Objective: Obstructive adenoid and tonsillar hypertrophy may present with retardation of growth. Interruption of growth hormone-insulin-like growth factor I axis resulting from abnormal nocturnal growth hormone secretion is among the postulated causes. Growth hormone (GH) mediates its anabolic effects on tissues through insulin-like growth factor I (IGF-I). Most of the circulating IGF-I is bound to insulin-like growth factor binding protein 3 (IGFBP3). The objective of this study is to determine blood serum levels of IGF-I and IGFBP3 in patients with adenoid and tonsillar hypertrophy. Furthermore, we want to investigate the effect of tonsillectomy and adenoidectomy (T&A) on these levels.

Study Design: The blood serum levels of IGF-I and its binding protein IGFBP3 were examined in 41 randomly selected children with a diagnosis of upper airway obstruction resulting from hypertrophic tonsils and adenoids. Methods: Blood samples were taken preoperatively and repeated at 3 to 6 months (mean, 4.3 mo) following T&A operation. Coated-tube immunoradiometric assay (IRMA) method was used to analyze IGF-I and IGFBP3 levels.

Results: Thirty-two of 41 children were eligible for the analysis. When the preoperative and postoperative results were compared, it was found that there was a statistically significant increase in serum IGF-I levels in these 32 children (P < .001). In 7 of the 32 patients, the preoperative serum IGF-I levels were below normal. Postoperatively these levels increased within normal range. This was also statistically significant (P = .016). Conclusion: These findings revealed that obstructive adenoid and tonsillar hypertrophy may cause decreased serum IGF-I levels by affecting the GH-IGF-I axis, and T&A is an effective therapeutic measure in these patients. Key Words: Tonsil hypertrophy, T&A, IGF-I, growth hormone, growth retardation.

INTRODUCTION

It is well known that tonsil and adenoid hypertrophy (TAH) can cause upper airway obstruction in children. Growth retardation (GR) may also coexist in these patients. The pathogenesis of GR is a complex and challenging topic. Postulated causes are abnormal nocturnal growth hormone secretion, poor appetite and dysphagia causing low caloric intake, nocturnal hypoxemia, nocturnal acidosis, and increase in energy expenditure resulting from the increased work of breathing. These children are surgically treated with tonsillectomy and adenoidectomy (T&A). It has been shown that there was a significant increase in height and weight of children following T&A. In children with GR, T&A induced height and weight scales to be reached to the levels of the same age as well.

Insulin-like growth factor I (IGF-I) is a growth factor that has both endocrine and paracrine effects. The secretion is under the control of the growth hormone (GH). Most of the circulating IGF-I is bound to a carrier protein called insulin-like growth factor binding protein 3 (IGFBP3). The synthesis of IGFBP3 is also controlled by GH. The anabolic effects of GH on tissues are conducted through IGF-I. The serum levels of IGF-I and IGFBP3 reflect the quantity of daily mean GH and is used as an index for GH assessment.

The aim of this study is to determine the influence of TAH on blood levels of IGF-I and its binding protein IGFBP3, and to compare that data with results after T&A.

MATERIALS AND METHODS

The study population was randomly selected from children who were referred to the Department of Otolaryngology–Head and Neck Surgery at Hacettepe University Faculty of Medicine. Subjects for this study comprised 41 children having the following criteria:

- Ages between 4 and 8 years with no chronic disease.
- Obstructive symptoms such as long-lasting nocturnal snoring, sleep apnea, open mouth breathing, difficulty in swallowing, and poor appetite.
- Hypertrophic tonsils causing oropharyngeal airway obstruction. A standardized grading classification proposed previously was used for the clinical examination.8
ing to that scale, grade 3 and 4 hypertrophic tonsils were included.

- Adenoid hypertrophy with partial or complete obstruction of the posterior choana without any other reasons causing nasal obstruction such as acute infection, allergic rhinitis, septal deviation, or anatomic deformities. Because objective evaluation of blocking adenoids is difficult, anterior rhinoscopy, lateral radiographs, palpation, and flexible fiberoptic examination, if tolerated by the child, were performed alone or combined for the assessment.

The parents of all children gave informed consent. Nine of 41 children were lost to follow-up and excluded from the study, yielding 32 subjects. There were 10 girls (31%) and 22 boys (69%) with mean age 5.8 ± 1.2 years (mean ± standard deviation).

Preoperative anesthetic evaluation was done, including routine blood and urinary tests together with chest x-ray. Initial heights and weights of the children were obtained. The patients were told to come to the hospital in the morning on the day of blood sampling without having breakfast. They were given a breakfast with a caloric equivalent of 450 to 500 kcal 1 hour before the venous blood samples were drawn for IGF-I and IGFBP3 levels. This was done to avoid fasting status interfering with the serum levels of IGF-I and IGFBP3. The serum was extracted from the blood samples, centrifuged, and stored frozen at -20°C.

To analyze the serum IGF-I and IGFBP3 levels, the coated-tube immunoradiometric assay (IRMA) method was performed using Diagnostic System Laboratories Inc. (Houston, TX) immunoradiometric assay kits. The same technician in the Pediatric Endocrinology Research Laboratory did the procedures.

All subjects underwent T&A. Curettage adenoidectomy and dissection tonsillectomy were performed under general anesthesia on an outpatient basis. The patients were seen 3 to 6 months after the procedure (mean ± standard deviation).

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To analyze the normal levels of serum IGF-I and IGFBP3, Hacettepe University Pediatric Endocrinology Research Laboratory normograms were used. The values in these normograms are compatible with the values of the control groups of studies conducted in the Turkish population.

For the statistical analysis, Shapiro-Wilk test was used for the assessment of normal distribution of the study group. Paired sample t-test was used for comparison of pre- and postoperative IGF-I and IGFBP3 levels and McNemar test (nonparametric test) was used for comparison of the number of patients with IGF-I levels below normal pre- and postoperatively.

### RESULTS

The height of only 1 patient (3%) was below the 3rd percentile in our study group. The others were distributed between the 3rd and 97th percentiles. The weights of all patients were between the 3rd and 97th percentiles.

When the preoperative and postoperative serum levels of IGF-I and IGFBP3 were compared, it was found that there was a statistically significant increase in both IGF-I and IGFBP3 levels of these 32 children (P < .001). The mean IGF-I level was increased by 35% from 85.1 ± 54.6 ng/mL to 115.6 ± 66.0 ng/mL, whereas the mean IGFBP3 level was increased by 12% from 2313.0 ± 583.6 ng/mL to 2592.1 ± 585.2 ng/mL (Table I).

In 7 of the 32 patients, the preoperative serum IGF-I levels were below normal. Postoperatively these levels increased within normal range. This was also statistically significant (P = .016) (Table II). In 5 patients, the preoperative serum IGFBP3 levels were below normal. In 3 of them, postoperative levels reached normal range; however, this was not statistically significant (P = .25, McNemar test).

### DISCUSSION

GR resulting from hypertrophic tonsils and adenoids was previously reported in the literature, but most of these publications are case reports.1,2 There are a few articles presenting more than 20 cases. According to previous studies, the prevalence of GR varies from 1% to 46%.3,10 In a retrospective study done by Williams et al.,3 the prevalence of GR was 46%. However, the majority of patients studied in their series had severe obstruction (obstructive sleep apnea) and additional medical problems along with TAH. In our study, we were not able to demonstrate such a high rate of GR in children with TAH. The weights of all children were in normal limits. Only 1 of the 32 children had a height below the 3rd percentile (the prevalence is 3%). The children had no chronic medical conditions other than TAH. Similarly, Alqvist-Rastad et al.10 analyzed 122 children and found only 1 patient who had GR (less than 1%). Their patients had milder clinical symptoms and no other systemic disease. Therefore, the severity of upper airway obstruction and the presence of other medical problems may affect the prevalence of GR in children with TAH. In this study, the pre- and postoperative heights and weights of the children were not compared, because a 3- to 6-month interval (mean, 4.3 mo) is not enough for the assessment of height and weight changes and evaluation of growth in children.

There were two studies reported in the literature concerning TAH and IGF-I. Bar et al.4 demonstrated a statistically significant increase in IGF-I levels after T&A on 14 children with obstructive sleep apnea resulting from TAH. However, there was no significant increase in IGF-I levels postoperatively.
FBP3 levels. They also found a statistically significant increase in slow wave sleep. Previously, it has been shown that GH secretion is closely associated with different stages of sleep.\textsuperscript{12–14} Therefore, it is possible that upper airway obstruction caused by TAH alters sleep pattern, consequently affecting GH secretion.

Chiba et al.\textsuperscript{15} demonstrated an increase in IGF-I levels in 8 of 10 patients after tonsillectomy. They also found an increase in urinary GH levels in 7 of 10 patients. This study is the only one found in the literature that showed an increase in GH levels after tonsillectomy. However, the measurement of IGF-I is more reliable than urinary GH levels, because IGF-I represents daily mean levels of GH.\textsuperscript{16}

In the studies by Bar et al.\textsuperscript{4} and Chiba et al.,\textsuperscript{15} there were limited numbers of cases. In the present study, however, there were 32 children eligible for statistical analysis. We found a statistically significant increase in both serum IGF-I and IGFBP3 levels after T&A. In 7 of the 32 patients, serum IGF-I levels were below normal, including the patient whose height was below the 3rd percentile. Postoperatively the IGF-I levels of these 7 children increased within normal range. This finding reveals that T&A is an effective therapeutic measure to reverse the adverse effects of TAH on serum IGF-I levels.

The measurement of IGF-I and IGFBP3 levels were delayed at least 3 months to avoid any effect of “surgery” on these levels. Moreover, in a study done by Wojnar et al.\textsuperscript{17} in trauma patients, the IGF-I and IGFBP3 levels were found to be decreased on both admission to the hospital and during discharge from the hospital. Therefore, the elevation we found in these levels is probably not the result of just surgery, but T&A.

The increase in IGFBP3 levels was also statistically significant. However, the limits of IGFBP3 were apparently lower than the increase of IGF-I levels. This can be explained by the binding of IGFBP3, because IGFBP3 is not only bound to IGF-I but also to IGF-II in blood. The blood levels of IGF-II are not totally under the control of GH.\textsuperscript{18}

The change in IGF-I and IGFBP3 levels is minimal with growth in the prepubertal period. The difference is particularly insignificant between 4 and 8 years of age.\textsuperscript{19} All children in the present study were prepubertal, and this is the reason why we include the children aging between 4 and 8 years. The time interval between the two measurements of IGF-I and IGFBP3 levels was relatively short. Also, each patient in the study group acts as his or her own control. Therefore, the alteration in these levels cannot be attributed to time and age parameters.

**CONCLUSION**

Serum IGF-I and IGFBP3 levels were shown to be significantly elevated in children with TAH following T&A. The increase in serum IGFBP3 levels was demonstrated for the first time in the literature. In addition, obstructive adenoid and tonsillar hypertrophy may cause decreased serum IGF-I levels in patients by affecting the GH–IGF-I axis. The findings revealed that T&A is an effective therapeutic measure in such patients.

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**TABLE II.**

The Comparison of Number of Patients Whose Pre- and Postoperative IGF-I Levels Were Below Normal.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>IGF-I Values</th>
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<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Preoperative</td>
<td>7</td>
</tr>
<tr>
<td>Postoperative</td>
<td>0</td>
</tr>
</tbody>
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Statistics: McNemar test *P* = .016
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