Original Article

Effects of adenoidectomy on markers of endothelial function and inflammation in normal-weight and overweight prepubescent children with sleep apnea

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Abstract

BACKGROUND: This trial study aimed to assess the effects of adenoidectomy on the markers of endothelial function and inflammation in normal-weight and overweight prepubescent children with obstructive sleep apnea (OSA).

METHODS: This trial study was conducted in Isfahan, Iran in 2009. The study population was comprised of 90 prepubescent children (45 normal-weight and 45 overweight children), aged between 4-10 years old, who volunteered for adenoidectomy and had OSA documented by validated questionnaire. The assessment included filling questionnaire, physical examination, and laboratory tests; it was conducted before the surgery and was repeated two weeks and six months after the surgery.

RESULTS: Out of the 90 children evaluated, 83 completed the 2-week evaluation and 72 patients continued with the study for the 6-month follow up. Markers of endothelial function, i.e., serum adhesion molecules including endothelial-leukocyte adhesion molecule (E-selectin), intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (sVCAM-1), and the markers of inflammation, i.e., interleukin-6, and high-sensitive C-reactive protein (hs-CRP) decreased significantly in both normal-weight and overweight children after both two weeks and six months. After six months, the total and LDL-cholesterol showed a significant decrease in the overweight children.

CONCLUSIONS: The findings of the study demonstrated that irrespective of the weight status, children with OSA had increased levels of the endothelial function and inflammation markers, which improved after OSA treatment by adenoidectomy. This might be a form of confirmatory evidence on the onset of atherogenesis from the early stages of the life, and the role of inflammation in the process. The reversibility of endothelial dysfunction after improvement of OSA underscores the importance of primordial and primary prevention of chronic diseases from the early stages of the life.

KEYWORDS: Sleep, Endothelial Function, Inflammation, Child, Prevention.

Obstructive Sleep Apnea (OSA) is a prevalent medical condition, with an estimated prevalence of 2–3% in children; it is characterized by repetitive upper airway obstruction, resulting in continued breathing effort with diminished airflow.[1-4]

Although the main symptom of OSA is daytime hypersomnolence, patients with OSA are at a higher risk of metabolic disorders[5,6] and the incidence of cardiovascular disease (CVD) morbidity and mortality.[7] It was previously assumed that these complications are related to obesity; however, the recent data suggests that OSA may have an independent association with cardio metabolic risk factors.[8]

There is a growing body of evidence on the

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interaction of OSA with the metabolic dysfunction, which is known as a risk factor for CVD in adults.[8,9] Although it is well-documented that CVDs origin from the early stages of life and the CVD risk factors tend to track from childhood into the adulthood,[10-12] limited experience exist on the association of OSA and cardio metabolic risk factors in the pediatric age group.

Improvement of OSA by adenoidectomy might have beneficial effects on metabolic dysfunction. The current trial aimed to assess the effects of adenoidectomy on the markers of endothelial function and inflammation in the normal-weight and overweight prepubescent children with OSA.

Methods

This clinical trial study was conducted among children who volunteered for adenoidectomy in Isfahan, the second large city in Iran from May to December 2009.

Participants

The study population were comprised of 90 prepubescent children (45 normal-weight and 45 overweight children), aged between 4-10 years old, who volunteered for adenoidectomy and had OSA documented by a validated questionnaire. Those children with syndromic obesity, endocrine disorders, any physical disability, and or history of any chronic medication use were not included in the trial. Two groups of normal-weight and overweight children[13] were selected consecutively among the children who were referred for adenoidectomy.

The study was conducted according to the Declaration of Helsinki, and was approved by the Ethics Committee of the School of Medicine, Isfahan University of Medical Sciences. After providing detailed oral information to the children and their parents, written informed consents were obtained from the parents of eligible children.

OSA was documented by a widely used and validated questionnaire.[14] The questionnaire was extended with questions concerning (i) Child's demographic data (i.e., gender, age, height, weight, household smoking, and pa-

rental education), (ii) Daytime behavior (e.g., hyperactive-inattentive behavior and tiredness), (iii) Frequent sleep problems (i.e., sleep-onset delays, enuresis, night waking, nightmares, and sleep walking), and (iv) the Current health status (e.g., frequency of upper respiratory tract infections).

Except for the first three items, which were on a 4-point rating scale: 'Never', 'occasionally', 'frequently', and 'always', most questions were to be answered on a 5-point rating scale ('never', 'rarely', 'occasionally', 'frequently', 'almost always').

Anthropometric Measurement and Clinical Examination

All measurements were made by a trained team of general physicians and nurses under supervision of the same pediatrician, using calibrated instruments and standard protocols. The weight (Wt) and the height (Ht) were measured by calibrated scale and Stadiometer (Seca, Japan) with participants lightly clothed and barefooted nearest to 0.1 cm and 0.1 kg, respectively. Body Mass Index (BMI) was computed as Wt (kg) divided by Ht (m) squared. The BMI percentiles was compared to the BMI charts of the Centers for Disease Control and Prevention; the BMI levels corresponding the age and gender-specific 5th-85th percentile were considered as normal-weight, and the BMI ≥ 85th percentile was considered as overweight.[13] The blood pressure (BP) was measured using mercury sphygmomanometer under the standard protocol. The readings at the first and the fifth Korotkoff phase were taken as systolic and diastolic BP (SBP and DBP), respectively. The average of the two BP measurements was recorded.[15]

Biochemical measurements

Participants were asked to fast for 12 hours before the screening and compliance with fasting was determined by interview on the morning of examination. While one of the parents accompanied the child, fasting blood samples were taken from the ante-cubital vein, and within 30 minutes after venipuncture were centrifuged

for 10 minutes at 3000 rpm. The fasting blood glucose (FBG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and high-sensitive C-reactive protein (hs-CRP) were measured using auto-analyzer. HDL-C level was determined after dextran sulphate-magnesium chloride precipitation of non-HDL-C.[16] Serum adhesion molecules, i.e., intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and endothelial-leukocyte adhesion molecule (E-selectin), as well as interleukin-6 (IL-6) were measured by enzyme-linked immunosorbent assay (ELISA) method using standard kits (Bender Med Systems, GmbH, Vienna, Austria).

Comparisons
All the baseline assessments including filling the questionnaire, physical examination and laboratory tests were repeated within two weeks and six months after adenoidectomy to determine the short-term and long-term changes in both groups after the OSA treatment.

Statistical Analysis
The data was stored in a computer database. Statistical analyses were performed using SPSS for Windows software (version 15.00, SPSS, Chicago, IL.). The descriptive data are presented as mean ± standard deviation (SD). The normality of the distribution of variables was verified by Kolmogorov- Smirnov test. The time trend of the changes within and between the groups was analyzed by the analysis of variance (ANOVA) and post-hoc tests. The significance level was considered at $p < 0.05$.
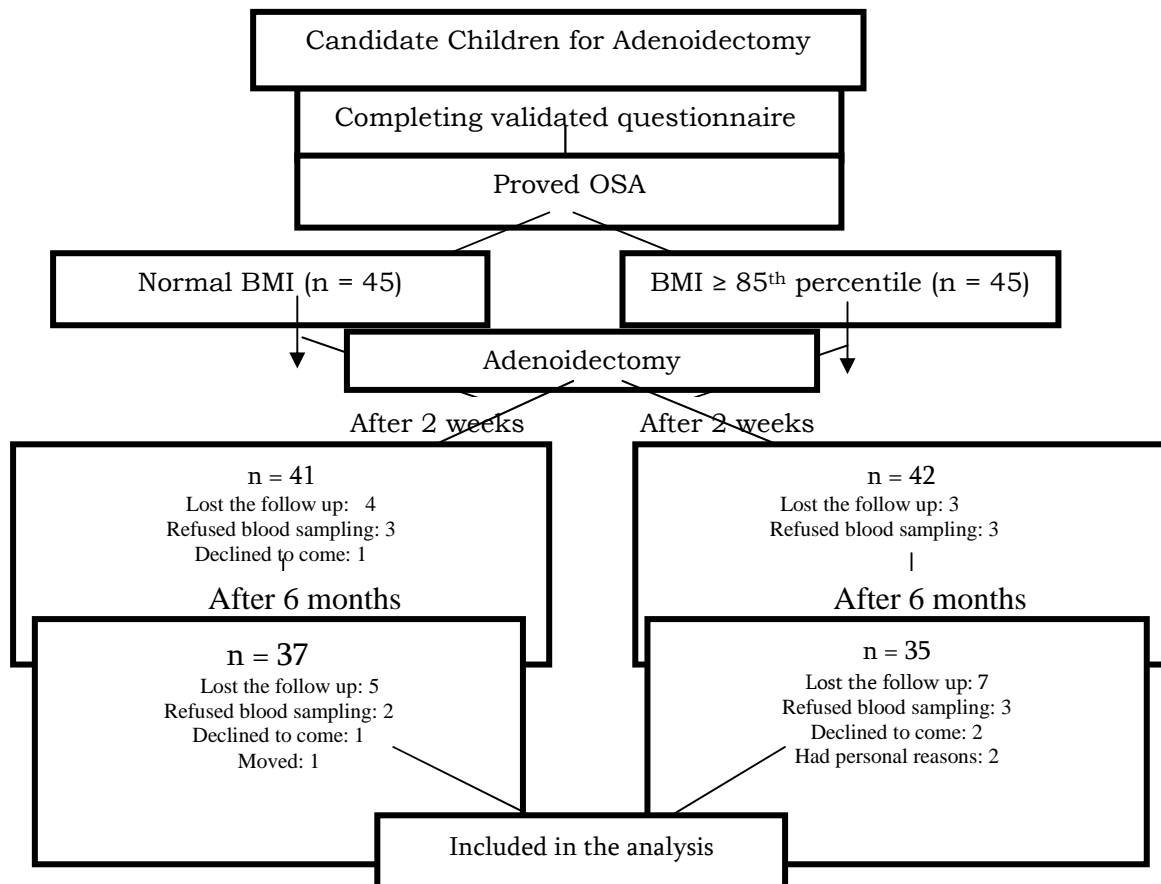

Figure 1. Participants' retention vs. attrition

Table 1. Mean (SD) of variables studied from baseline to 2 weeks and 6 months after adenoidectomy in normal-weight and overweight children

	Total	BMI < 85th percentile	BMI ≥ 85th percentile
Fasting Plasma Glucose (mg/dl)			
Baseline	80.4(5.3)	81.8(5.3)	89.0 (7.7)
After 2 Weeks	81.7(5.7)	83.1(7.1)	88.7 (4.1)
After 6 Months	80.8(6.7)	82.1(5.7)	89.0 (7.2)
Total Cholesterol (mg/dL)			
Baseline	170.7(22.7)	158.3 (28.1)	179.2 (24.0)
After 2 Weeks	170.8(22.5)	154.7 (28.6)	179.7 (24.5)
After 6 Months	171.1(21.7)	153.1 (28.7)	174.2 (23.5)†¶
LDL-Cholesterol (mg/dl)			
Baseline	101.6 (10.1)	101.2(10.7)	107.0 (30.2)
After 2 Weeks	102.4 (10.4)	100.7(15.9)	105.4 (31.1)
After 6 Months	100.7 (10.8)	100.9(10.8)	101.8 (31.4)†
HDL- Cholesterol (mg/dl)			
Baseline	36.0(7.9)	36.2(6.7)	35.8 (9.2)
After 2 Weeks	36.2(7.8)	36.4(6.8)	35.4 (9.1)
After 6 Months	36.7(8.4)	36.8(7.2)	36.1 (9.5)
Triglycerides (mg/dL)			
Baseline	156.8 (26.8)	145.0(22.0)	158.6(28.4)
After 2 Weeks	157.4 (26.5)	145.4(21.2)	157.1(27.1)
After 6 Months	155.2 (26.1)	146.1(24.1)	159.1(21.8)
s-ICAM-1 (ng/ml)			
Baseline	226.1(41.5)	226.3(42.7)	229.1(40.4)
After 2 Weeks	222.3(42.0)*	221.0 (43.2)*	224.2 (45.7)*
After 6 Months	218.5 (41.2)†¶	217.9(41.6)†¶	219.5(45.1)†¶
s-VCAM-1 (ng/ml)			
Baseline	619.1 (150.5)	618.3 (142.5)	622.6(146.4)
After 2 Weeks	615.2 (151.7)*	611.3 (142.1)*	617.8(143.2)*
After 6 Months	607.5(154.1)†¶	608.1(141.5)†¶	610.6(145.1)†¶
SE-selectin (ng/ml)			
Baseline	95.1(21.7)	94.4 (27.4)	99.5(28.7)
After 2 Weeks	92.7 (22.4)*	91.8 (27.7)*	97.4 (28.1)*
After 6 Months	88.6 (22.1)†¶	87.7 (27.5)†¶	91.7(24.1)†¶
Interleukin-6 (pg/ml)			
Baseline	9.5(2.1)	9.7 (2.3)	10.2(1.8)
After 2 Weeks	7.8(2.2)	8.1 (2.6)*	8.7(2.4)*
After 6 Months	6.1(2.4)†¶	7.2 (2.4)†¶	7.1(2.1)†¶
C-reactive Protein (mg/dl)			
Baseline	1.48(0.02)	1.41(0.04)	1.55(0.02)
After 2 Weeks	1.04 (0.04)*	1.21(0.05)*	1.28(0.01)*
After 6 Months	1.01(0.01)†¶	1.01(0.06)†¶	1.04 (0.01)†¶

BMI: Body Mass Index

In each column: *: $p < 0.05$ After 2 weeks vs. baseline; $p < 0.05$ After 6 months vs. baseline; $p < 0.05$ After 6 months vs.2 weeks

Results

As presented in Figure 1, among the 90 potential candidates who initially agreed to participate in the study, there were 41 children in group A (normal BMI) and 42 children in group B (BMI ≥ 85th percentile) after two weeks follow up, because some participants refused the blood sampling or declined to come for the follow up visits. At the 6-month follow up, the number of participants reduced to 37 in group A and 35 in group B. Based on the data obtained from the questionnaires, the OSA symptoms disappeared in both study groups.

Table 1 shows the metabolic and inflammatory changes in the normal-weight and overweight children before the operation and two weeks and six months after undergoing the adenoidectomy.

After six months, the total and LDL-cholesterol had significant decreases in overweight children. The most remarkable changes were the decline in the levels of markers of endothelial function and inflammation, i.e., ICAM-I, VCAM-I, E-Selectin, IL-6, and hs-CRP, which decreased in both normal-weight and overweight participants after both two weeks and six months.

Discussion

This trial revealed an independent association between OSA and the level of endothelial function and inflammation markers, which decreased after adenoidectomy in normal-weight and overweight children. These changes occurred in absence of the changes in most conventional cardio metabolic risk factors.

The relationship of the inflammatory processes with the progress of atherosclerosis provides important links between underlying mechanisms of atherogenesis and CVD risk factors. Therefore, the inflammatory biomarkers are considered as potential predictors of the present and future risk of CVD. Up-regulation of endothelial adhesion molecules, i.e., endothelial-leukocyte adhesion molecule (E-selectin), intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (sVCAM-1), might have a crucial role in

the earliest phases of atherosclerosis.[17,18] Concentrations of inflammation markers and soluble adhesion molecules were found to be higher in obese children than those in lean children.[19,20] These findings suggest early stages of endothelial dysfunction in children.

Atherosclerosis starts from the fetal life and its natural course consists of interrelations between the traditional risk factors and inflammatory and endothelial biomarkers. The features of chronic inflammation can be detected in fatty streaks, i.e., the first stage of atherosclerotic lesions.[21] Childhood obesity has become a health issue problem among Iranian children, even in those as young as six years of age,[22] and considering that many studies have documented the presence of atherosclerosis and inflammation surrogate markers as well as structural arterial changes among obese children,[23-26] the importance of the prevention and controlling this type of nutritional disorder is underscored.

The findings of the current study suggested the independent association of OSA with the inflammation marker levels in the normal-weight and overweight children. Concentration of these markers declined shortly after the OSA treatment. Children with OSA, experience a combination of oxidative stress, inflammation, autonomic activation, and disruption of sleep homeostasis.[27] The independent association of the OSA with markers of inflammation in the normal-weight and overweight prepubescent children documented in the current trial is consistent with the independent association of the OSA with the metabolic syndrome in adults.[28]

Our findings are in line with the findings of a previous study conducted in the normal-weight children with OSA who underwent adenoidectomy, which reported a decrease in the endothelial function markers levels.[29]

It was also found that children with resolution of OSA abnormalities experienced a change in the total and LDL-cholesterol levels, supporting the hypothesis that reversal of OSA may also reverse the progression of dyslipidemia over time, which is an important implication for the future CVD risk.[30]

The main limitation of this study was the questionnaire-based diagnosis of OSA, because of the high costs of polysomnography (PSG). The main novelty of the study is the measurement of markers such as adhesion molecules that have not been previously examined in trials among children with OSA.

Conclusion

The findings of the study demonstrated that irrespective of the weight status, children with OSA had increased the endothelial function and inflammation markers level, which improved after the OSA treatment by adenoidectomy. This might be complementary evidence on the onset of atherogenesis from the early stages of life and the role of inflammation in this process. The reversibility of endothelial dysfunction after the OSA treatment underscores the importance of the primordial and primary prevention of chronic diseases from the early stages of life. Future longitudinal studies documenting OSA by polysomnography (PSG) are recommended.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

RK participated in the design and conducting the study, drafted and edited the manuscript; NN participated in the design and conducting the study; AO participated in the design and conducting the study; BA participated in the design and conducting the study; PP helped to draft and edit the manuscript; MR participated in the design and conducting the study. All authors read and approved the final manuscript.

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