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Oxidative stress in obese children and adolescents with and without type 2 diabetes mellitus is not associated with obstructive sleep apnea

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Abstract

Purpose Obesity, obstructive sleep apnea (OSA), and type 2 diabetes mellitus (T2DM) are associated with chronic low-grade inflammation and oxidative stress. In adults, increased lipid peroxidation, a marker of oxidative stress, was found in both metabolic syndrome and OSA. Studies on oxidative stress in children with T2DM and OSA are scarce.

Methods Plasma oxidized low-density lipoprotein (Ox-LDL) levels were evaluated in obese children and adolescents with/without T2DM, and the contribution of OSA to oxidative stress was investigated.

Results Ten patients with T2DM, 8 with impaired glucose tolerance (IGT), and 20 body mass index-standard deviation score (BMI-SDS)-matched non-diabetic children (controls) were studied. They all underwent overnight polysomnography. Fasting plasma concentrations of Ox-LDL were measured and compared to the glycemic status and to the presence of OSA. Fourteen patients (36%) were diagnosed with OSA and 21 (55%) with hypertension. There were no significant group differences in plasma Ox-LDL levels or between patients with/without OSA. Plasma Ox-LDL levels were significantly higher among patients with hypertension compared to controls ($P = 0.01$), while they correlated with homeostasis model assessment ($P = 0.02$), BMI-SDS ($P = 0.049$), and systolic blood pressure ($P = 0.002$).

Conclusions The findings of this pilot study suggest that increased lipid peroxidation is associated with insulin resistance and hypertension in obese children and adolescents, while OSA has most likely minor influence.

Keywords Insulin resistance · Type 2 diabetes mellitus · Obesity · Obstructive sleep apnea · Ox-LDL

Introduction

Childhood obesity has reached epidemic proportions worldwide and has become a major public health issue [1]. It is associated with an increased prevalence of obesity-related comorbidities at an early age, including type 2 diabetes mellitus (T2DM) [2] and obstructive sleep apnea (OSA) [3]. Obesity is a risk factor of OSA, and both conditions are associated with chronic low-grade inflammation and oxidative stress [4, 5], which promote insulin resistance (IR), T2DM [6], and cardiovascular morbidity [7]. Oxidative stress results from an increased pro-oxidant/anti-oxidant ratio, initiating a vicious cycle, leading to sympathetic activation and inflammation, which, in turn, potentiates oxidative stress. The oxygen free radicals are produced within the vasculature damage and alter the biological functions of vital biomolecules, such as lipids, proteins, DNA, and carbohydrates [8–10]. Various circulating markers of oxidative stress are increased in patients with OSA at levels that correlate with OSA severity, and they are partially normalized following treatment [10–15]. Oxidative stress is also a common persistent pathogenic factor that mediates the appearance of IR as well as the transition from IR to overt diabetes while increasing the risk of endothelial dysfunction and atherosclerosis [16, 17].

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Lipids are the biomolecules most susceptible to oxidation, and they are used as surrogate markers of atherosclerosis and cardiovascular morbidity in adults and in children. In adults, oxidized low-density lipoproteins (Ox-LDL), a well-established marker of oxidative stress, are associated with obesity [18], IR, metabolic syndrome [19], and cardiovascular disease [20]. In children and adolescents, Norris et al. [21] reported higher levels of Ox-LDL in those who were obese compared to normal-weight peers, and Kelly et al. [22] demonstrated that plasma Ox-LDL in children was associated with IR.

We have recently reported that OSA in children is associated with increased lipid peroxidation in a severity-dependent manner, and that lipid peroxidation levels are correlated with the degree of intermittent hypoxia [23]. Taken together, oxidative stress may be a common pathogenic mechanism in OSA, in impaired glucose homeostasis, and in the cardiovascular morbidity associated with both conditions.

The aims of this prospective cross-sectional pilot study were to evaluate plasma Ox-LDL levels in obese children and adolescents with T2DM compared with children and adolescents without T2DM matched for body mass index-standard deviation scores (BMI-SDS). In addition, the contribution of OSA to oxidative stress was evaluated in obese patients with and without T2DM.

Methods

Setting and patients This study is part of a larger clinical trial from which several publications regarding several research questions are generated with the use of the same original participant sample. The study protocol was described in detail previously [24, 25]. The major eligibility criteria for inclusion were the following: children and adolescents with T2DM (study group) and without T2DM (control group), age 6–21 years, and a BMI ≥ 95th percentile for age and gender for patients younger than 18 years or a BMI ≥ 30 for patients aged 18–21 years. All participants were attending the Institute of Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel. Patients were excluded if they had any other significant chronic disease or a psychiatric disorder that was likely to affect their compliance.

The diagnosis of T2DM was based on clinical presentation with a fasting blood glucose level > 126 mg/dl or a glucose level > 200 mg/dl measured at 2 h after an oral glucose tolerance test (OGTT) in the absence of pancreatic autoantibodies (insulin antibodies [IAA], islet cell antibodies [ICA512], and glutamic acid decarboxylase [GAD] II antibodies). In addition, patients without a diagnosis of diabetes underwent a 2-h oral OGTT (glucose 50%, 45 g/m^2, maximum 75 g) at the Institute of Endocrinology and Diabetes of Schneider Children's Medical Center of Israel, in order to identify those with impaired glucose tolerance (IGT) or silent diabetes. Impaired fasting glucose was defined as a fasting blood glucose level of > 100 mg/dL; IGT was defined as a blood glucose level of 140–199 mg/dL measured at 2 h after OGTT.

IR was evaluated by the homeostasis model assessment method (HOMA-IR), calculated by dividing the product of insulin (microunits/milliliter) and glucose (millimoles/liter) by 22.5 [26]. IR was defined by abnormal values of age- and sex-specific HOMA-IR cutoffs [27].

All the study participants completed a questionnaire on past and present sleep-disordered breathing (SDB) and underwent a physical examination, fasting blood tests, and overnight polysomnography. The obstructive apnea/hypopnea index (AHI) was calculated by the number of apneas and hypopneas per hour of total sleep time (TST). In patients 18 years and younger, OSA was defined as an AHI greater than 1/h TST. In patients older than 18 years ($n = 3$), OSA was defined as an AHI greater than 5/h TST [28].

Blood pressure (BP) measurements were conducted three times at 1 min apart using oscillometric monitors (Welch Ayllen) while the subjects were seated, and the two last measurements were averaged for analysis. BP measurements were taken after 15 min of being seated on a bed between 20:00 and 23:00 on the night of polysomnography [29]. Hypertension was defined as systolic and/or diastolic BP ≥ 95th percentile for age, gender, and height in patients younger than 18 years [29], and as systolic BP > 140 mmHg or diastolic BP > 90 mmHg in patients older than 18 years [30].

Prior to recruitment, written informed consent was obtained from the patients or their parents. The study was approved by the Institutional Ethics Review Board of Schneider Children's Medical Center of Israel and the Tel Aviv Souraski Medical Center, and the study protocol complied with the provisions of the Declaration of Helsinki.

Biochemical analysis Blood samples were obtained from each participant on the morning after polysomnography and after a 10-h overnight fast for the measurement of glucose, insulin, HbA1C, liver enzymes, and lipid profile (cholesterol, triglycerides [TG], low-density lipoprotein [LDL], and high-density lipoprotein [HDL]). The blood samples were immediately centrifuged, and plasma was frozen at − 80 °C until assay.

Insulin levels were measured using radioimmunoassay kit (DiaSorin, Italy) with intra-assay coefficient of variation (CV) of 5.5–10.6% and an inter-assay CV of 6.2–10.8%. HbA1C was measured with high-performance liquid chromatography using an automated glycohemoglobin analyzer (Tosoh Bioscience, Japan). Glucose, cholesterol, HDL, and TG levels were measured using photometric assay (Advia 1650; Siemens Healthcare Diagnostics, NY USA) within a variability of 1.0%, 0.5%, 0.7, and 1.7%, respectively, and a total variability of 1.7%, 1.3%, 2.4, and 3.7%, respectively. Plasma Ox-LDL levels were measured using commercially

available enzyme-linked immunosorbent assay (ELISA) methods (Mercodia, Sweden) according to the manufacturer's instructions and by using three external standard samples with known values.

Data and statistical analysis The statistical analysis was conducted using SPSS software (version 21; SPPS Inc., Chicago, IL). Comparisons of variables were performed between the study groups, which were subdivided into patients with IGT and patients with normal results on the OGTT, and the controls. In order to further investigate the contribution of both the glucose state and OSA to oxidative stress, the cohort was divided into four groups: patients with T2DM and OSA, patients with OSA and no T2DM, patients with T2DM and no OSA, and patients with no OSA and no T2DM. Since plasma Ox-LDL levels were found to be elevated among subjects with hypertension (HTN), the relative contribution of both HTN and OSA on oxidative stress was also analyzed by dividing the cohort into four other groups: patients with HTN and OSA, patients with OSA and no HTN, patients with HTN and no OSA, and patients with no OSA and no HTN.

The results were expressed as means ± standard deviation when the data were normally distributed, and as median (interquartile range) when the data were not normally distributed.

Comparisons for normally distributed variables were performed using an independent *t* test or analysis of variance (ANOVA) followed by post hoc comparisons, with *P* values adjusted for unequal variances when appropriate (Levene's test for equality of variances), or chi-square (χ^2) analyses with Fisher's exact test (dichotomous outcomes). Comparisons of variables that were not normally distributed were performed with the Wilcoxon Mann–Whitney non-parametric test and the Kruskal–Wallis test. Correlations between plasma Ox-LDL levels and clinical, biochemical, or polysomnography measures were performed using Spearman's correlation analysis. *P* values less than 0.05 were considered to be statistically significant.

Results

The demographic, anthropometric, biochemical, and polysomnographic measures of all participants have been described elsewhere [24, 25]. The current study presents the data for 38 out of 41 subjects whose Ox-LDL status was evaluated. Of those, 10 were diagnosed with T2DM and 8 with IGT, and the remaining 20 were obese subjects without IGT. The mean duration of diabetes was 3.3 ± 2.1 years (range 0.3–7 years). All children with T2DM were treated (5 used insulin only, 1 used hypoglycemic medication only, and 4 used combined insulin and oral hypoglycemic medications) for a mean duration of 2.1 ± 1.7 years (range: 2 months–6 years).

The main clinical, biochemical, and polysomnographic data of the three groups (T2DM, subjects with IGT, and subjects without IGT) are presented in Table 1. As shown, except from some expected metabolic differences, patients with T2DM were older compared to controls. Fourteen of the patients (36%) were diagnosed with OSA, and the percentage of OSA was similar for the three groups. No significant differences in any of the sleep measures were found between the three groups. Twenty-one patients (55%) had HTN. The percentage of HTN was not different among those three groups (50% in T2DM, 57% in IGT, and 63% in controls, $P = 0.79$), nor between patients with OSA compared to those without OSA (55 vs. 64%, respectively, $P = 0.56$).

There were no significant differences in plasma Ox-LDL levels among the three groups (T2DM, 50.3 ± 10.8 U/L; IGT, 45.8 ± 4.9 U/L; controls, 49.8 ± 12.6 U/L, $P = 0.64$). There also was no significant difference in plasma Ox-LDL levels among patients with OSA compared to those without OSA (48.7 ± 9.6 vs. 49.3 ± 11.7 U/L, respectively, $P = 0.88$). However, plasma Ox-LDL levels were found to be significantly higher among patients with HTN compared to the non-HTN controls (53.1 ± 11.3 vs. 44.1 ± 8.5 U/L, respectively, $P = 0.014$) (Fig. 1).

There were no differences in the main clinical biochemical and polysomnographic data of children with HTN compared to children without HTN (Table 2). Comparisons of the plasma Ox-LDL levels according to the group assignment based on the four combinations of HTN (HTN and OSA, OSA and no HTN, HTN and no OSA, and no OSA and no HTN) did not reveal any significant differences among those four groups. There were also no correlations between plasma Ox-LDL levels and any of the polysomnographic measures.

Plasma Ox-LDL levels correlated with HOMA-IR ($r = 0.37$, $P = 0.02$), insulin level ($r = 0.39$, $P = 0.016$), BMI-SDS ($r = 0.33$, $P = 0.049$), and systolic BP ($r = 0.48$, $P = 0.002$). Plasma Ox-LDL levels also correlated with cholesterol and LDL levels ($r = 0.39$, $P = 0.015$ and $r = 0.51$, $P = 0.001$, respectively. No correlation was found between plasma Ox-LDL levels and diabetes duration.

Linear regression analysis with plasma Ox-LDL as a dependent variable and BMI, HOMA-IR, hypertension, and AHI as covariates revealed that HTN and HOMA-IR were the only significant variables ($P = 0.028$ and $P = 0.048$, respectively), indicating a strong association of oxidative stress with measures of the metabolic syndrome.

Plasma Ox-LDL levels were assessed according to group assignment based on the glucose state and OSA (T2DM and OSA, OSA and no T2DM, T2DM and no OSA, and no OSA and no T2DM) did not reveal any significant differences among those four groups either.

Table 1 Clinical, biochemical, and polysomnographic data of patients with T2DM, IGT, and controls (without IGT or T2DM)

	T2DM $n = 10$ (% or range)	IGT $n = 8$ (% or range)	Control $n = 20$ (% or range)	*P*
Clinical characteristics				
Gender (male), *n*	5 (45.5)	5 (62.5)	16 (80.0)	0.14
Age, years	15.9 ± 3.6*	13.1 ± 2.5	12.6 ± 3.3	0.03
Tanner stage, *n*				
I	0	2 (25.0)	5 (22.7)	0.70
II–IV	5 (45.4)	3 (37.5)	10 (45.5)	
V	6 (54.5)	3 (37.5)	7 (31.8)	
BMI-SDS	2.4 ± 0.5	2.6 ± 0.3	2.4 ± 0.4	0.41
Systolic blood pressure. mmHg	133.9 ± 9.6	133.0 ± 9.7	129.5 ± 12.7	0.53
Diastolic blood pressure, mmHg	84.6 ± 10.9	78.1 ± 10.0	73.6 ± 14.7	0.09
Biochemical characteristics				
HOMA–IR	12.8* (6.3–23.5)	11.8 (5.7–15.0)	6.6 (3.6–9.7)	0.026
HbA1C (%), mmol/mol	8.4*^ (7.8–9.0)	5.8 (5.3–6.4)	5.4 (5.2–5.7)	< 0.0001
Cholesterol, mg/dl	176.0 (152.0–185.0)	159.5 (149.0–171.0)	165.0 (154.0–185.0)	0.36
Triglycerides, mg/dl	141.5* (117.0–203.0)	115.0 (93.5–130.0)	104.0 (82.0–136.0)	0.03
HDL-cholesterol, mg/dl	36.9 (32.8–47.1)	39.2 (36.1, 45.0)	43.8 (37.7–47.5)	0.29
LDL-cholesterol, mg/dl	105.0 (93.0–118.0)	96.0 (91.0. 105.0)	99.0 (89.0–115.0)	0.36
Plasma Ox-LDL, U/L	50.3 ± 10.8	45.8 ± 4.9	49.8 ± 12.6	0.64
Polysomnographic characteristics				
Apnea hypopnea index, events/h	1.3 (0.2–8.6)	1.4 (0.5, 5.7)	0.7 (0.2–4.0)	0.62
Mean Spo2, %	97.0 (96.0–97.4)	96.9 (95.7–97.4)	97.7 (97.0–98.0)	0.09
SpO2 nadir, %	92.0 (80.0–93.0)	90.5 (86.0–94.0)	92.0 (90.0–94.0)	0.79

The data are expressed as means ± standard deviation when normally distributed and as median (interquartile range) when not normally distributed

BMI-SDS, body mass index-standard deviation score; *HOMA-IR*, homeostasis model assessment; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *HbA1C*, hemoglobin A1C; *Ox-LDL*, oxidized LDL

*$P < 0.05$ T2DM vs. controls

^ $P < 0.05$ IGT vs. controls

# $P < 0.05$ T2DM vs. IGT

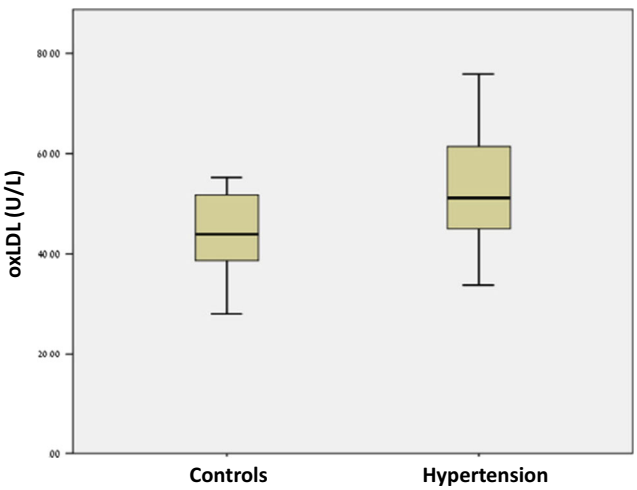

Fig. 1 Plasma Ox-LDL levels in patients with hypertension compared to controls ($n = 38$)

Discussion

Impaired glucose homeostasis and OSA are strongly associated with adiposity as well as with chronic subclinical inflammation and oxidative stress, two underling mechanisms that promote cardiovascular morbidity in both conditions [31]. The aim of the present study was to evaluate the relative contribution of each of those conditions to oxidative stress in obese children and adolescents. The findings of the current pilot study demonstrated that lipid peroxidation was related to insulin resistance but not to the degree of breathing disorder in obese children and adolescents. In addition, lipid peroxidation was increased in those patients who had HTN and correlated with systolic BP, a finding that while it is not surprising, is not predicted a priori.

The plasma Ox-LDL levels correlated with HOMA-IR, supporting the role of oxidative stress in the development of insulin resistance and diabetes [16]. Despite the associations found between plasma Ox-LDL levels and insulin resistance,

Table 2 Clinical, biochemical, and polysomnographic data of patients with hypertension and without hypertension

	Hypertension $n = 21$ (% or range)	No hypertension $n = 16$ (% or range)	*P*
Gender (male), *n*	13 (62)	11 (70)	0.47
Age, years	14.3 ± 2.9	13.8 ± 3.7	0.65
Tanner stage, *n*			
I	3 (14.3)	3 (18.7)	0.70
II–IV	7 (33.3)	7 (43.8)	
V	11 (52.3)	6 (37.5)	
BMI-SDS	2.4 ± 0.4	2.4 ± 0.4	0.52
HOMA-IR	9.7 (6.5–13.0)	5.6 (3.6–10.3)	0.14
Cholesterol (mg/dl)	172.0 (148.0–187.0)	164.0 (150.0–185.0)	0.80
Triglycerides (mg/dl)	134.0 (111.0–149.0)	98.0 (82.0–127.0)	0.10
HDL-cholesterol (mg/dl)	41.6 (33.9–47.2)	39.0 (34.8–48.8)	0.85
LDL-cholesterol (mg/dl)	99.0 (87.5–117.5)	97.5 (88.8–107.3)	0.75
Apnea hypopnea index (events/h)	1.1 (0.4–4.9)	0.5 (0.1–7.8)	0.39
Mean Spo2 (%)	97.0 (95.8–98.0)	97.6 (97.0–98.0)	0.75
SpO2 nadir (%)	92.0 (87.0–94.0)	93.0 (88.5–94.5)	0.81

The data are expressed as means ± standard deviation when normally distributed and as median (interquartile range) when not normally distributed

BMI-SDS, body mass index-standard deviation score; *HOMA-IR*, homeostasis model assessment; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *HbA1C*, hemoglobin A1C; *Ox-LDL*, oxidized LDL

no differences in lipid peroxidation were found among the subjects with T2DM, IGT, or controls in the current cohort. Possible explanations for those results are the relatively short duration of diabetes among the patients with T2DM, the treatment for T2DM, the severity of OSA that was quite similar among the three groups, and the small number of subjects in each group. In addition, there were no differences between the three groups in the percentages of those with HTN and OSA, both of which largely affect oxidative stress and, concomitantly, Ox-LDL values.

The lack of associations between Ox-LDL levels and any of the polysomnographic measurements is in contrast to our previous publication [23] and may be explained by the small sample size and the relatively mild cases of OSA in the present cohort. In addition, it is possible that the role of OSA may not be as apparent in post-pubertal and pubertal subjects as in younger children. Another explanation may be the role of genetics in oxidative stress. Unfortunately, family history was not assessed in the present study. However, it can also indicate that the contribution of OSA is quite minimal in obese children and adolescents with conditions of impaired glucose homeostasis. Previous publications have indicated that the degree of lipid peroxidation is closely related to the degree of adiposity [18, 19], but the participants in the current study were similar in the degree of adiposity; thus, the contribution of obesity to the degree of lipid peroxidation was well controlled.

HTN is common among overweight and obese children. Several factors are involved in the development of their HTN, including endocrine determinants, such as corticosteroids and adipokines, sympathetic activation, and disturbed sodium homeostasis, as well as oxidative stress, inflammation, and endothelial dysfunction [32]. Thus, the finding of increased levels of Ox-LDL in the obese children and adolescents with HTN is not surprising. While both insulin resistance and OSA may lead to lipid peroxidation and the development of systemic HTN, the increased lipid peroxidation found in the present study in patients with HTN was most likely mediated by impaired glucose homeostasis [17, 20, 33] and not related to the presence of OSA.

The current findings support previously reported data that showed a positive correlation between 8-isoprostane, a different marker of oxidative stress, and systolic BPe measurements as well as increased levels of 8-isoprostane in obese children with hypertension [34]. A correlation between Ox-LDL levels and HTN had also been found in another study on children with chronic kidney disease [35]. The mechanism linking oxidative stress and HTN in obese patients is thought to involve adipocytokine release and renin-angiotensin-aldosterone system activation [36].

The major limitations of this study are the small sample size and the use of a cross-sectional and not a longitudinal follow-up design. The broad range and diversity in Tanner stage is another limitation. It is nevertheless noteworthy that T2DM has a low prevalence among children and adolescents

in Israel, and it accounts for only 3–5% of all cases of diabetes in this age group. However, to the best of our knowledge, this is the first study that examined the contribution of conditions of impaired glucose homeostasis and OSA to oxidative stress in obese children and adolescents.

Conclusions

The present pilot study found that increased lipid peroxidation was associated with insulin resistance and HTN in obese children and adolescents, while the contribution of OSA is most likely minor. Further larger scale studies are warranted to understand the precise contribution of impaired glucose homeostasis and sleep-disordered breathing on the development of HTN in obese children and adolescents and to validate our current preliminary findings.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional research committee (Schneider Children's Medical Center of Israel and the Tel Aviv Souraski Medical Center) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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