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The effect of recurrent tonsillitis and adenotonsillectomy on growth in childhood

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KEYWORDS	Summary
Children; Recurrent tonsillitis; Adenotonsillectomy; IGF-1; IGFBP-3	<i>Objective:</i> Tonsil and adenoid hypertrophy may cause recurrent tonsillitis and upper airway obstruction in children. A reduced dietary intake and failure to gain weight is frequently reported by parents of children with a history of recurrent acute tonsillitis and adenotonsiller hypertrophy. The purpose of this prospective study was to evaluate whether surgical treatment of adenotonsillar hypertrophy affects the circulating concentrations of insulin-like growth factor-1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) along with IGF-1 SDS and IGFBP-3 SDS's adjusted to age which are more important in evaluating growth in childhood. <i>Methods:</i> Thirty-eight prepubertal children 24 boys and 14 girls participated in this study. The mean age at surgery was 6.66 ± 1.84 years (range 4–10 years). Weight, height, IGF-1 and IGFBP-3 levels and standard deviation scores were evaluated before and 12–18 months after adenotonsillectomy (T&A). <i>Results:</i> The number of infections in a year reduced from $8.6 \pm 4.4 \text{ to } 0.37 \pm 0.68$ after operation. The mean Weight standard deviation score (SDS) increased significantly after T&A ($p < 0.01$). The mean IGFBP-3 level increased from -3.0 ± 0.58 SDS to -1.96 ± 1.27 SDS ($p: 0.001$). However, the mean serum IGF-1 level increased from 80.3 ± 48.5 to 116.8 ± 105.9 ng/ml ($p: 0.135$), and IGF-1 SDS increased from -1.36 ± 0.51 SDS to -1.31 ± 1.14 SDS ($p: 0.701$), which were both not statistically significant. <i>Conclusions:</i> We have demonstrated postoperative weight gain and significant increase in IGFBP-3 concentrations and IGFBP-3 SDS, accompanying significant decrease in the number of tonsility and IGFBP-3 SDS, accompanying significant
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1. Introduction

Tonsil and adenoid hypertrophy may cause recurrent tonsillitis and upper airway obstruction in children. A reduced dietary intake and failure to gain weight is frequently reported by parents of children with a history of recurrent acute tonsillitis [1,2]. There are also many reports in the literature of children experiencing rapid weight gain following adenoton-sillectomy (T&A) [3–5]. The pathogenic mechanisms of failure to thrive due to tonsil and adenoid hypertrophy include low calorie intake, increase in energy consumption because of difficult night breathing, nocturnal hypoxemia and interruption of the growth hormone-insulin like growth factor axis secondary to abnormal nocturnal growth hormone secretion [6-8].

The purpose of this prospective study was to evaluate whether surgical treatment of adenotonsillar hypertrophy affects the circulating concentrations of insulin-like growth factor-1 (IGF-1) and IGFbinding protein 3 (IGFBP-3) along with their standard deviation scores which are significant in the evaluation of growth in childhood.

2. Methods

2.1. Study population

Prepubertal children aged 4–10 years (mean = 6.7 ± 1.82 years) were enrolled in the study. Study subjects were randomly selected from the patients who were referred to the Department of Otolaryngology—Head and Neck Surgery during the period 2000–2002 for an assessment of their need for operation because of adenotonsiller hypertrophy. Children with known upper airway anomalies, any underlying disease predisposing to upper airway obstruction, facial anomalies, asthma or perennial allergy and patients having chronic diseases and other reasons causing nasal obstruction were excluded from the study.

Tonsillectomy alone is usually performed for recurrent or chronic pharyngotonsillitis. Although there are no strict criteria for number of infections, clinical indicators developed by the American Academy of Otolaryngology and Head and Neck Surgery suggest the occurrence of 3 or more treated infections per year as sufficient to warrant surgical intervention [9]. The criteria for both tonsillectomy and adenoidectomy for recurrent infection are the same as those for tonsillectomy alone. The other major indications for performing both procedures together is upper airway obstruction secondary to adenotonsiller hypertrophythat results in sleep-disordered breathing, failure to thrive, craniofacial or occlusive developmental abnormalities, speech abnormalities or rarely cor pulmonale.

The diagnosis of recurrent tonsillitis was based on registrations of the hospital and a detailed clinical history; diagnosis of disturbed sleep pattern was based on detailed clinical history obtained by using a standard questionnaire and physical examination [10]. The clinical history of each child was obtained from the parent and the following information related to obstructive sleep apnea (OSA) was obtained using a standardised questionnaire:

- night-time symptoms, which included loudness and frequency of snoring, difficulty in breathing, observed apnea during sleep, necessity for parents to shake the child to breathe, restless sleep, varying sleep posture, enuresis, and night sweating;
- (2) daytime symptoms which included excessive daytime sleepiness, behavioural problems, morning headache, and mouth breathing.

Sleep disturbance and/or snoring is one of the symptoms included in sleep-disordered breathing syndrome [11]. Sleep-disordered breathing can be strongly suspected based on reports of well-known symptoms, such as snoring or noisy breathing during sleep, daytime mouth breathing, low growth, or recurrent airway infection. Sleep quality is usually measured with electroencephalography, eye movements and EMG recordings in adults [7]. However, others believe that children with sleep apnea can be diagnosed by skilled observation and that sophisticated monitoring is usually not necessary [12,13]. We were unable to measure the sleep quality technically.

Questions were devised according to symptoms about sleep apnoea in children that have been reported by Stradling et al. [7]. We evaluated the child for sleep disturbance and/or snoring by inquiring sleep problems, e.g., getting to and staying asleep, restless sleep, odd sleeping positions, nocturnal sweating, enuresis, daytime sleepiness, hyperactivity, aggression, learning difficulties, morning headaches, snoring, and coughs and colds with two-point answers as yes or no.

Forty-five prepubertal children (26 boys and 19 girls) were included in the study. Seven subjects (16%) were lost to follow-up and excluded from the study, yielding 38 subjects. Fourteen girls (36%) and 24 boys (64%) with a mean age of 6.66 ± 1.84 years were enrolled. Preoperative and postoperative evaluation including detailed physical examination, height, weight and routine blood tests were obtained. All preoperative and postoperative heights and weights were obtained by a pediatric endocrinologist in the

outpatient pediatric clinics. All weights were obtained with minimal undergarments worn. The same scale was used for pre- and postoperative weight and height measurements and the accuracy of the scale was verified.

Standard deviation score (SDS) to assess changes in weight and height for age was by the following equation: z = (observed measurement - mean)/standard deviation [14]. The standard deviation score (SDS) was used to assess changes in IGF-1 and IGFBP-3 levels for age by the following equation: z = (observed measurement - mean)/standard deviation [15].

The parents of all children gave informed consent to participate in this study. The study protocol was approved by the ethical committee of Kocaeli University and was conducted according to the principles of the Declaration of Helsinki.

2.2. Blood sampling

All venous blood samples were drawn by venipuncture in the morning preoperatively. The patients were followed-up for 12–18 months postoperatively and a second blood sample was obtained for measurement of serum IGF-1 and IGFBP-3. All the blood samples taken pre- and postoperatively were centrifuged immediately and stored at -20 °C until assay.

2.3. Laboratory methods

All blood samples were studied in the biochemistry laboratory of Kocaeli University by an experienced technician. Serum samples were studied by the coated-tube immunoradiometric assay (IRMA) method using a commercial kit provided by "Diagnostics Systems Laboratories Inc." (DSL-5600 Active IGF-1 with extraction and DSL-6600 Active IGFBP-3 IRMA). Hemolyzed and lipemic serums were not used. All procedures were performed by the same technician in the laboratory. The determination of all serum IGF-1 and IGFBP-3 levels were performed in one assay.

2.4. Statistical analysis

All calculations were done by using SPSS computer software. All data were expressed as mean \pm S.D.

Table 1Characteristics of patiestudy (n: 38)	ents included in the
n	38
Girls/boys	14/24
Mean age of surgery	$ m 6.66 \pm 1.84$ years
	(4—10 years)
History of sleep disturbance	16 (42%)
Snoring	30 (79%)
Upper airway infections/year	$\textbf{8.6} \pm \textbf{4.4}$

Wilcoxon test (nonparametric test) was used for the comparison of preoperative and postoperative paired IGF-I, IGFBP-3 levels and growth parameters. A two-tailed p value less than 0.05 was considered significant.

3. Results

Thirty-eight prepubertal children 24 boys and 14 girls participated in this study (Table 1). All children were still in Tanner stage I (prepubertal) at the last follow-up. The mean age at surgery was 6.66 ± 1.84 years (range 4–10 years). History of sleep disturbance and snoring was positive in 16 (42%) and 30 (79%) of children, respectively. These symptoms resolved completely postoperatively. Number of upper airway infections per year reduced from 8.6 ± 4.4 to 0.37 ± 0.68 after operation.

While the height of only one patient (% 2.6) was below the -2 SDS in the preoperative period, the height of all patients were between -2 SDS and +2 SDS postoperatively. The weight of all patients were in normal ranges both in the preoperative and the postoperative period.

There was a significant increase in body weight SDS in the postoperative period $(-0.37 \pm 0.79 \text{ SDS})$ versus $-0.07 \pm 0.65 \text{ SDS}$, p < 0.01). Postoperative values in the height SDS did not reach statistical significance (Table 2).

The preoperative and postoperative serum levels of IGF-I and IGFBP-3 were compared. There was no statistically significant increase in IGF-I, while IGFBP-3 levels increased significantly. The mean serum IGF-1 level increased from 80.3 ± 48.5 to 116.8 ± 105.9 ng/ml (p: 0.153). The mean IGFBP-3 level increased from 1911.9 ± 511.5 to 2989 ± 1124.9 ng/ml (p < 0.001). No statistically

 Table 2
 Baseline and follow-up anthropometrics of the study population (n: 38)

	· · ·		
	Preoperative (mean \pm S.D.)	Postoperative (mean \pm S.D.)	р
Body weight SDS	-0.37 ± 0.79	-0.07 ± 0.65	<0.01
Height SDS	$\textbf{0.02} \pm \textbf{1.0}$	-0.05 ± 1.04	0.51
SDS: standard doviation	scoro: $n < 0.05$; significant		

SDS: standard deviation score; p < 0.05: significant.

	Before T&A (mean \pm S.D.)	After T&A (mean \pm S.D.)	р	Power		
IGF-1 (ng/ml)	$\textbf{80.3} \pm \textbf{48.5}$	$\textbf{116.8} \pm \textbf{105.9}$	0.153	0.81		
IGF-1 SDS	-1.36 ± 0.51	-1.31 ± 1.14	0.701	0.12		
IGFBP-3 (ng/ml)	$\textbf{1911.9} \pm \textbf{511.5}$	$\textbf{2989} \pm \textbf{1124.9}$	<0.001	1.0		
IGFBP-3 SDS	$-\textbf{3.00}\pm\textbf{0.58}$	-1.96 ± 1.27	0.001	1.0		

 Table 3
 Serum growth factor levels and growth before and after adenotonsillectomy (n: 38)

T&A: adenotonsillectomy; IGF-1: insulin-like growth factor-1; IGFBP-3: IGF-binding protein 3; SDS: standard deviation score; p < 0.05: significant.

significant difference was observed between preoperative and postoperative IGF-1 standard deviation scores. However, IGFBP-3 SDS increased significantly in this period (p: 0.001) (Table 3).

In the postoperative period, an overall % 55.2 (*n*: 21) increase in appetite was detected. In the group with increased appetite a significant increase in weight SDS from -0.33 ± 0.89 SDS to 0.06 ± 0.68 SDS (*p*: 0.039) was detected. On the other hand, in the group with no increase in appetite, no significant weight gain was recorded (-0.52 ± 0.58 SDS preoperatively versus -0.27 ± 0.51 SDS postoperatively, p > 0.05) (Table 4).

4. Discussion

In this study, weight SDS and IGFBP-3 levels increased in children after adenotonsillectomy compared to preoperative period. To our knowledge this is the first report of a case series who evaluated the SDS scores of patients with adenotonsiller hypertrophy preoperative and postoperatively. According to our study IGFBP-3 levels increased statistically. IGFBP-3 SDS's also seem to increase significantly. However there was no statistically significant increase in IGF-1 SDS values. We considered that even if serum concentrations of IGFBP-3 values increased significantly consistent with the literature, results about IGF-1 and IGFBP-3 SDS's are remarkable. Besides IGFBP-3 might be superior to IGF-1 assays and these parameters should be evaluated cautiously because they are usually taken into consideration together. Increase in IGFBP-3 levels alone may not be significant clinically.

A reduced dietary intake, failure to gain weight is frequently noted in children with tonsil and adenoid

hypertrophy. The precise mechanisms of this is unknown. The improvement in growth after surgical removal of the nasopharyngeal airway obstruction is a well-known phenomenon, possibly involving multiple factors such as increased GH secretion, increased caloric intake, decreased energy expenditure and an increase in serum IGF-1 and IGFBP-3 levels [8,16,17]. Ahlqvist et al. postulated that increased postoperative weight may involve a reversal of a preoperative catabolic state to a postoperative anabolic state mediated by a reduction in catecholamine secretion [18]. Barr et al. showed that the 83% of parents reported an increase in children's appetites following tonsillectomy or adenotonsillectomy [5]. Camillari has suggested that the postoperative weight gain may be in response to the surgeons instruction to eat well during the recovery period [19]. In our study an overall 55.2% increase in the postoperative period in appetite was detected. In the group with increased appetite a significant increase in weight was detected. Possible explanations of the accelerated weight gain following tonsillectomy include an increased nutritional intake secondary to a reduction in the number of episodes of tonsillitis.

In contrast to GH, serum levels of IGF-I and IGFBP-3 show little diurnal variation. The determination of IGF-I and IGFBP-3 serum levels has been widely used as screening parameters in the evaluation of growth disorders. Serum IGF levels are greatly influenced by chronologic age, degree of sexual maturation and nutritional status. IGFs circulate in plasma complexed to a family of binding proteins named IGF binding proteins (IGFBP). IGFBP-3 is the major IGFBP in normal human serum and demonstrates clear growth hormone dependence. It is suggested that radioimmunoassay

 Table 4
 Pre- and postoperative weight standard deviation scores (SDS) of patients with increased appetite and patients with no increase in appetite

	Preoperative weight SDS	Postoperative weight SDS	р
Increased appetite (n: 21) No increase in appetite (n: 17)	$\begin{array}{c} -0.39 \pm 0.89 \\ -0.52 \pm 0.58 \end{array}$	$\begin{array}{c} 0.06 \pm 0.68 \\ -0.27 \pm 0.51 \end{array}$	0.039 >0.05
SDS_{1} standard doviation scores $n < 0.05$	· statistically significant		

SDS: standard deviation score; p < 0.05: statistically significant.

determination of serum concentrations of IGFBP-3 might be superior to IGF-1 assays in the diagnosis of growth hormone deficiency, because young children may have very low levels of IGF-1 [20]. Because IGFBP-3 determinations reflect not only IGF-1 levels but also IGF-2 levels, their age dependency is not as striking as that of IGF-1. Besides, IGFBP-3 radioimmunoassays are technically simple and normal serum concentrations of IGFBP-3 are quite high, so assay sensitivity s not an issue.

Bar et al. showed that the improvement in growth after resolution of OSAS in children is accompanied by a significant increase in serum IGF-1 levels [6]. Other studies demonstrated that the IGF-1 and IGFBP-3 concentrations increased significantly in the operated children with obstructive adenotonsillar hypertrophy [8,21,22].

Ersoy et al. [23] compared 28 children with adenotonsiller hypertrophy with 20 healthy children of similar ages for 1 year after adenotonsillectomy. IGF-1 levels of the patient group, which were significantly lower than those of the controls preoperatively (p < 0.001), increased to similar levels 1 year after the operation. IGFBP-3 levels of the patient group increased significantly after postoperative sixth month (p = 0.002). They concluded that although children with adenotonsiller hypertrophy do not have significant growth retardation, their growth rate is slower and increase in weight and IGF-1 levels followed by the increase in height leads to an acceleration in growth rate after A&T. These results have led to the conclusion that either the levels or effect of growth hormone (GH) increase following A&T.

On the other hand Vontetsianos et al. [24] studied the effect of adenotonsillectomy on somatic growth on 57 children who were operated with an indication of adenotonsiller hypertrophy with or without recurrent infections. Weight was significantly improved following T&A in all children. The improvement in height was significant only for children under 5 years. Although the values of GH and IGF1 did not significantly increase post-op the IGF-1/GH ratio increased, possibly indicating improved IGF1 generation.

A significant reduction in sleep disturbances after T&A has been reported, as well as catch-up growth [6,7,25]. In our study, the weight SDS and IGFBP-3 levels increased in children after adenotonsillectomy surgery compared to preoperative period.

Serum levels of IGF-1 and IGFBP-3 reflect the endogenous 24-h GH secretion in healthy children. The good reproducibility of IGFBP-3 on repeated testing makes it an interesting parameter for the evaluation of the GH-IGF-axis. IGFBP-3 measurements may substitute for GH profiles in many cases, when the goal is an estimation of the GH secretion rate [26]. Bereket et al. [15] previously presented that there are large biological variations in serum IGFBP-3 and IGF-I levels in all ages. Compared to their published reference data, the most prominent difference was higher IGFBP-3 levels, especially in prepubertal children. They also emphasize that the standard deviation scores of these parameters based on age, sex and puberty enhances the power and utility of IGF-1 and IGFBP-3 in evaluating growth. As IGF-1 and IGFBP-3 levels normally increase with age it may be necessary to use age adjusted z-scores (SDS) when comparing results obtained at different ages. They also stated that locally established reference ranges for IGF-1 and IGFBP-3 values are important. In our study the postoperative increase in the IGFBP-3 levels and IGFBP-3 SDS were significant statistically. The increase in the serum levels of IGF-1 and IGF-1 SDS scores were not significant. In previous studies the SDS scores were not used [6,8,21,22]. For this reason it is difficult to interpret the reflected increase in IGF-1 and IGFBP-3 levels in children after T&A. As IGF-1 and IGFBP-3 levels normally increase with age it is necessary to use age adjusted z-scores (SDS) when comparing results obtained at different ages.

In this study, the number of tonsillitis episodes after T&A decreased from 8.6 ± 4.4 to 0.37 ± 0.68 annually. The inflammation may potentially have an adverse influence on linear growth by inducing malnutrition and inflammatory mediators that inhibit the hypothalamic-pituitary-growth axis. Alternatively airway obstruction itself without causing sleep symptoms may affect GH secretion.

Obstructive sleep apnea syndrome due to adenoid hypertrophy, is clinically characterized by snoring, difficulty in breathing during sleep, and repeated obstructive apnea [10]. The gold standard for the diagnosis of OSA syndrome (OSAS) is still the overnight multichannel polysomnography, which enables detection of obstructive apneas, hypopneas, and arousals. However, the system is very expensive to set up and run; consequently it is not widely available in all public hospitals. Various studies have looked at other screening methods, for example, symptom score and pulse oxymetry. It was found that these methods have good sensitivity [25,27]. The limitation of our study is the inadequate number of patients. Besides we diagnosed the patients as having sleep disturbance and/or snoring only with a detailed clinical history obtained from the parents. We could not perform nocturnal polysomnography, electroencephalography or pulse oxymetry to the patients.

According to our study only one of our patients (2.6%) was below -2 height SDS preoperatively. All of the patients' weight SDS were in normal ranges

both in the preoperative and postoperative period. We do not believe that determination of these growth parameters should be obligatory for the decision of surgical treatment. IGF-1 and IGFBP-3 values may be helpful only in patients who have really failure to thrive. In conclusion, we have demonstrated postoperative weight gain and significant increase in IGFBP-3 concentrations accompanying significant decrease in the number of tonsillitis episodes after adenotonsillectomy similar with other studies. However serum IGF-1 levels and IGF-1 SDS's did not increase significantly as expected. Larger controlled studies are needed in order to establish if IGF-1 SDS and IGFBP-3 SDS's of children show increase according to age after adenotonsillectomy.

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