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Research Article

Vascular Endothelial Growth Factor (VEGF) as a Predictor of Active Acromegaly

Alper Cagri Karci,[1] Zeynep Canturk,[2] Ilhan Tarkun,[2] Berrin Cetinarslan[2]

[1]Department of Endocrinology and Metabolism, Bagcilar Training and Research Hospital, Istanbul, Turkey
[2]Department of Endocrinology and Metabolism, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

Abstract

Objectives: To compare vascular endothelial growth factor (VEGF) levels between active and controlled acromegaly patients, to investigate the relationship of VEGF levels with growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels, and to examine the predictive value of VEGF for active disease.

Methods: Adults (≥18 years) diagnosed with acromegaly were included. Blood samples were collected to measure GH, IGF-1, and VEGF levels. Disease activity was determined according to the criteria established in 2010 by the Acromegaly Consensus Group.

Results: Seventy-four acromegaly patients (28 with active disease, and 46 with controlled acromegaly, mean age 48±14 years) were enrolled. The basal GH and IGF-1 levels were significantly higher in the active acromegaly group than the controlled acromegaly group (p<0.001). The VEGF levels did not differ significantly between the groups (p=0.113). Correlation analysis demonstrated a significant negative correlation between the VEGF and basal GH levels for all patients (r=-0.274, p=0.034) and a significant negative correlation between the VEGF and basal GH levels in the controlled patients (r=-0.360, p=0.026).

Conclusion: These data indicate that plasma VEGF levels were similar between active and controlled acromegaly patients and that VEGF doesn't seem to be a useful marker in determining disease activity in acromegaly patients.

Keywords: Acromegaly, Growth hormone, IGF-1, VEGF (vascular endothelial growth factor)

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Acromegaly is a chronic progressive disease characterized by excessive somatic growth and distorted body proportions. The condition usually results from a pituitary adenoma with excessive secretion of growth hormone (GH) that leads to increased levels of insulin-like growth factor 1 (IGF-1). Although it is a relatively rare condition, acromegaly poses a significant burden due to frequent comorbid conditions and lifelong treatment.[1,2] In its management, the primary goal is to reduce adenoma mass, to normalize GH secretion, and to preserve pituitary functions.[2,3] The treatment options include pituitary surgery, radiotherapy, and medical treatment (somatostatin receptor analogs (SRA), dopamine agonists (DA), and GH receptor antagonists).[4,5] Controlling the disease via early diagnosis would improve the quality of life and reduce morbidity and mortality rates. GH and IGF-1 are measured to diagnose acromegaly and assess disease activity. However, discordance between GH and IGF-1 levels is encountered in nearly %25.7 patients. Patients with discordant results are monitored with metabolic parameters.[2,6]

Vascular Endothelial Growth Factor (VEGF) is an angiogenic factor involved in developing new capillaries by inducing

Address for correspondence: Alper Cagri Karci, MD. Bagcilar Egitim ve Arastirma Hastanesi Endokrinoloji ve Metabolizma Anabilim Dali, Istanbul, Turkey
Phone: +90 505 517 37 12 **E-mail:** alpercagrkarc@yahoo.com
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endothelial cell proliferation and migration as a response to hypoxia. VEGF also plays a role in vascular permeability and secretion and the regulation of other endothelial functions.[7] Angiogenesis makes a significant contribution to wound healing, tissue repair, and tumor development. Previous studies showed the overexpression of VEGF and its receptors in pituitary adenomas. VEGF is suggested to have a critical role in the development and growth of pituitary adenoma, as in other tumors.[8-11]

This study aimed to compare VEGF levels between active and controlled acromegaly patients, investigate the correlation of VEGF levels with GH and IGF-1, and study VEGF as a novel marker for disease activity in GH and IGF-1-discordant patients. Besides, the predictive value of VEGF levels for an active disease was also investigated.

Methods

Study Design and Setting

This study was conducted in the hypophysis polyclinics of the Department of Endocrinology and Metabolism Diseases at the Kocaeli University Hospital between April 2012 and October 2012. The study was approved by the Ethics Committee of Kocaeli University (date: March 20, 2012, approval no. 2012/68), and written informed consent of the patients was obtained.

Patients

Patients over the age of 18 years, registered for follow-up with the diagnosis of acromegaly were included in the study. Acromegaly was diagnosed based on increased levels of age-adjusted IGF-1 and GH levels of > 1µg/L after performing an oral glucose tolerance test (OGTT) with 75 g glucose. Hospital records were reviewed to retrieve the patients' demographic data and medical data, including detailed information about therapeutic procedures and comorbidities. All patients had adenomas documented on pituitary MRI. Patients with pituitary hormone deficiencies were on appropriate regular replacement therapies. Of the 79 patients registered for follow-up, three could not be contacted, and two refused to join the study (Fig. 1).

Variables

All participants were invited to the hospital for data collection. Blood samples of the patients were collected after at least 8 hours of fasting. The blood samples were transferred to the central laboratory for the measurements of GH and IGF-1 levels, and stored at –80ºC until the analysis for the measurements of VEGF levels.

Disease activity was determined following the criteria established in 2010 by the Acromegaly Consensus Group.[12]

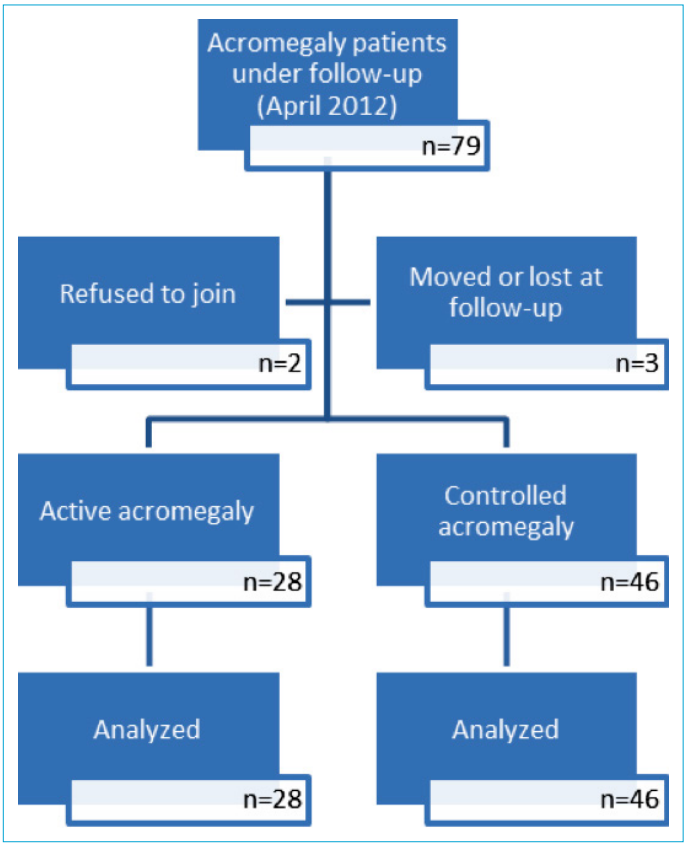

Figure 1. Study flow diagram.

According to these criteria, "controlled acromegaly" was defined as follows: 1) age-adjusted IGF-1 level within the normal ranges and the lowest GH level below 0.4 µg/L during OGTT performed with 75 g glucose for the drug-free patients or for the previously operated patients after 3 months of surgery and 2) a basal GH of <1 µg/L and age-adjusted IGF-1 level within the normal ranges for the patients receiving SRA and/or DA. Additionally, two patients treated with the combination of SRA and pegvisomant and had a normal age-adjusted IGF-1 level were considered to have "controlled acromegaly." Patients who did not meet these criteria, as well as newly diagnosed treatment-naive patients, were assigned to the active acromegaly group. According to these criteria, patients with elevated GH and normal IGF-1 levels or those with high IGF-1 levels and normal GH levels were considered discordant.

Measurements

Chemiluminescent immunoassay (IMMULITE® 2000 immunoassay system; Siemens, United Kingdom) was used to measure GH. Recombinant GH IS 98/574, an international standard recommended by the World Health Organization (WHO), was used as the calibrator. In this measurement method, the analytical sensitivity for GH was 0.01 µg/L, and the range of measurement was 0.05–40 µg/L. IGF-1 was

analyzed by the immunoenzymometric assay (IEMA; Immunodiagnostic Laboratories, Boldon, United Kingdom). In this method, IS 87/518 was used as the calibrator. The sensitivity of the IGF-1 measurement was defined as 3.1 µg/L. IGF-1 levels were interpreted based on the reference values according to age. Enzyme-linked immunosorbent assay (ELISA; Ray Biotech, Inc. Norcross, USA) was used to measure VEGF levels. The sensitivity, intra-assay coefficient of variation, and inter-assay coefficient of variation for VEGF measurement were <10 pg/mL, <10%, and <12%, respectively.

Sample Size

Using the G*Power program (Heinrich Heine University, Düsseldorf, Germany), a post-hoc sample size calculation was performed based on the primary outcome variable VEGF. A total sample size of 74 participants (28 active acromegaly+46 controlled acromegaly) provides a power of 82.1% to compare the two groups for VEGF levels with a two-tailed alpha error of 0.05 and an effect size of 0.7, which enables to make a comparison given a mean 1 of 280, mean 2 of 365, and a standard deviation of 120.

Statistical Analysis

The Predictive Analytic Software (PASW) version 18.0 for Windows program was used for the statistical analyses. Descriptive statistics were expressed as number and percentage for categorical variables and median, 25th percentile (the first quartile, Q1), and 75th percentile (the third quartile, Q3) for numerical variables. The comparison of two independent groups was performed by the Mann-Whitney U test for non-normally distributed numerical variables. Two-group comparisons of categorical variables were performed using the Chi-square test statistics (or Fisher's exact test). The relationships between non-normally distributed numerical variables were analyzed using Spearman's rho test. The predictive value of VEGF level for an active disease was examined by the Receiver Operating Characteristics (ROC) curve analysis. The level of statistical significance was accepted as $p<0.05$.

Results

The study included 74 acromegaly patients with a mean age of 48±14 years (min. 20, max. 85), of whom 39 were male, and 35 were female. Seven of the patients were newly diagnosed treatment-naive patients. The remaining 67 patients received at least one of the following treatments: surgery, medical treatment, or radiotherapy. While 5 of the 12 non-operated patients were on primary medical treatment, the remaining 7 patients were recently diagnosed. The general characteristics of the patients are presented in Table 1.

Table 1. General characteristics of the participants

	n (%)	Median (Q1-Q3)
Gender		
Male	39 (52.7)	
Female	35 (47.3)	
Age, year		48.5 (36-55)
Symptom duration (years)		6 (5-8)
Time from diagnosis (years)		4 (2-7)
Adenoma type		
Micro	16 (21.6)	
Macro	58 (78.4)	
Adenoma size (mm)		17 (10-22)
Pituitary surgery		
Non-operated	12 (16.2)	
Transsphenoidal	61 (82.4)	
Transcranial	1 (1.4)	
Number of surgical procedures		1 (1-1)
Radiotherapy		
None	63 (85.1)	
Conventional	2 (2.7)	
Gamma-knife	9 (12.2)	
Medical therapy		
None	50 (67.6)	
Somatostatin analogue	18 (24.3)	
Somatostatin analogue-cabergoline	5 (6.8)	
Somatostatin analogue-pegvisomant	1 (1.4)	
Comorbid disease/condition		
Left ventricular hypertrophy	42 (56.8)	
Goiter (diffuse/nodular)	36 (48.6)	
Colon polyp	32 (43.2)	
Hypertension	28 (37.8)	
Impaired glucose tolerance	18 (24.3)	
Diabetes mellitus	16 (21.6)	
Hepatomegaly	13 (17.6)	
Malignancy	7 (9.5)	
Heart failure	5 (6.8)	
Splenomegaly	5 (6.8)	
Basal GH (µg/L)		0.94 (0.26-2.79)
IGF-1 (µg/L)		171.5 (130-269)
VEGF (pg/mL)		316.02 (115.17-508.05)
Disease status		
Active	25 (33.8)	
Controlled	38 (51.4)	
Elevated IGF-1, normal GH	3 (4.1)	
Normal IGF-1, elevated GH	8 (10.8)	

Q1: the first quartile; Q3: the third quartile; GH: Growth hormone; IGF: ınsulin-like growth factor; VEGF: vascular endothelial growth factor.

Of the patients, 28 had active, and 46 had controlled disease. There were 11 patients with discordance between GH and IGF-1 levels, of whom 3 had elevated IGF-1 and normal GH levels, and 8 patients had normal IGF-1 and elevated GH levels. These 3 patients with elevated IGF-1 levels were assigned to the "active acromegaly" group, and the 8 patients with normal IGF-1 were included in the "controlled acromegaly" group.

The groups were compared concerning general characteristics. The rate of the patients undergoing pituitary surgery was higher, and the time from diagnosis was longer in the controlled acromegaly group than in the active acromegaly group. No significant difference was determined between the two groups regarding other acromegaly-related characteristics, demographic characteristics, or comorbidities (Table 2).

As was expected, the basal GH and IGF-1 levels were significantly higher in the active acromegaly group. However, the VEGF levels did not differ between the two groups (Table 3). Reanalysis of the parameters presented in Table 1 and Table 2, for the active (n=25) and controlled acromegaly (n=38) groups excluding 11 patients with discordance between GH and IGF-1 levels revealed no significant differences between the groups.

The correlation analysis demonstrated a significant negative correlation between the VEGF and basal GH levels (n=74). This negative correlation between the VEGF and basal GH levels persisted when the analysis was repeated, excluding 11 patients with discordance between the GH and IGF-1 levels. On the other hand, while the VEGF level was not correlated with the basal GH and IGF-1 levels in

Table 2. Characteristics of active and controlled acromegaly patients

	Active acromegaly, n=28	Controlled acromegaly, n=46	p
Gender			
Male	13 (46.4)	26 (56.5)	0.399
Female	15 (53.6)	20 (43.5)	
Age (year)	45 (36-60)	50 (39-54)	0.780
Symptom duration (years)	6 (5-7)	7 (5-8)	0.068
Time from diagnosis (years)	3 (1-5)	5 (2-8)	0.019
Adenoma type			
Micro	7 (25)	9 (19.6)	0.582
Macro	21 (75)	37 (80.4)	
Adenoma size (mm)	19.5 (9.5-25)	15 (10-20)	0.257
Pituitary surgery			
Non-operated	8 (28.6)	4 (8.7)	0.047
Operated	20 (71.4)	42 (91.3)	
Number of surgical procedures	1 (0-2)	1 (1-1)	0.434
Radiotherapy			
Not received	25 (89.3)	38 (82.6)	0.518
Received	3 (10.7)	8 (17.4)	
Medical treatment			
Not on treatment	18 (64.3)	32 (69.6)	0.638
On treatment	10 (35.7)	14 (30.4)	
Comorbid disease/condition			
Left ventricular hypertrophy	18 (64.3)	24 (52.2)	0.308
Goiter (diffuse/nodular)	14 (50)	22 (47.8)	0.856
Colon polyp	14 (50)	18 (39.1)	0.487
Hypertension	13 (46.4)	15 (32.6)	0.235
Impaired glucose tolerance	6 (21.4)	12 (26.1)	0.651
Diabetes mellitus	9 (32.1)	7 (15.2)	0.086
Hepatomegaly	4 (14.3)	9 (19.6)	0.755
Malignancy	3 (10.7)	4 (8.7)	1.000
Heart failure	2 (7.1)	3 (6.5)	1.000
Splenomegaly	3 (10.7)	2 (4.3)	0.360

The values are shown as median (Q1-Q3) or number (%), where appropriate.

Table 3. Levels of growth hormone, insulin-like growth factor-1, and vascular endothelial growth factor in the active and controlled acromegaly patients

	Active acromegaly, n=28 Median (Q1-Q3)	Controlled acromegaly, n=46 Median (Q1-Q3)	p
Basal GH, µg/L	2.8 (1.49-4.56)	0.37 (0.2-1.0)	<0.001
IGF-1, µg/L	307 (246.5-443.5)	141.5 (104-169)	<0.001
VEGF, pg/mL	277.88 (18.32-431.9)	364.09 (131.26-574.7)	0.113

Q1: the first quartile; Q3: the third quartile; GH: Growth hormone; IGF: Insulin-like growth factor; VEGF: Vascular endothelial growth factor.

the active patient group, there was a significant negative correlation between the VEGF and basal GH levels in the controlled patients (Table 4).

The ROC analysis, which was performed to identify a cut-off value for the VEGF level in predicting active disease in acromegaly patients, revealed an area under the curve of 0.560 and failed to indicate a significant cut-off value where the sensitivity and specificity were together within acceptable levels (Fig. 2).

Discussion

GH and IGF-1 are principal biomarkers used to assess disease activity in acromegalic patients. But in some cases there may be discrepancy between GH and IGF-1 results. There are two types of discrepancy; one is abnormal GH levels with IGF-1 values within the reference range called high GH discrepancy, the other pattern is elevated IGF-1 and normal GH levels called High IGF-1 discrepancy. In a study including 5626 acromegalic patients the prevalence of discrepancy between GH and IGF-1 was %25,7. The majority of discrepant cases was High IGF-1 type (%15,3). If there is discordance ; the clinician should evaluate possible confounding factors and assess clinical sign and metabolic parameters for active disease. In clinically active disease with GH and IGF-1 discrepancy the priority should be normalization of IGF-1 within age and sex matched reference ranges. Finding a new marker that correlates with disease activity in patients with discordance may lead to a need for treatment modification in these patients. In this study we analysed the plasma VEGF levels and disease activity in acromegalic patients.[6] We demonstrated a similarity be-

Table 4. Correlation analysis of vascular endothelial growth factor measurements with growth hormone and insulin-like growth factor 1 levels

	VEGF	
	rho	p
Overall patients (n=74)		
Basal GH	-0.247	0.034
IGF-1	-0.061	0.604
Overall patients* (n=63)		
Basal GH	-0.275	0.029
IGF-1	-0.093	0.468
Active acromegaly (n=25)		
Basal GH	0.162	0.438
IGF-1	0.197	0.346
Controlled acromegaly (n=38)		
Basal GH	-0.360	0.026
IGF-1	0.069	0.683

*Excluding 11 patients with discordance between growth hormone and insulin-like growth factor-1 levels. GH: Growth hormone; IGF: Insulin-like growth factor; VEGF: Vascular endothelial growth factor.

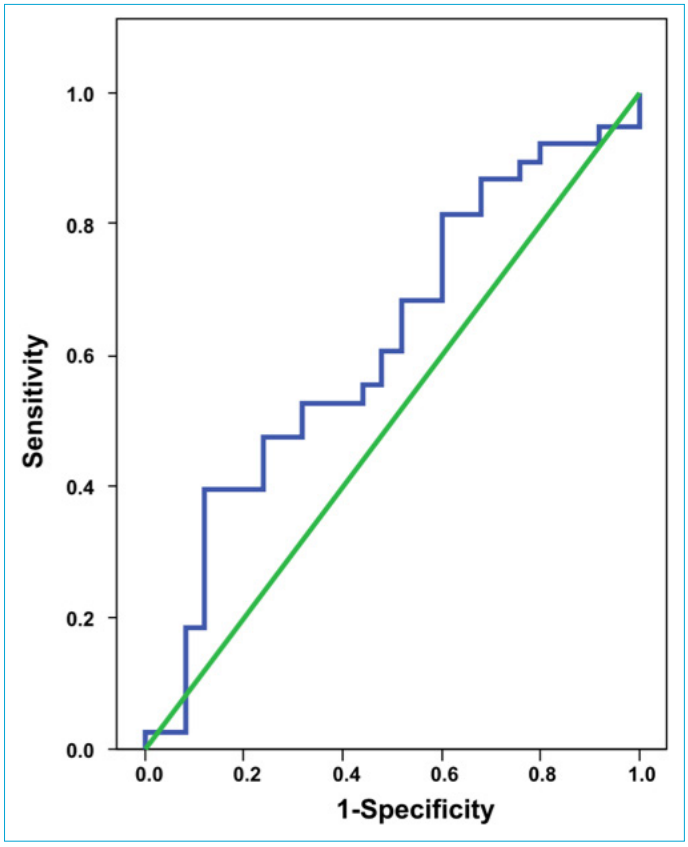

Figure 2. Receiver operating characteristics (ROC) curve for vascular endothelial growth factor (VEGF).

tween groups in terms of demographic features and acromegaly-related characteristics. Also, we failed to determine a significant difference between the VEGF levels of the two groups, or identify a cut-off VEGF level to discriminate active acromegaly from a controlled disease.

Many experimental and clinical studies investigated the relationship of VEGF levels with GH and IGF-1 in various pathological situations.[13-18] However, the limited number of studies show controversies regarding the relationship of VEGF with GH and IGF-1 levels in patients with pituitary adenoma/acromegaly. While some studies have reported higher VEGF levels in patients with pituitary adenoma/acromegaly than healthy individuals,[19,20] other studies have reported VEGF levels similar to that of healthy individuals.[21,22] Gruszka et al.[19] reported higher serum VEGF values in patients with pituitary adenoma (n=71; 20 patients with somatotropinoma, 3 patients with corticotropinoma, 6 patients with prolactinoma, and 42 patients with nonfunctional pituitary adenoma) as compared to the healthy controls (n=14) (423±45 pg/mL and 194±32 pg/mL, respectively; p<0.005). Likewise, Lee et al.[20] determined higher VEGF levels in patients with pituitary adenoma (n=5) as compared to the healthy controls (n=10) (baseline VEGF level: 89.5 pg/mL and 29.3 pg/mL, respectively, p=0.050). They reported VEGF levels to be 74.1 pg/ml after one week and 79 pg/mL after one month of stereotactic radiosurgery performed with gamma-knife. VEGF reduction after one month compared to the baseline was not significant (p=0.812), and the VEGF level was still higher as compared to the control group (p=0.033).

Nagai et al. conducted a study in active acromegaly patients (n=13) and age- and gender-matched healthy controls (n=16). They found that the mean plasma VEGF levels of acromegaly patients were not higher than those of healthy subjects (253±61 pg/mL vs. 197±30 pg/mL, p=0.390). Furthermore, they reported that plasma VEGF was not correlated with GH or IGF-I levels.[21] On the other hand, Silha et al. determined no significant difference between the VEGF levels of untreated acromegaly patients (n=35) and a healthy control group (n=101).[22] However, Paisley et al. showed reduced IGF-1 levels following pegvisomant therapy (from 620.1±209.3 ng/mL to 237.5±118.5 ng/mL, p<0.001) in acromegaly patients (n=20). In the same study, a significant reduction with treatment was determined in VEGF levels (from 283.4±233.6 pg/mL to 229.1±157.4 pg/mL; p=0.008).[23]

In this study, we investigated the relationship of VEGF with GH and IGF-1 levels in acromegaly patients. As was expected, the GH and IGF-1 levels were higher in the active acromegaly patients than in the controlled subjects. However, the VEGF measurements did not differ between the controlled and active acromegaly patients. This data supports previous studies reported by Nagai et al. and Silha et al. that VEGF levels are not increased in active acromegaly patients.[21,22] Moreover, in the present study, a specific cut-off point for VEGF in predicting active disease in acromegaly patients could not be determined in the ROC analysis.

Angiogenesis is a critical component of numerous physiological processes, and thereby, VEGF plays a role in many physiological conditions (such as female sexual cycle, corpus luteum formation, placenta formation, tissue growth, and differentiation processes, and tissue repair processes).[24] Moreover, the relationship of ischemic, inflammatory, and neoplastic conditions, including diabetes, cancer, and cardiovascular diseases with VEGF, has been documented.[25-29] The characteristics of pituitary adenoma can also influence VEGF levels.[30-32] In the present study, the controlled and active acromegaly groups were considered comparable for VEGF levels since there were no significant differences between the groups regarding age, gender, adenoma type, treatment status, and comorbidities.

In the present study, there was a significant negative correlation between VEGF and basal GH levels in all acromegaly patients as well as the group with controlled acromegaly. High VEGF levels have been reported in adults with GH deficiency.[33] This might indicate the negative correlation between these two parameters. However, Nagai et al.[21] failed to show a relationship between the VEGF and GH levels in active acromegaly patients. Also, we found no correlation between the VEGF and GH levels in active acromegaly patients.

Although, the sample size in our study is larger than that of previous studies, our research has some potential drawbacks. First, a healthy control group could provide additional comparative data. Also, the follow-up durations of the patients was not included in the analyses, which may be a potential confounder.

Conclusion

In conclusion, VEGF levels do not seem to be a useful marker to determine disease activity in acromegaly patients. Serum VEGF measurements may play a less critical role in the growth of pituitary adenomas or hormone secretion. Further studies with larger sample sizes, longer duration of follow-ups, and repeated measurements of the variables are warranted to reach more precise conclusions.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Kocaeli University (Date: March 20, 2012, approval no. 2012/68), and written informed consent of the patients was obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.Ç.K., Z.C.; Design – A.Ç.K., Z.C.; Supervision – B.Ç.; Materials – A.Ç.K., İ.T.; Data collection &/or processing – A.Ç.K., Z.C.; Analysis and/or interpretation – İ.T., B.Ç.; Literature search – A.Ç.K., İ.T.; Writing – A.Ç.K.; Critical review – Z.C., B.Ç.

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