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What is This?
Impact of Adenotonsillectomy on High-Sensitivity C-Reactive Protein Levels in Obese Children with Obstructive Sleep Apnea

Lijuan Chu, MS¹, Hongbing Yao², and Bing Wang, PhD²

No sponsorships or competing interests have been disclosed for this article.

Abstract
Objective. To evaluate the effect of adenotonsillectomy (T&A) in obese children with obstructive sleep apnea (OSA) and to compare changes in high-sensitivity C-reactive protein (hs-CRP) levels before and 6 months after T&A in obese children with OSA.

Study Design. Before and after study with planned data collection.


Subjects and Methods. Seventy-five obese children with OSA were included. Clinical information such as the apnea-hypopnea index (AHI), nadir oxyhemoglobin saturation (SaO₂), and body mass index (BMI) were recorded. The hs-CRP level was determined before T&A and at the 6-month follow-up examination.

Results. Reductions in AHI (21.96 ± 9.287 before T&A vs 8.64 ± 5.997 after 6 months of T&A) and higher levels of nadir SaO₂ (74.08 ± 7.860 before T&A vs 86.87 ± 5.586 after 6 months of T&A) were observed. The hs-CRP level was determined before T&A and at the 6-month follow-up examination.

Conclusions. T&A treatment improves clinical signs and symptoms in obese children but does not reduce chronic inflammation as reflected by hs-CRP. To lower the risks of cardiovascular disease and diabetes mellitus morbidity, other treatments should be taken into account.

Keywords
adenotonsillectomy, hs-CRP, obese children, OSA

Obstructive sleep apnea (OSA) is a disease characterized by partial or complete narrowing of the pharyngeal airway during sleep and manifests clinically as repeated episodes of airflow cessation, oxygen desaturation, and sleep interruption. Plasma levels of inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and C-reactive protein (CRP) are elevated in patients with OSA. Obstructive sleep apnea occurs frequently in children, with an estimated prevalence of 2% to 3% of all children and a high prevalence of 33.3% in obese children. The dysfunction in neuromotor control of the pharynx is thought to be a potential trigger of OSA in children, and adenotonsillar hypertrophy further narrows the airway and exacerbates OSA. Adenotonsillectomy (T&A) is usually effectively treated by adenotonsillectomy (T&A). However, OSA persists after T&A in 76% of obese children. Although an improvement was observed in these children, they still exhibited an apnea-hypopnea index (AHI) >5 events/h.

C-reactive protein, an important circulating marker of inflammation, is one of the proposed links between OSA and inflammation. This protein, which is synthesized in the liver in response to upstream inflammatory signaling pathways involving IL-6, has also been shown to directly participate in atheromatous lesion formation and insulin resistance. A high-sensitivity CRP (hs-CRP) test is widely used to measure low levels of CRP and recognized as a potent predictor of future cardiovascular disease (CVD) and diabetes mellitus (DM) events. An increase in hs-CRP among children with OSA and a significant decrease after T&A treatment have been reported. However, no published report has examined the evolution of CRP after T&A therapy in obese children with OSA.

To better understand the impact of T&A therapy on obese children with OSA and the follow-up risks of CVD and DM, we collected clinical information such as AHI,
nadir oxyhemoglobin saturation (SaO₂), and body mass index (BMI) and examined the plasma levels of hs-CRP before T&A and at the 6-month follow-up examination. Then we assessed the correlation of hs-CRP with AHI and BMI, and compared the evolution of OSA before and after treatment.

Methods

Subjects and Study Design

Three hundred children who were shown to have obstructive sleep apnea by polysomnography (PSG) were enrolled in the study. The subjects included in this study were all patients at Chongqing Children’s Hospital (which is affiliated with Chongqing Medical University) from December 2009 to June 2010. Body mass index and AHI were chosen to reflect the degrees of obesity and OSA. The inclusion criteria were as follows: BMI greater than 28, AHI greater than 5 events/h, and hypopnea greater than 4% desaturation before T&A.¹⁶ The exclusion criteria were as follows: previous T&A, craniofacial syndromes, neuromuscular disease, developmental delay, psychiatric disorders, recent clinical infections or inflammation, the recent use of anti-inflammatory or antibiotic drugs, and systemic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus. A total of 75 obese children diagnosed with OSA were finally included and were studied twice: at the time of OSA diagnosis and 6 months after undergoing T&A. The effectiveness of T&A for OSA was evaluated using polysomnography. In addition, we divided these children into 2 groups based on postoperative AHI. The group with an AHI of less than 5 events/h was classified as the nonpersistent OSA group (cure group). In contrast, the group with an AHI of more than 5 events/h was classified as the persistent OSA group (no cure group). Cure was defined as no clinical signs and symptoms, as well as AHI <5 events/h and nadir SaO₂ >90%.

Ethical approval was granted by the Institutional Review Board of the Children’s Hospital, Chongqing Medical University, China, which is in compliance with the Helsinki Declaration. Written consent was obtained from all participants’ parents or guardians prior to enrollment in the study.

Polysomnography

Polysomnographic assessments were performed on all children at the time of OSA diagnosis and 6 months after T&A treatment; they were performed during normal sleep time for up to 9 hours in a quiet, darkened room in the company of a parent. Sleep parameters were recorded using a minimum of 5 channels, including electroencephalography (EEG), electro-oculography (EOG), and submental electromyography (EMG). The respiratory variables investigated included thoracic and abdominal wall movement, nasal airflow (pressure and thermister), and nadir SaO₂. A sleep medicine physician interpreted the polysomnography results. Obstructive AHI, which is defined as the average number of obstructive apneas and hypopneas per hour of sleep, was used for the diagnosis of OSA. Obstructive apnea was defined as a total absence of airflow through the mouth and nose with continued chest and abdominal movement for at least 2 respiratory cycles. Hypopnea was defined as a decrease in nasal flow of greater than 50% or a corresponding decrease in oxygen saturation of greater than or equal to 4% with an arousal.¹⁷

Measurement of hs-CRP

All subjects went to bed at 9 PM and were awakened at 6 AM. Samples of peripheral venous blood were collected at 6 AM (immediately after awakening), after the conclusion of the experiment, and 6 months after T&A. Venipuncture was completed in the morning after polysomnography. Serum levels of hs-CRP were measured with a latex agglutination immunoassay (Mitsubishi Kagaku Yatoron, Tokyo, Japan). The lower CRP detection limit was 0.01 mg/dL.

Statistical Analysis

Values were presented as means ± SD. Paired t test was used to investigate variability. Pearson’s correlation was used to analyze the correlations between hs-CRP and other parameters (BMI and AHI). All data were processed using SPSS Version 17.0 (SPSS, Inc, an IBM Company, Chicago, Illinois). P values less than .05 were considered statistically significant.

Results

Descriptive Clinical Study

Three hundred patients (180 males and 120 females) with suspected OSA underwent overnight-attended polysomnography. Fifty-one and 163 of the patients were excluded due to AHI values ≤5 events/h and BMI ≤28, respectively. On the basis of the exclusion criteria mentioned above, another 11 patients were removed. The remaining 75 patients participated in our study (Figure 1).

Impact of T&A Therapy on Obese Children with OSA

The severity of various OSA parameters before and after T&A therapy is presented in Table 1. The mean ± SD age of these patients was 6.38 ± 4.21 years. Apnea-hypopnea index values were significantly lower (21.96 ± 9.277 before T&A vs 8.64 ± 5.997 after 6 months of T&A, P < .001), and levels of nadir SaO₂ were significantly higher after T&A therapy as compared with that before (7.860 before T&A vs 9.277 after 6 months of T&A, P < .001). Mean relative BMI was similar in both groups (P = .592).

Impact of BMI and AHI on hs-CRP Levels

Correlation analysis of measurements obtained before T&A therapy revealed that the increase in hs-CRP was accompanied by a significant increase in BMI (r = 0.7948, P < .001; Figure 2A). In contrast, no correlation was observed between hs-CRP and AHI (r = 0.0579, P = .6217; Figure 2B).

Impact of T&A Therapy on Levels of hs-CRP

The study sample was further divided into 2 groups (non-persistent and persistent groups) according to the value of
AhI after T&A therapy. Figure 3 provides the patient characteristics: the nonpersistent group included 31 children, whereas the persistent group included 44 children. Apnea-hypopnea index >5 events/h were observed in 58.7% (44/75) of obese children postoperatively, who showed no cure. In the persistent group, all subjects had hs-CRP levels beyond the normal range, with no significant difference before as compared with 6 months after T&A therapy (before, 3.0605 ± 2.1074 vs 6 months after, 2.9600 ± 1.91689, P = .372; Figure 3A). The nonpersistent group exhibited no obvious clinical symptoms. No significant changes in CRP levels were observed before or after 6 months of T&A therapy (before, 2.9723 ± 2.18868 vs 6 months after, 2.8832 ± 1.98089, P = .707; Figure 3B). Whole-sample comparison also showed that pre- and postoperative values were similar (before, 3.0225 ± 2.12796 vs 6 months after, 2.9269 ± 1.93121, P = .421; Figure 3C).

Discussion

This study shows that the severity of OSA is significantly reduced in obese children after T&A. Mean AhI decreased from 21.96 ± 9.277 to 8.64 ± 5.997. Nadir SaO2 (%) increased from 74.08 ± 7.860 to 86.87 ± 5.586. Relatively few studies have examined the outcome of T&A for OSA in obese children. Kudoh and Sanai18 studied 25 obese children for a period of 5 to 6 days after T&A for OSA. The results obtained during this brief follow-up period showed that surgery was effective in decreasing irregular breathing and oxygen desaturation during sleep as measured by pulse oximetry. Mitchell and Kelly19 studied 33 obese and 39 normal-weight children with OSA and found that postoperative AhI values were significantly lower than the preoperative values for obese and normal-weight children. Similarly, the variations of nadir SaO2 were consistent with the data in our study, which suggested OSA could be improved significantly in obese children with T&A therapy.

No BMI changes occurred pre- or postoperatively. Nevertheless, 58.67% of obese children have been found to exhibit persistent OSA when using an AhI greater than 5 as the definition for OSA. O’Brien et al20 reported that persistent OSA occurred after T&A treatment in 22% of normal-weight children and in 55% of obese children. A recent meta-analysis of studies evaluating T&A in obese children found that the procedure led to a reduction in AhI but was less likely to result in a cure. Only 49% of obese children had postoperative AhI values <5 events/h.21 Therefore, our results indicated that T&A improved the clinical signs and symptoms of OSA but did not heal OSA in the majority of obese children. Further parameters might be required to evaluate the follow-up complications in obese children with OSA after T&A therapy.

In previously published pediatric studies, hs-CRP levels correlated with AhI in children with OSA. Tauman et al22 studied 81 children with OSA and showed that plasma CRP levels were elevated among some children with OSA and statistically linearly correlated with AhI. Chen and Duo23 also found that levels of hs-CRP were higher in children with OSA than in those with primary snoring. In our study, plasma levels of hs-CRP were significantly associated with BMI, whereas no significant association with AhI was observed in obese children with OSA. This trend indicated that elevated levels of hs-CRP might be attributable to obesity rather than to OSA in children with OSA. The same as

Table 1. Characteristic Data (before and after T&A Therapy)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before Therapy (n = 75)</th>
<th>After Therapy (n = 75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>6.38 ± 4.2100</td>
<td>6.88 ± 4.2073</td>
<td></td>
</tr>
<tr>
<td>Sex, male/female, No.</td>
<td>47/28</td>
<td>47/28</td>
<td></td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>41.1878 ± 5.4726</td>
<td>56.9322 ± 5.2095</td>
<td>.592</td>
</tr>
<tr>
<td>AhI, events/h, mean ± SD</td>
<td>21.96 ± 9.277</td>
<td>8.64 ± 5.997</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nadir SaO2, %, mean ± SD</td>
<td>74.08 ± 7.860</td>
<td>86.87 ± 5.586</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AhI, apnea-hypopnea index; BMI, body mass index; T&A, adenotonsillectomy.
a study by Valle et al\textsuperscript{24} that a positive correlation between hs-CRP and BMI, low-grade systemic inflammation has been observed to correlate with a range of variables associated with metabolic syndrome in very young obese children. Obese patients exhibit chronic and low-grade inflammation due to the overproduction of cytokines induced by adipocyte enlargement.\textsuperscript{25} In contrast to the classic inflammation response caused by common infections, the reaction in obese children is a chronic inflammation primarily mediated by adipose tissue\textsuperscript{26} and responds with the upregulation of cytokines and CRP expression as well as elevated white blood cell (WBC) numbers and activity.\textsuperscript{27,28} The National Health and Nutrition Examination Survey (NHANES) confirmed that overweight children with systemic chronic inflammation exhibit high levels of hs-CRP.\textsuperscript{29} This type of inflammation is observed even in extremely young children. Previous reports have demonstrated elevated expression of hs-CRP, IL-6, and TNF-\textgreek{a} in obese as compared with normal-weight individuals. These factors strengthen the inflammatory response\textsuperscript{29} but may also increase the likelihood of complications (eg, insulin resistance and atherosclerosis).\textsuperscript{11}

Until now, hs-CRP has been recognized as a systemic marker of low-grade inflammation and an effective marker for long-term risk assessment.\textsuperscript{30} It is well documented that long-term elevation of hs-CRP predicts CVD and DM.\textsuperscript{31,32} The pathogenesis of CVD involves damaging endothelial cells by increasing low-density lipoprotein (LDL) uptake into macrophages, inhibiting endothelial nitric oxide synthase expression, activating macrophages to secrete tissue factor, and attracting monocytes to the site of injury.\textsuperscript{11} Impairing insulin signaling, fostering the development of insulin resistance, and inducing \textbeta-cell dysfunction could cause DM.\textsuperscript{11,33} All of these progressions mentioned above could be reflected by hs-CRP. Obesity is characterized as another independent predictor for the emergence of CVD and DM.\textsuperscript{34,35} A higher BMI indicates an increased likelihood of dyslipidemia and glycometabolism.\textsuperscript{36} As higher levels of hs-CRP were observed in obese children in the present study, other treatments should be introduced to lower the values of hs-CRP, thus reducing the morbidity of CVD and DM.

This is the first study to investigate the evolution of hs-CRP in obese children with OSA under T&A treatment over the course of a 6-month follow-up period. Overall hs-CRP values were similar before T&A therapy and at the 6-month follow-up period. We divided the patients according to varying degrees of surgical success, which yielded 2 groups. This allowed us to further evaluate the impact of T&A on hs-CRP levels. In the persistent group, no significant hs-CRP decrease was observed 6 months after the operation as compared with levels observed before the operation, which indicated not only the lack of a cure in the majority of obese children after T&A therapy but also the lack of any improvement in chronic inflammation. In the nonpersistent group, no significant difference between pre- and postoperative values was observed. Our results suggest that T&A therapy can achieve a cure despite the lack of any improvement in the severity of chronic inflammation. As shown in our results, the level of hs-CRP was largely tied to obesity-related factors in obese children with OSA. This finding explains how an obvious improvement in the clinical signs and symptoms of OSA could be observed in obese children with OSA who submitted to T&A therapy despite a lack of improvement in the severity of chronic inflammation.

Our study has several potential limitations. Long-term observations are lacking, and the sample size was small. Moreover, we used BMI rather than obesity classifications for assessment. To overcome these limitations, we plan to enlarge the sample size and prolong the follow-up period. Additional therapies will be introduced for OSA.

In summary, T&A treatment can improve clinical signs and symptoms in obese children with OSA. However, OSA is not completely cured in all patients. Because changes in hs-CRP levels are affected most strongly by obesity-related

Figure 2. Correlation analysis before adenotonsillectomy therapy. (A) Increases in high-sensitivity C-reactive protein (hs-CRP) correlate with changes in body mass index (BMI; \(r = 0.7948, P < .001\)). (B) No correlation between hs-CRP and apnea-hypopnea index (AHI; \(r = 0.0579, P = .6217\)).
factors, which are similar pre- and post-T&A, the risks for CVD and DM remain unchanged even when T&A therapy leads to dramatic improvements in obese patients. Other supplementary tools may be required for further therapy of obese children with OSA.

Author Contributions
Lijuan Chu, data analysis, writer; Hongbing Yao, data collection; Bing Wang, conceived the study and supervised it, participated in its design and coordination, and helped to draft the manuscript.

Disclosures
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Figure 3. Comparison of high-sensitivity C-reactive protein (hs-CRP) levels before and 6 months after adenotonsillectomy (T&A) therapy. The middle horizontal line inside the box represents the median values. The bottom and top of the box indicate upper and lower quartile. Asterisk and circle indicate extreme and mild outliers, respectively. ◇ indicates no significant difference (P > .05). (A) Persistent group, (B) nonpersistent group, and (C) all study samples.

References


