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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Relationship Between Early Postoperative Growth Hormone Levels and Resected Tumor Volume in Acromegaly: Contribution to Remission

Akromegali'de Erken Postoperatif Growth Hormon Düzeyleri ile Rezekte Edilen Tümör Hacmi Arasındaki İlişki: Remisyona Katkı

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ABSTRACT

Aim: The aim of this study was to investigate the relationship between early postoperative growth hormone (GH) levels and resected tumor volume in acromegaly patients. While previous studies have explored the correlation between resected tumor volume and early postoperative GH changes, this study aimed to investigate this relationship in a larger population of GH-secreting pituitary adenomas using both endoscopic and microscopic transsphenoidal approaches.

Material and Method: A retrospective analysis was conducted, analyzing preoperative, postoperative 24-hour, and postoperative 3-month GH hormone levels in relation to resected tumor volume. GH levels were measured before surgery, 12-24 hours postoperatively, and during 3-month follow-up visits. Tumor volumes were assessed using pre- and postoperative MRI images.

Results: The study included 28 acromegaly patients. The analysis showed no significant correlation between tumor volume reduction and GH decrease within 24 hours after surgery. Similarly, no significant correlation was found between tumor volume reduction and GH decrease at the 3-month follow-up.

Conclusion: Early postoperative GH levels may not accurately reflect the volume of the resected tumor. Therefore, determining the probability of remission based solely on GH levels within the first 24 hours after surgery may not be reliable.

Keywords: Acromegaly, growth hormone, tumor volume

ÖZ

Amaç: Bu çalışmanın amacı, akromegali hastalarında erken postoperatif Growth hormon (GH) düzeyleri ile rezekte edilen tümör hacmi arasındaki ilişkiyi araştırmaktır. Daha önceki çalışmalar rezekte edilen tümör hacmi ile erken postoperatif GH değişiklikleri arasındaki ilişkiyi araştırmış olsa da, bu çalışma bu ilişkiyi endoskopik ve mikroskopik transsfenoidal yaklaşımları kullanan daha geniş bir GH salgılayan hipofiz adenom popülasyonunda incelemeyi amaçlamıştır.

Gereç ve Yöntem: Retrospektif bir analiz yapılmış olup, rezekte edilen tümör hacmi ile ilişkilendirilmiş preoperatif, postoperatif 24 saatlik ve postoperatif 3 aylık GH hormon düzeyleri analiz edilmiştir. GH düzeyleri ameliyat öncesinde, ameliyat sonrası 12-24 saatte bir ve 3 aylık takip ziyaretlerinde ölçülmüştür. Tümör hacimleri preoperatif ve postoperatif MR görüntüleri kullanılarak değerlendirilmiştir.

Bulgular: Çalışma 28 akromegali hastasını içermektedir. Analiz, ameliyat sonrası 24 saat içinde tümör hacmi azalması ile GH düşüşü arasında anlamlı bir ilişki bulunmadığını göstermiştir. Benzer şekilde, tümör hacmi azalması ile 3 aylık takip süresince GH düşüşü arasında anlamlı bir ilişki bulunmamıştır.

Sonuç: Erken postoperatif GH düzeyleri, rezekte edilen tümör hacmini doğru bir şekilde yansıtmayabilir. Bu nedenle, ameliyat sonrası ilk 24 saat içindeki GH düzeylerine dayalı olarak remisyon olasılığını belirlemek güvenilir olmayabilir.

Anahtar Kelimeler: Akromegali, büyüme hormonu, tümör hacmi

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INTRODUCTION

Pituitary adenomas that secrete growth hormone (GH) are non-benign tumors with associated morbidity and mortality. The size of the adenoma, along with the elevation of GH and insulin-like growth factor-I (IGF-I), contributes to the morbidity and mortality. In the treatment of these adenomas, achieving remission is particularly important, which requires the reduction of GH and IGF-I levels to the thresholds defined by consensus criteria (1). The extent of adenoma resection greatly influences the short-term or long-term decreases in these levels (2-5). The prolonged half-life of IGF-I in plasma provides insights into remission based on the early postoperative decrease in GH plasma levels (4,6). In a limited number of studies in the literature, the correlation between the resected adenoma volume and the early postoperative GH changes has been investigated (2). In our study, we aimed to examine the potential relationship and contribution to remission between the changes in plasma GH levels during the early postoperative period and the ratio of resected adenoma volume by comparing the endoscopic and microscopic transsphenoidal approaches in a significantly larger population of GH-secreting pituitary adenomas than previous studies.

MATERIAL AND METHOD

This study was prepared in accordance with the Law on Protection of Personal Data, by anonymizing patient data and in accordance with the 2013 Brazil revision of the Helsinki Declaration and guidelines for Good Clinical Practice.

An attempt was made to investigate the relationship between preoperative, postoperative 24-hour, and postoperative 3-month GH hormone levels and the resected adenoma volume through a retrospective analysis. Only patients who underwent endonasal transsphenoidal endoscopic and microscopic resection of pituitary adenomas were included in the study. GH levels were measured in the morning between 07:00 and 08:00, without performing a glucose suppression test, for patients clinically diagnosed with acromegaly but not receiving any medical treatment, recorded prior to surgery. GH levels were also examined between 12 and 24 hours postoperatively and during the 3-month follow-up visits after discharge, again without a glucose suppression test, in the morning between 07:00 and 08:00.

Furthermore, routine clinical practices were employed to assess tumor volumes before and after surgery by analyzing pituitary MRI images obtained within 24-36 hours before the operation, within the first 24 hours postoperatively, and at the 3-month postoperative period. Axial images with a slice thickness of 1 mm were acquired in T1, T2-weighted, and post-contrast T1-weighted 3D sequences. Three-dimensional reconstructions were generated from the axial, sagittal, and coronal planes. Postoperative imaging included sagittal pre-contrast T1, coronal T2, coronal dynamic post-contrast T1, and sagittal post-contrast T1-weighted images, acquired with a slice thickness of 2 mm for the pituitary MRI protocol. The images were transferred to the Syngo.Via VB30 (Siemens) workstation. On post-contrast coronal images, the circumference of the mass was manually delineated slice by slice in the anterior-posterior direction, and the volume of the mass was calculated by the software (**Figure 1**).

Figure 1. Volume Measurement in MRI Imaging

Statistical Analysis

The data obtained from the research was analyzed using the SPSS (Statistical Package for Social Sciences) 18.0 software package on a computer. In descriptive analyses, frequency data were presented as number (n) and percentage (%), while numerical data were presented as mean ± standard deviation, median (minimum-maximum). The normal distribution of numerical data was examined using the Shapiro-Wilk test. Independent Samples T-test was used to analyze the distribution of normally distributed data between two independent groups. The relationship between two normally distributed numerical variables was examined using Pearson correlation analysis. The correlation relationships were categorized as follows: r=0.05-0.30 indicates low or insignificant correlation, r=0.30-0.40 indicates low-moderate correlation, r=0.40-0.60 indicates moderate correlation, r=0.60-0.70 indicates good correlation, r=0.70-0.75 indicates very good correlation, and r=0.75-1.00 indicates excellent correlation. The results were evaluated with a 95% confidence interval and a significance level of $p<0.05$.

RESULTS

A total of 28 patients diagnosed with acromegaly were included in this study conducted at the Neurosurgery Clinic of Selçuk University Medical Faculty Hospital. Of the patients, 60.7% (n=17) were male. The mean age of the patients was determined as 48.64±14.10 years. It was recorded that 60.7% of all patients underwent microscopic transsphenoidal surgery, while the remaining underwent endoscopic transsphenoidal surgery. The demographic characteristics of the patients, distribution of tumor volume and hormone levels before the initial surgical intervention, at postoperative 24 hours, and at postoperative 3 months were presented in **Table 1**.

Table 1: Demographic characteristics, preoperative, postoperative 24 hours, and postoperative 3 months distribution of tumor volume and growth hormone levels

Variables	n=28	
Gender		
Female	11 (39,3)	
Male	17 (60,7)	
Age (years)	48,64±14,10	51,00 (18-75)
Surgery		
Endoscopic	11 (39,3)	
Microscopic	17 (60,7)	
Preoperative volume (cm³)	7,49±5,72	7,19 (0,38-20,09)
Postoperative 24-hour volume (cm³)	2,58±2,25	2,80 (0,00-8,21)
Postoperative 3-month volume (cm³)	2,20±2,11	2,00 (0,00-7,34)
Preoperative GH	9,87±18,27	2,73 (0,35-85,00)
Postoperative 24-hour GH	3,54±8,92	0,88 (0,07-44,47)
Postoperative 3-month GH	3,51±9,40	0,54 (0,02-40,56)

n (%), Mean ± Standard Deviation, Median (min-max)

Second surgery was performed in 25.0% of acromegaly patients (n=7). Among these patients, 57.1% (n=4) were male, and the mean age was 46.00±17.09 years. The demographic characteristics, tumor volume, and hormone levels before surgery, as well as during the early and late postoperative periods for these patients, were presented in **Table 2**.

Tablo 2: Distribution of Demographic Characteristics, Tumor Volume, and Growth Hormone Levels Before Second Surgery, at Postoperative 24 Hours, and at Postoperative 3 Months for Patients Undergoing Second Surgery

Variables	n=28	
Gender		
Female	3 (42,9)	
Male	4 (57,1)	
Age (years)	46,00±17,09	41,00 (26-67)
Surgery		
Endoscopic	3 (42,9)	
Microscopic	4 (57,1)	
Preoperative volume (cm3)	6,52±2,42	6,98 (3,10-9,50)
Postoperative 24-hour volume (cm3)	3,58±1,50	2,96 (2,07-6,04)
Postoperative 3-month volume (cm3)	3,30±0,78	2,98 (2,65-4,82)
Preoperative GH	10,99±23,61	0,90 (0,16-64,20)
Postoperative 24-hour GH	9,29±20,25	0,77 (0,12-55,00)

n (%), Mean ± Standard Deviation, Median (min-max)

There was no statistically significant difference in the distribution of GH decrease rates based on gender (p>0.05). The rate of tumor resection until 24 hours after the second surgery was found to be higher in male patients compared to female patients (p=0.049) (**Table 3**).

There was no statistically significant difference observed in the distribution of tumor resection rates according to surgical technique (p>0.05). However, there was a statistically significant difference in GH decrease rates until 24 hours after the initial surgery based on the surgical technique (p=0.035). The amount of GH reduction was found to be lower in patients who underwent endoscopic surgery compared to those who underwent microscopic surgery.

There was no observed relationship between tumor volume reduction and hormone decrease until 24 hours after the initial surgery (p>0.05) (**Figure 2**). Similarly, there was no statistically significant correlation between tumor resection volume and hormone decrease until 3 months after the initial surgery (p>0.05) (**Figure 3**).

Table 3: Distribution of Tumor Resection and GH Reduction Rates in Surgically Treated Patients

Variables	All Patients	Male	Female	p*
Tumor Resection Rate (%) by Postoperative 24 Hours after the Initial Surgery	67,13±23,76 75,56 (9,68-100,00)	65,85±25,56	69,10±21,71	0,731
Tumor Resection Rate (%) by Postoperative 3 Months after the Initial Surgery	71,68±21,86 76,30 (23,06-100,00)	70,97±21,31	72,77±23,69	0,836
GH Reduction Rate (%) by Postoperative 24 Hours after the Initial Surgery	59,78±27,15 63,37 (9,30-98,00)	55,72±27,92	65,30±26,34	0,385
GH Reduction Rate (%) by Postoperative 3 Months after the Initial Surgery	73,88±22,90 77,84 (15,79-98,75)	77,78±19,84	68,55±26,58	0,320
Tumor Resection Rate (%) by Postoperative 24 Hours after the Second Surgery	39,56±25,81 36,42 (8,39-70,09)	55,22±20,27	18,69±15,41	0,049
GH Reduction Rate (%) by Postoperative 24 Hours after the Second Surgery	18,33±10,73 14,44 (3,37-31,90)	17,44±13,25	19,51±8,88	0,826

Mean±Standard Deviation, Median (min-max), *: Independent Samples T-Test

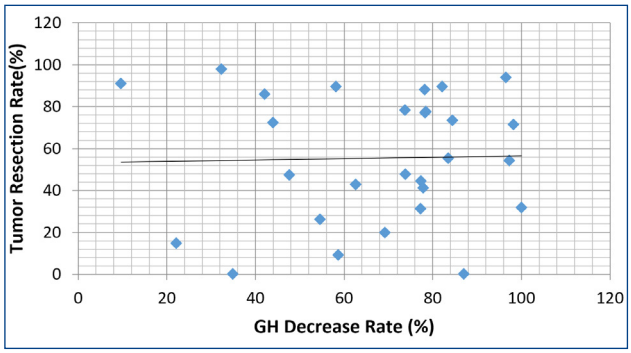

Figure 2: The Relationship Between Percent Tumor Resection and Percent Hormone Decrease up to Postoperative 24 Hours in Patients after Initial Surgery

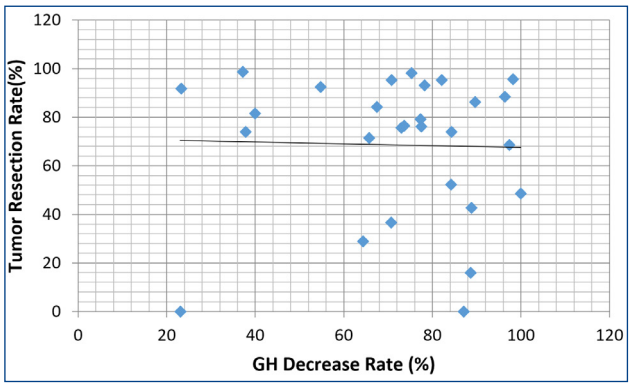

Figure 3: Relationship Between Percent Tumor Resection and Percent Hormone Decrease in Patients up to 3 Months Post Initial Surgery

During the period from 24 hours after the initial surgery to 3 months postoperatively, tumor volume increased in 6 patients and GH levels increased in a total of 9 patients, with only 1 patient among them. A moderately significant negative correlation was found between tumor resection volume and hormone decrease from 24 hours to 3 months after the initial surgery (r=-0.408; p=0.031) (**Figure 4**).

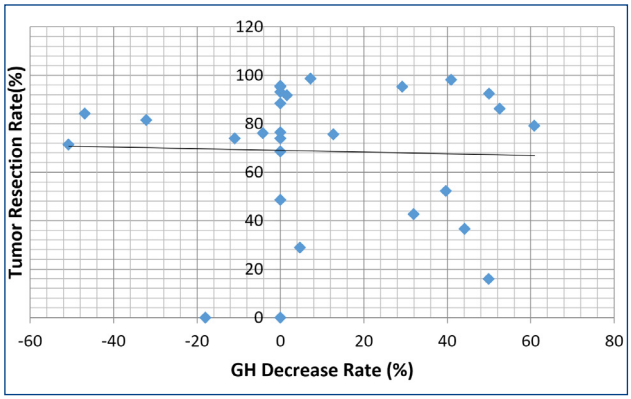

Figure 4: Relationship Between Percent Tumor Resection and Percent Hormone Decrease from 24 Hours up to 3 Months Postoperatively in Patients Undergoing Initial Surgery

There was no significant relationship between tumor resection volume and hormone decrease until 24 hours after the second surgery (p>0.05) (**Figure 5**).

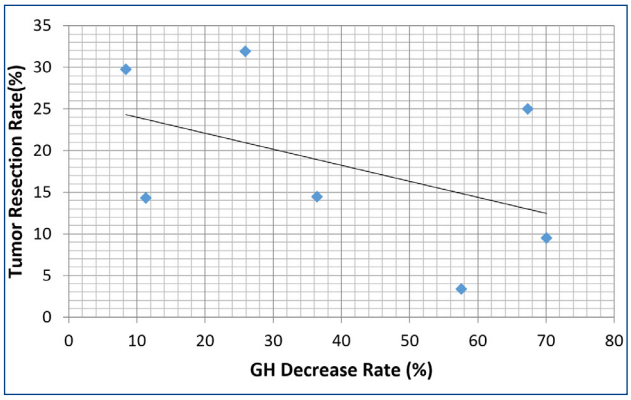

Figure 5: Relationship Between Percent Tumor Resection and Percent Hormone Decrease from Postoperative 24 Hours up to Second Surgery in Patients Undergoing Subsequent Surgical Procedures

DISCUSSION

In acromegaly, disease remission is considered when insulin-like growth factor 1 (IGF-1) levels fall within the normal range, random growth hormone (GH) levels are less than 1 µg/L, or GH levels below 0.4 µg/L are obtained after an oral glucose tolerance test (OGTT). (4) Additionally, the size of GH-secreting pituitary adenomas will also affect the amount of GH secretion. Consequently, a reduction in tumor volume is expected to be accompanied by a decrease in GH levels in the peripheral blood (5).

In our study conducted based on these criteria, no correlation was found between the percent tumor resection volume of growth hormone-secreting pituitary adenomas operated through the endonasal transsphenoidal approach and percent hormone decrease in randomly measured GH values within the first 24 hours after surgery. The lack of correlation may be attributed to the pulsatile secretion of GH, which can vary from patient to patient. Moreover, when GH reaches a certain level in the blood, receptor saturation can affect the measured GH levels. The inter-individual variability in GH secretion can be attributed to variations in GH receptors (5). Additionally, studies involving frequent sampling of GH have demonstrated that, like in healthy individuals, pulsatile GH secretion does occur in acromegaly patients. However, it has been shown that the secretory bursts in acromegaly are much less pronounced compared to the high basal GH concentration (7-9).

There are also studies indicating that each adenoma may have different levels of GH secretion (10-12). In particular, immunohistochemical staining and electron microscopy studies have reported a higher likelihood of increased GH secretion in high-granulated tumors compared to low-granulated tumors. In the literature, the size and invasiveness of the adenoma, as well as preoperative GH levels, are important determinants of postoperative hormonal remission in acromegaly. However, all of these

factors affect the GH levels measured in the blood within the first 24 hours after surgery, regardless of the volume of the resected tumor (4). Therefore, just like in this study, the GH level measured in the blood after surgery does not provide information about the volume of the resected tumor. Similarly, the volume of the resected tumor does not provide information about the GH level in the blood to be measured after the operation.

Several studies in the literature have investigated the effect of adenoma volume on remission. In these studies, it has been reported that in macroadenomas, the majority of the lesion is resected or that operated microadenomas have a higher probability of entering postoperative remission. It is also shown in these studies that adenomas with parasellar extension are associated with lower cure rates (1,4). In our patients, we observed an average reduction of 75% in adenoma volume. Although this may be considered a low rate, the most important factor influencing this is that the majority of the included adenomas had parasellar, suprasellar, and infrasellar extensions. Despite this rate, we determined the average postoperative plasma GH value in our study as 0.88 µg/L. This finding meets the criterion for remission, which requires the plasma GH level measured within the first 24 hours after surgery to be less than 1 µg/L. However, according to the literature, if we consider the resected adenoma volume, we should not have reached postoperative GH values that meet the remission criterion (13-15).

In our study, we found that the decrease in GH levels within the first 24 hours after surgery differed significantly according to the surgical technique. Although we did not find a statistically significant difference in the distribution of tumor resection rates according to the surgical technique, the postoperative GH decline was greater in patients who underwent microscopic resection compared to those who underwent endoscopic resection. These findings support the situation described so far. Although the resected tumor volume did not vary between the two surgical techniques, the rate of GH decline in the blood after surgery differed. This suggests that GH secretion can vary among individuals and tumors.

In patients who underwent a second surgery, as in their first surgeries, there was no significant relationship between tumor resection volume and hormone decrease until the 24th hour after surgery. The fact that there was no change between the first and second surgeries and that the results were statistically the same was also significant.

To minimize errors and shortcomings in the analysis of adenoma size on preoperative and postoperative pituitary MRIs, we used the 3D adenoma volume measurement technique. It is known that 3D volume measurements are generally better predictors for postoperative outcomes in anterior pituitary tumors (2). This technique particularly helps obtain more accurate results in macroadenomas with lateral extension to the cavernous sinuses and/or irregular growth.

In future studies, it is important to note that including a larger number of patients and measuring GH values both before and after surgery, including after an OGTT, may yield different results.

Learning points: Unlike many other studies, there is no correlation between the resection volume of pituitary adenoma and the decrease in postoperative GROWTH hormone level. The probability of remission cannot be determined by the resected volume.

CONCLUSION

In this study, randomly measured GH levels within the first 24 hours after endonasal transsphenoidal surgery for pituitary adenomas corresponded to remission criteria. However, statistically, there was no correlation between the ratio of resected adenoma volume and GH levels measured within the first 24 hours after surgery. Drawing conclusions about the amount of resected adenoma based on these early GH levels would not be accurate. Therefore, it is not appropriate to determine the probability of remission based on the ratio of resected adenoma volume.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was prepared in accordance with the Law on Protection of Personal Data, by anonymizing patient data and in accordance with the 2013 Brazil revision of the Helsinki Declaration and guidelines for Good Clinical Practice.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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