	T1	1.6±0.9	1.5±1.0*	1.9±0.9	2.0±0.3
CRP mg/L	T0	2.5±2.7	2.7±2.1	6.7±20.3	4.0±4.9
	T1	2.2±2.5	3.1±2.8	2.5±4.2	4.7±7.9

FPI insulin µU/mL	T0	14.7±7.9	16.0±6.8	17.4±10.4	20.8±18.0
	T1	15.9±7.5	17.3±8.2	20.5±12.4	18.9±8.3
HOMA		3.1±1.7	3.2±1.2	3.3±1.9	4.8±5.1
	T1	3.4±1.7	3.8±2.3	4.3±2.4	3.9±1.8

* $p<0.05$

CRP, C-reactive protein; FPI, fasting plasma insulin; HDL cholesterol, high-density lipoprotein; HOMA, homeostasis model assessment of insulin resistance; LDL cholesterol, low-density lipoprotein; T0, baseline; T1, follow-up

Table 5. Metabolic values at baseline (T0) and follow-up (T1) in children initially included in Groups 3 and 4.

		Group 3 (moderate-severe OSAS treated surgically) Resolved surgically Mean±SD *n*=12	**Group 3 (moderate-severe OSAS treated surgically) Residual surgically Mean±SD *n*=9**	**Group 4 (moderate-severe OSAS treated with CPAP) Mean±SD Resolved CPAP *n*=5**	**Group 4 (moderate-severe OSAS treated with CPAP) Mean±SD Residual CPAP *n*=1**
Glucose mg/dL	**T0**	90.5±9.9	87.4±6.6	87.2±7.4	120.0±
	T1	89.0±7.8	92.1±7.4	89.4±2.9	95±
Triglycerides mg/dL	**T0**	87.2±41.9	79.0±45.0	109.8±29.7	172.0±
	T1	69.8±27.7*	98.6±56.0	92.0±31.3	81.0±
Cholesterol mg/dL	**T0**	156.0±18.82	162.50±35.59	171.20±19.79	301.0±
	T1	159.2±29.1	164.5±23.1	177.2±23.2	182.0±
HDL cholesterol mg/dL	**T0**	48.7±14.9	49.1±12.2	43.0±8.1	43.0±
	T1	54.6±13.3*	50.0±9.9	45.4±7.9	48.0±
LDL cholesterol mg/dL	**T0**	89.9±15.0	97.4±27.6	106.0±20.6	224.0±
	T1	90.8±24.1	95.4±23.8	114.6±17.3	118.0±
Cholesterol total/HDL cholesterol	**T0**	3.4±0.8	3.4 ±0.7	4.1 ±0.7	7.0±
	T1	3.0±0.8*	3.4±0.9	3.9±0.6	3.8 ±
LDL cholesterol/ HDL cholesterol	**T0**	1.9±0.6	2.0±0.6	2.5±0.6	5.2±
	T1	1.8 ±0.7	1.9±0.6	2.6±0.4	2.5 ±
Triglycerides /HDL cholesterol	**T0**	2.1±1.7	1.7±1.2	2.6±0.9	4.0±
	T1	1.4 ±0.7*	2.2±1.7	2.1±0.9	1.7 ±

CRP mg/L	T0	2.0±1.6	4.2±4.7	8.6±8.2	4.0±
	T1	2.5±2.7	4.2±6.1	5.4±3.4	4.0 ±
Insulin µU/mL	T0	12.3 ±6.5	14.7 ±6.6	15.6±4.5	12.0 ±
	T1	15.9±10.2	16.5 ±6.6	24.6±13.5	23.5 ±
HOMA	T0	2.8 ±1.6	3.1±1.3	3.4±1.2	3.6 ±
	T1	3.6±2.7	3.8±1.7	5.4±2.9	5.5 ±

* $p<0.05$

CRP, C-reactive protein; FPI, fasting plasma insulin; HDL cholesterol, high-density lipoprotein; HOMA, homeostasis model assessment of insulin resistance; LDL cholesterol, low-density lipoprotein; T0, baseline; T1, follow-up

Secondary outcomes

Correlation analyses

Statistically significant correlations are shown in Table 6 and Table 7. For the total cohort, BMI *z*-score was associated with triglycerides, CRP, FPI and HOMA at T0, and these associations persisted at T1. Analyses of follow-up groups revealed that BMI was positively correlated with CRP in the persistent group, and with FPI and HOMA in the non-OSAS, remission, and resolved groups at T0.

Table 6. Statistically significant correlations between metabolic variables and BMI or polysomnographic measures at T0.

	All subjects *n*=113	**Non OSAS group 2 *n*=40**	**Incident Group 1 *n*=11**	**Remission Group 4 *n*=17**	**Persistent Group 3 *n*=18**	**Resolved surgically Group 8 *n*=12**	**Residual surgically Group 6 *n*=9**	**Re Cl Gr *n*=**
BMI								
Triglycerides mg/dL	0.314**							
CRP mg/L	0.183*				0.499*			
FPI (insulin) µU/mL	0.468**	0.368*		0.665**		0.699*		0.9
HOMA	0.436**	0.309*		0.577*		0.657*		0.9
RDI								
Glucose mg/dL	0.237*							
Triglycerides mg/dL						0.606*		
HDL cholesterol mg/dL	–0.245**					–0.678*		
AHI								
Glucose mg/dL	0.203*							
Triglycerides mg/dL						0.774**		
HDL cholesterol mg/dL	–0.337**					-0.853**		
Arousals index								
Glucose mg/dL	0.346**		0.733*			0.576*		

Cholesterol mg/dL						0.708*		
FPI (insulin) µU/mL	0.216*							
HOMA	0.258**					0.594*		
Desaturation index								
Glucose mg/dL		0.341*						

*p<0.05
**p<0.001
AHI, apnea-hypopnea index; BMI, body mass index; CRP, C-reactive protein; FPI, fasting plasma insulin; HDL cholesterol, high-density lipoprotein; HOMA, homeostasis model assessment of insulin resistance; LDL cholesterol, low-density lipoprotein; RDI, respiratory disturbance index; T0, baseline

Table 7. Statistically significant correlations between metabolic variables and BMI or polysomnographic measures at T1.

	All Groups *n*=113	**Non OSAS Group 2 *n*=40**	**Incident Group 1 *n*=11**	**Remission Group 4 *n*=17**	**Persistent Group 3 *n*=18**	**Resolved surgically Group 8 *n*=12**	**Residual surgically Group 6 *n*=9**
BMI							
Glucose mg/dL	0.245*	0.332*					
Triglycerides mg/dL	0.310*						
Cholesterol mg/dL					0.492*		
HDL cholesterol mg/dL	–0.257**	–0.337*					
LDL cholesterol mg/dL					0.475*		
Reactive C Proteinmg/L	0.183*						
FPI (insulin) µU/mL	0.572**	0.580**		0.738**	0.564*		0.762*
HOMA	0.575*	0.594**		0.741**	0.492*		0.762*
RDI							
Glucose mg/dL	0.237*		0.772**				
Triglycerides mg/dL		0.415**					
HDL cholesterol mg/dL	–0.245**						
Insulin			0.609*				
HOMA			0.682*				

				Arousal index			
HDL cholesterol mg/dL	–0.256**						
				Desaturation index			
Glucose mg/dL						0.695*	
CRP mg/L	0.248**			0.727**			

*p<0.05

**p< 0.001

AHI, apnea-hypopnea index; BMI, body mass index; CRP, C-reactive protein; FPI, fasting plasma insulin; HDL cholesterol, high-density lipoprotein; HOMA, Homeostasis Model Assessment of Insulin Resistance; LDL cholesterol, low density lipoprotein; RDI, Respiratory Disturbance Index; T1, follow-up

RDI and AHI were positively associated with fasting glycemic levels in the whole cohort, and were also significantly correlated with triglyceride levels in the surgically resolved group, and negatively correlated with HDL cholesterol levels in both the whole cohort, and the surgically resolved group at T0. In addition, the arousal index was positively associated with fasting glucose levels in the whole cohort, as well as in the incident and surgically resolved groups, and with HOMA in the total cohort and the surgically resolved group at T0. Finally, the oxygen desaturation index was positively correlated with glucose levels in the whole cohort at T0. Correlations between sleep and metabolic parameters persisted after controlling for BMI**.**

Predictors of incidence, persistence and residual OSAS

The study examined the associations between age, BMI and metabolic parameters and RDI at follow-up to explore whether any baseline variable could predict post-intervention OSAS. Although multiple factors showed statistical trends in the stepwise regression analyses, there were no significant predictors that would have reliably identified OSAS at T1. Of all the variables analyzed, statistical trends that emerged were as follows: HOMA appeared to be associated with increased risk for incident OSAS (OR: 1.97; 95% CI: 0.18-21.27, p=0.057) and persistent OSAS (OR: 1.10; 95% CI: 0.04-27.77, p=0.953), while CRP levels trended to predict residual OSAS after controlling for BMI and age (OR: 1.41; 95% CI: 0.74-2.67, p=0.089).

Complementary analysis

General linear model of OSA treated

In order to assess the effects of OSAS treatment on the metabolic and inflammatory profiles, a general linear model of repeated measures before and after treatment was performed. For this analysis, the non-OSAS group was excluded from the analysis and those who underwent surgical or CPAP treatment (n=27) were compared to those who only received dietary treatment (n=35), while adjusting for the BMI percentile. In these analyses, statistically significant differences were observed only in glucose values (p=0.037).

General linear model persistent OSAS versus resolved OSAS

To assess the effect of treatment on the metabolic and inflammatory profile, a general linear model of repeated measures was performed before and after treatment to compare persistent

OSAS (n=28) versus resolved OSAS (n=34), while controlling for percentile BMI. Although these analyses showed a trend toward improvements in metabolic and inflammatory parameters in the resolved OSAS group when compared with persistent OSAS, there were no significant differences in any of the analyzed parameters.

Pubertal status

The aforementioned analyses were not performed while adjusting for pubertal state. However, to avoid the confounding effect of puberty on the metabolic profile, an analysis was performed dividing the population of study according to age: children younger or older than 9 years of age. A general linear model of repeated measures before and after treatment that controlled for the dichotomized age and the change in BMI z-score was used to assess the effect of treatment on the metabolic and inflammatory profile. Significant effects of the treatment emerged on glucose profile (p=0.003), cholesterol total/ HDL ratio (p=0.044), LDL cholesterol/HDL cholesterol ratio (p=0.019) and CRP (p=0.023), regardless of age stratum and BMI z-score change.

Discussion

This study prospectively assessed the impact of various treatment modalities on metabolic profiles in a community-based cohort of obese children, in whom their primary care physicians diagnosed obesity. The high prevalence of both snoring and OSAS in otherwise 'healthy' obese children has previously been described [13]. The second phase of the study, which focused around treatment outcomes [21] that were further confirmed in the present study, revealed that T&A improved HDL cholesterol and triglyceride levels, suggesting that OSAS could be involved in creating an adverse metabolic state independent from obesity. The present study reported on the findings that HOMA showed statistical trends as a predictor of incidence and persistence of OSAS, suggesting that if obese children present evidence of insulin resistance, the likelihood of underlying OSAS is markedly greater. However, it should be noted that the relatively low number of cases in each of the eight sub-groups did not allow for definitive conclusions. Furthermore, the observations showing that CRP levels increased in both the incident and persistent groups at T1, as well as the presence of higher CRP levels in children with residual OSAS when compared with the surgically resolved group, suggest that CRP may provide value as an adjunt biomarker of risk for the presence of OSAS during prospective follow-up [27]. The diferences between treated groups compared with the non-OSAS group further reinforce the effect of treatment on metabolic and inflammatory parameters. Indeed, in this prospective study it was found that serum lipid profiles were significantly improved after T&A in the group of children with moderate-severe OSAS whose sleep-disordered breathing was completely resolved and resulted in normalization of their PSG. In contrast, no lipid profile improvements occurred in the surgically treated group whose post-treatment PSG attested to the continued presence of OSAS. These findings support the contention that OSAS, at least among obese children, independently and adversely alters the lipid profile, and thus confers increased cardiovascular risk. These results are also in close agreement with those reported recently in a cohort of 69 children with OSAS (mean age: 5.9 years (range 3-16), 68% non-obese) who underwent T&A for OSAS treatment, whereby HDL cholesterol levels improved significantly after surgery [28]. However, since the present study exclusively involved obese children, the current findings further emphasize the association of OSAS with cardiovascular risk.

Perusal of the several pediatric studies that explored the impact of OSAS on metabolic function yields contradictory findings; while some of the studies reported significant associations between OSAS and insulin resistance independent of obesity, others have found

no independent associations [29-32]. In addition to these association studies, those studies that have examined the effect of OSAS treatment upon metabolic measures in children have been similarly contradictory. For example, the only randomized multicenter trial of T&A in children found no improvements in circulating lipoproteins, or in any other cardiometabolic markers in children aged 5-9 years with OSAS undergoing T&A [33]. Similarly, Apostolidou and colleagues assessed the effect of adenoidectomy and/or tonsilectomy on serum markers of inflammation and on fasting insulin levels in 58 children with OSAS and 17 controls, and found no improvements in insulin resistance [34]. In contrast, an earlier study on 62 children with OSAS (35 obese and 25 non-obese) reported T&A-associated improvements in total cholesterol, HDL, and LDL among all children, but improvements in triglycerides and insulin resistance were exclusively restricted to obese children [35]. In a cohort of 459 children aged 5-12 years, obesity was the primary driver of most associations between OSA and metabolic measures [36]. It should be pointed out that the age cut-off of the aforementioned studies was younger than in the present study, and it is likely that younger children may be less prone to developing signifcant metabolic changes in the context of OSAS. Indeed, studies in adolescents have found associations between OSAS and insulin resistance measures independent of obesity [29,30,37], and the present study would seem to further indicate that effective treatment of OSAS would ameliorate insulin resistance when the latter is present.

Few studies have evaluated the effects of weight loss on metabolic profile in obese OSAS children. One study of obese adolescents with a mean age of 15.5 years performed an inpatient-based dietary intervention for weight loss in 50 patients. Except for glycemic values, all parameters improved significantly after weight loss, both for patients with and without OSAS, and HDL cholesterol improved proportionaly with the decrease in BMI-z-score [38]. In the present study, the group of children with mild OSAS who underwent only dietary treatment did not show evidence of significant changes in metabolic parameters at follow-up. However, such children were younger and less obese than the children included in the study by Hoorenbeeck and colleagues [38]. The present subgroup analyses at follow-up further reinforce the putative effect of OSAS on insulin resistance; an effect that appears to be superimposed on the independent effect of obesity on insulin resistance.

C-reactive protein (CRP) levels have been shown to be increased in the presence of obesity in children [39], and CRP is a significant inflammatory mediator and independent marker of cardiovascular disease [40]. It is produced in the liver, and is thought to actively participate in atheromatous lesion formation through induction and enhanced expression of adhesion

molecules [41]. The association between CRP concentrations and pediatric OSAS has now been inferred from a large body of work that generally indicates, albeit with some notable exceptions that may be explained by genetic and environmental interactions [42,43], the presence of increased circulating levels of CRP with increasing severity of OSAS [44]. Furthermore, a recent meta-analysis that included eight original studies came to the conclusion that T&A significantly reduces CRP levels in children with OSAS [45]. Thus, CRP has emerged as a potentially useful biomarker of OSAS-mediated end-organ morbidity, including the ability to identify children who are at increased risk of adverse neurocognitive functioning [46]. Additionally, in a recent multicenter study conducted in four European and US pediatric sleep centers, which included 182 children with OSAS treated with T&A, the presence of residual moderate-severe OSAS following surgery (post T&A AHI >5/hour TST) exhibited significantly higher CRP levels when compared with those children in whom T&A led to resolved OSAS (ie, post T&A AHI <1.5/hour TST) [27]. In the present study, CRP levels decreased at follow-up in the non-OSAS and remission groups, whereas levels increased in the incident and persistent groups. Furthermore, those children with residual OSAS in the surgically treated group also presented higher CRP levels when compared with the surgically resolved group, with the highest levels of CRP being observed in the group of children treated with CPAP. Therefore, it is believed that additional studies will be needed to show the usefulness of CRP as a longitudinal biomarker of OSAS [47-49].

Some methodological issues and limitations of the present study deserve comment. First, the prospectively designed recruitment of the cohort was based on the diagnosis of obesity during routine well-child visits by pediatricians in the community, thereby obviating any potential a priori selection bias. Consequently, none of the study subjects had been previously evaluated for snoring, or had been clinically suspected or treated for OSAS. Based on their initial PSG findings, four groups were defined for intervention (non-treatment, dietary treatment, surgical treatment and CPAP treatment), and therefore eight groups emerged in the follow-up assessments (using the dichotomous variable of OSAS present or absent), resulting in substantial fragmentation of the cohort at follow-up into small cell numbers. It is believed that this is the first study to examine different treatment approaches according to the severity of OSAS. Although this obviously constitutes strength of the study, it imposes the presence of smaller sample sizes for each of the subgroups studied, and their potential for inducing a beta 2 error. However, the total follow-up sample consisted of 113 obese children, which is the largest obese cohort studied thus far in a prospective fashion. Nonetheless, the wide age distribution of the present cohort could have affected interpretation

of insulin resistance and dyslipidemia, given the inclusion of both pre-pubertal and pubertal children. To attempt and reduce this limitation, an analysis was preformed to divide the study population into children aged <9 years and >9 years, and the findings remained unchanged. Taken together, the current findings provide a strong incentive for a large, prospective interventional study that enables a clearer and more definitive set of conclusions.

In summary, effective treatment of OSAS improved lipid profiles and insulin resistance in obese children when such abnormalities in metabolic function were present. Furthermore, CRP levels appeared to be useful for potentially predicting follow-up status regarding OSAS, particularly in obese children in whom a very high proportion was likely to manifest persistence of their sleep-disordered breating after treatment. However, additional multicenter studies will be necessary to confirm these preliminary observations. Finally, HOMA values were associated with incidence or persistence of OSAS, suggesting that insulin resistance may contribute to worsening of the risk for OSAS.

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Highlights

- In obese children with obstructive sleep apnea syndrome (OSAS) the impact of treatment on metabolic function is unclear.
- Effective treatment of OSAS improves lipid profiles in obese children from the community.
- Effective treatment of OSAS could improve glucose metabolism in obese children with OSAS from the community.