Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Acromegaly and its clinical outcomes: A 10-year retrospective analysis of a cohort of patients with acromegaly from a university setting

Ali Pir[a], Irfan Nuhoglu[b,*]

[a]*Karadeniz Technical University, Faculty of Medicine, Department of Internal Medicine, Trabzon, Türkiye*
[b]*Karadeniz Technical University, Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Trabzon, Türkiye*

ARTICLE INFO

Keywords:
Acromegaly
Therapy
Surgery
Radiotherapy
Somatostatin analogs

Received: Oct 01, 2022
Accepted: Oct 14, 2022
Available Online: 22.10.2022

DOI:
10.5455/annalsmedres.2022.09.293

Abstract

Aim: We purpose to evaluate the demographic characteristics of patients with acromegaly, laboratory values when diagnosed and during follow-up, clinical symptoms, comorbid conditions during follow-up, treatment methods, and treatment response rates.

Materials and Methods: Data regarding patients with acromegaly who applied to Karadeniz Technical University Faculty of Medicine Endocrinology and Metabolic Diseases outpatient setting between 2010 and 2020 were included in the study. The patients' demographic characteristics, laboratory values, and clinical features when diagnosed and follow-up, and selected treatment methods were examined retrospectively.

Results: A total of 71 patients were eligible, of which 45.1% were female, and 54.9% male. The mean age at diagnosis was 48.5 years. The most common complaint of the patients was an enlargement of the hands and feet (53.5%). In diagnosis, 2.8% of the patients had secondary adrenal insufficiency, 1.4% secondary hypothyroidism, 7% hypogonadism, and 2.8% panhypopituitarism. Pituitary acromegaly was determined in 97.2% of the patients, and non-pituitary acromegaly in 2.8%. Regarding co-morbid conditions, 35.2% of the patients had hypertension, 23.9% had diabetes mellitus (DM), 1.4% had cardiovascular disease, and 5.6% had a malignancy history. Of the patients with pituitary adenoma, 71% had macroadenoma, and 29% had microadenoma. The mean adenoma size was 15.3±7.8 mm. Surgery was the preferred primary treatment in 76.1% of the patients. In 40.8% of the patients only surgical treatment was applied, while in 40.8% surgery+ medical treatment, 8.5% only medical treatment, 5.6% surgery +medical treatment + radiotherapy, 2.8% medical treatment + radiotherapy, 1.4% chemotherapy. After all treatments, 49.3% of the patients were in remission. In the follow-ups, colon malignancy was diagnosed in 4.2% and thyroid malignancy in 5.6%.

Conclusion: The clinical features of patients with acromegaly were generally similar to those in the literature. It was evident that early diagnosis and treatment initiation, and patient response to treatment was the prominent factors decreasing comorbidities.

Introduction

Acromegaly, characterized by increased serum growth hormone (GH) and insulin-like growth factor 1 (IGF-1) concentrations, is a rare disease that often result from non-cancerous tumor in the pituitary gland called a pituitary adenoma [1]. Its estimated prevalence is 30-70 per million, and its incidence ranges from 2 to 11 per million per year [2]. It has a balanced gender distribution, and the mean diagnosis age ranges from 40 to 50 years [3].

The clinical features of acromegaly are local effects due to enlargement of the pituitary mass, systemic complications, and poor life quality due to excessive secretion of GH and IGF-1. Although the typical facial and acral changes in acromegaly are significant, these findings usually emerge snakingly. Therefore, there is often a delay between when the first symptoms are recorded and when diagnosed [3]. Generally, the mortality of acromegaly is due to cardiovascular, cerebrovascular, and pulmonary complications [4]. Although the serum IGF-1 level is usually reliable to diagnose, the gold standard is the evaluation of GH secretion in the oral glucose tolerance (OGTT) test. GH levels are suppressed by <1 ng/mL (0.4 ng/mL by sensitive measurement methods) for 2 hours following OGTT in healthy

*Corresponding author:
Email address: irfannuhoglu@hotmail.com (Irfan Nuhoglu)

humans. However, GH levels are not suppressed and may paradoxically increase in acromegaly patients [5]. Imaging methods are applied to evaluate tumor size, localization, and paracellar tumor invasion in acromegaly patients diagnosed clinically and via laboratory tests. Magnetic resonance imaging (MRI) provides advantage over computed tomography (CT) because of its sensitivity and specificity in soft tissue contrast [6].

Surgical resection, medical treatment, and radiotherapy are choice of therapy for the acromegaly [6]. Transsphenoidal adenectomy is the primary treatment. Other treatment modalities are applied to patients who refuse surgery, have high surgical risk, or have invasive, unresectable tumors [1].

Despite evidence-based guideline has developed and under use for management of acromegaly, there is a to improve quality of evidence regarding outcomes of diagnose and management of the evaluation and management of acromegaly, including laboratory tests, surgery, medical monotherapy or combination therapy. Therefore we analyzed our 10-year data to contribute related literature.

Seventy-one acromegaly patients followed between 2010 and 2020 in Karadeniz Technical University Faculty of Medicine Endocrinology and Metabolic Diseases outpatient setting were retrospectively analyzed. The anamnesis, demographics, blood test results, treatments, pituitary MRI reports, colonoscopy reports, abdominal USG reports, echocardiography reports, and pathology reports of the patients were perused retrospectively. We aimed to collect data of patients with acromegaly, present our results in line with the literature, and discuss them.

Materials and Methods

Study design

The study protocol was approved by the Institutional Ethics Committee of Karadeniz Technical University (Turkey) (Protocol no: 2020/217).

A retrospective analysis of all acromegaly cases followed between 2010-2020 at Karadeniz Technical University Faculty of Medicine Endocrinology and Metabolic Diseases outpatient setting were retrospectively analyzed. Information concerning laboratory values when diagnosed and during follow-up, clinical symptoms, comorbid conditions during follow-up, treatment methods, and treatment response rates, and gender of patients were retrieved. Patients from the file records who had clinical, biochemical evidence of acromegaly and pathologically confirmed pituitary adenoma was included and those who did not meet the inclusion criteria were excluded.

Demographic characteristics (age at diagnosis, current age, gender), medical history, admission complaints, comorbid diseases, laboratory results (serum GH, lowest GH in OGTT, IGF-1 level at diagnosis, and other biochemical parameters from electronic patient files), preoperative MRI findings [tumor size (macroadenoma, microadenoma)], disease period, treatment modalities (surgery, medical therapy, radiation therapy), disease activity (controlled, active), follow-up time, abdominal ultrasounds, echocardiography, and colonoscopy reports were recorded retrospectively.

Laboratory measurement data

The acromegaly was diagnosed via clinical findings, inability to suppress serum GH levels to <0.4 ng/mL in 75gr OGTT, and serum IGF-I levels being higher than the normal range defined for the same age and gender. Patients were examined into two groups; remission and active disease due to treatment response. IGF-1 normalization and rarely GH<0.4 ng/mL after OGTT were accepted as remission criteria.

Biological analyses data

All biological assays were conducted by the Karadeniz Technical University Faculty of Medicine, Training and Research Hospital Clinic Laboratory on blood samples within 2h of blood collection. A Roche Modular E 170 autoanalyzer device (Indianapolis, IN, USA) was used to measure plasma glucose and lipid parameters. FPG and 2hPG were measured by enzymatic colorimetric method with glucose-oxidase technique. TGs were assayed by using an enzymatic colorimetric assay with glycerol phosphate oxidase. HDL-C was measured after precipitation of the apolipoprotein B containing lipoproteins with polyanions. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Fried Ewald equation. GH and IGF-1 levels were measured via the IMMULITE 2000 Immunoassay System (Siemens Healthcare Diagnostics) which is a solid phase enzyme-labeled, chemiluminescent immunometric assay.

Statistical analysis

SPSS 23.0 statistical package program was used in the data analysis. Descriptive statistics of data are given as numbers and percentages for categorical variables; Mean, standard deviation (ss), minimum (min), and maximum (max) for metric variables. The conformity to the normal distribution of the measurable variables was evaluated via the One-Sample Kolmogorov Smirnov test. The student-t test was used for comparisons between independent groups of measurable data that conformed to the normal distribution, and the Mann-Whitney U test for those that did not. The chi-square test was used to analyze the differences between the ratios of categorical variables in independent groups. The statistical significance level was accepted as $p<0.05$.

Results

After inclusion and exclusion criteria considerations, a total of 71 patients with acromegaly over 18-year-old were eligible for this analysis. They were followed up between 2010 and 2020 in Karadeniz Technical University Faculty of Medicine, Department of Internal Medicine; Endocrinology and Metabolic Diseases Clinic.

A total of 71 subjects (39 men, 54.9%; 32 women, 45.1%), with a mean age of 48.5±13.5 years, were included in the analysis (Table 1). The most common complaints at diagnosis were enlarged hands and feet (53.5%), headache (38%), and acromegalic changes in the face (33.8%) (Table 2). Hypertension (35.2%), diabetes mellitus (23.6%), and cardiovascular disease history (1.4%) were recorded comorbidities. The prevalence of hypertension was statistically significantly higher in female patients than in males

Table 1. Clinical characteristics of the patients with acromegaly.

Parameter	Result
Number of patients (M/F)	71 (39/32)
Age (years)	48.5 ± 13.5
BMI (kg/m²)	30.0 ± 5.6
Disease duration (years)	11.8 ± 7.0
Hypertension (%)	35.2%
Systolic blood pressure (mmHg)	120.0 [100-145]
Diastolic blood pressure (mmHg)	75.0 [55-100]
DM (%)	23.9%
HbA1c (%)	6.54 ± 1.45
Fasting glucose (mg/dL)	106.1 ± 43.8
Total-C (mg/dL)	195.67 ± 40.54
LDL-C (mg/dL)	122.48 ± 32.58
HDL-C (mg/dL)	45.22 ± 11.19
TG (mg/dL)	158.75 ± 102.83
Basal GH (ng/mL)	13.9 ± 20.9
IGF-I (ng/ml)	681.4 ± 296.1

Data are shown as mean ± standard deviation.
BMI: body mass index; DM: Diabetes mellitus; LDL-C: Very low-density lipoprotein; HDL: High-density lipoprotein; TG: Trigliseride; GH: Growth hormone; IGF-1: Insulin-like growth factor 1.

Table 2. Admission complaints of acromegaly patients.

Complaint	Frequency	
	n	%
Enlargement in hands and feet	38	53.5
Headache	27	38
Facial changes	24	33.8
Vision defect	8	11.3
Snoring	7	9.9
Numbness in hands	7	9.9
Enlargement in tongue	6	8.5
Excessive sweating	2	2.8
Loss of libido	1	1.4
Nonspecific	14	19.7

Table 3. Comparisons of the treatment modalities in the acromegalic patients.

Tumor diameter (mm) §	15.3 [±7.3]
Macroadenoma (%) ‡	49 (71)
Use of medications (%) var ‡	44 (62.0)
Types of medical treatment ‡	
Cabergoline	3 (4.2)
Somatostatin	33 (46.5)
Somatostatin+Cabergoline	7 (9.9)
Pegvisomant+Somatostatin	1 (13.0)
Surgical treatment (%) ‡	62 (89.9)
Use of Gamma Knife (%) ‡	6 (8.4)
Use of conventional radiotherapy ‡	0 (0.0)

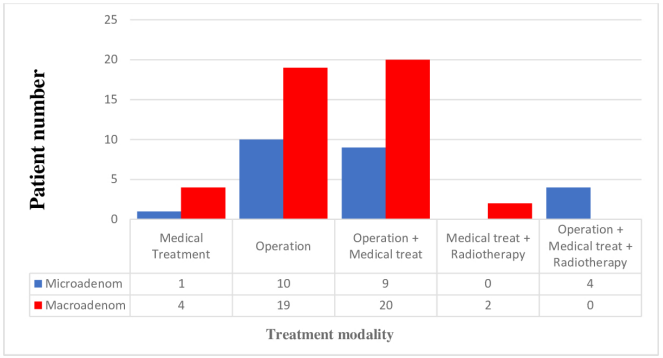

Figure 1. Comparison of adenoma size and treatment modalities.

(56.3% and 17.9%, respectively, p:0.02). 5.6% of the patients were previously diagnosed with malignancy (thyroid papillary cancer in two patients, colon cancer in one patient, and gastric cancer in one patient).

Considering the acromegaly etiology, it was seen due to pituitary adenoma in 97.2% (69 cases) and non-pituitary causes in 2.8% (2 cases). A neuroendocrine tumor was detected in one patient with nonpituitary acromegaly, and no primary underlying cause was identified in the remaining cases. The mean size of the pituitary adenoma at diagnosis was 15.3±7.8 mm, and most patients had macroadenoma (71.0%).

On admission, mean GH levels of the patients with microadenoma was 4.70±4.28 µg/L, and the mean IGF-1 value was 569.68±266.36µg/L. The mean GH of the patients with macroadenoma was 18.17±23.97µg/L, and the mean IGF-1 value was 733.79±300.37µg/L. The means of GH and IGF-1 were statistically significantly higher in those with macroadenoma than those with microadenoma (p: 0.001 vs p: 0.042, respectively).

Approximately 70% of the study population had some level glucose disorders. The overall prevalence of prediabetes and diabetes mellitus was 40.4% and 29%, respectively. The mean HbA1c value of the patients was 6.54±1.45%.

When we examined the study group for hypopituitarism, secondary adrenal insufficiency (12.7%) was the most common, followed by central hypothyroidism (5.6%) and hypogonadotropic hypogonadism (4.2%). Panhypopituitarism was present in 7% of the cases.

Colonoscopy results of 53 patients were available. Colon malignancy was developed in the clinical follow-ups of three patients (4.2%). Thyroid papillary cancer was diagnosed in four patients (5.6%) with thyroid ultrasound and fine-needle aspiration biopsy performed during malignancy screening.

The treatment methods performed according to the adenoma size are summarized in Figure 6.

The treatment methods performed to the study group were classified according to the adenoma size and summarized in Table 3. Surgery (transsphenoidal adenectomy in all cases) was administered as the primary treatment in 89.9% (62 patients) of the cases. While no residual tumoral tissue was detected in 55.4% of the patients in the postoperative imaging, residual tumoral tissue was smaller than 1 cm in 10.7% and larger than 1 cm in 33.9%. Due to dis-

ease activity, 38.7% of the patients were in remission after primary surgery. There was no statistically significant difference between microadenoma and macroadenoma groups in the rates of patients in remission after surgery (36.8% vs 39.5%, respectively, p: 0.19).

Six patients (9.7%) were reoperated during follow-ups. The need for reoperation was higher in the macroadenoma group than in the microadenoma group (11.6% vs. 5.3%, respectively).

Medical treatment was recommended for 61.9% (44 patients) of the patients. Medical treatment was administered in the majority of patients because remission could not be achieved after surgery. Medical therapy was applied as the primary treatment regimen in six (8.5%) patients without surgery. Somatostatin analogs (75%) and dopamine agonists (15.9%) together with the somatostatin analog were used in medical treatment most frequently. Only dopamine agonist was recommended in three patients, and growth hormone receptor antagonist in combination with somatostatin analog in one patient. One patient having acromegaly due to a neuroendocrine tumor received chemotherapy during the treatment.

Radiotherapy was applied to six patients (8.4%) with macroadenoma and a gamma knife was used in all cases.

Discussion

Acromegaly is a metabolic disease that occurs due to excessive GH secretion.

In our study, the rates of male patients were higher than female patients (59.4% vs. 45.1%). The mean age at diagnosis was 48.5-year-old, and men were diagnosed approximately six years earlier than women (45.7 years vs. 51.9 years, respectively). In the study including 405 acromegaly patients by Dal et al.; it was reported that 53% of the patients were male and 47% female and the mean age at diagnosis was 48.7-year-old [7]. In a review including 16130 patients with acromegaly by Maione et al. in 2019; male predominance (male/female ratio 1.26) was reported, and the mean age at diagnosis was 45.2-year-old [8]. Although it is stated in the literature that acromegaly presents with equal frequency in both genders, its prevalence was reported more frequently in men in our study and some other studies [7,8].

The most common complaints in our case group were enlarged hands and feet (53.5%), headache (38.0%), and facial changes (33.0%). Petrosian et al. reported that dysmorphic appearance, enlarged extremities, and headache were the most common symptoms in patients with acromegaly [9]. In the study by Tseng et al., the most common presenting symptoms were facial changes, enlarged extremities, snoring, and headache [10]. The admission complaints frequency of our patients in our study was consistent with the literature [9, 10].

Uncontrolled GH and IGF-1 hypersecretion in acromegaly causes increased cardiovascular, respiratory, metabolic, and malignancy-related complications and mortality risk compared to the normal population [11]. In our study group, the most common comorbid diseases were hypertension (35.2%) and DM (23.9%). The hypertension prevalence was higher particularly in the female patient group than in the male group. One of the reasons may be those female patients were diagnosed at an older age. In the study involving 3173 patients with acromegaly by Petrosian et al., it was reported that hypertension was in 28.8%, type 2 DM in 24.5%, and cardiovascular disease in 6.5%. In a study by Mercado et al., at the time of diagnosis, 35% of their patients had a hypertension history, 30% of DM, and 8% of coronary artery disease [12]. In our study, the cardiovascular disease rate at diagnosis was lower than in the literature. It was suggested that this situation might result from the small number of our patients. Other comorbid diseases increased in line with the literature.

Numerous studies have reported increased malignancy prevalence in patients with acromegaly [13]. In our study, the malignancy frequency in our patient group was 15.4%. In approximately one-third of these patients, malignant neoplasms were diagnosed before the acromegaly. In this respect, earlier diagnosis in acromegaly patients will provide screening for malignancy without delay and the diagnosis and effective treatment of these tumors at an early stage.

Consistent with the literature, in our study, we found that pituitary macroadenoma (69%) mainly played a role in the disease etiology. In a study by Petrosian et al., the macroadenoma incidence in acromegaly patients was stated as 71.8% [9]. This can be explained by that the time elapsed between the onset of acromegaly and the diagnosis is approximately 5-10 years.

Transsphenoidal surgery is recommended as first-line therapy in most acromegaly patients [14]. Besides, surgical treatment is effective in urgently treating the tumor effect, optic nerve, and headache; it is also the only treatment method that gives a chance of cure [14]. In our patient group, 89.9% of patients with pituitary adenoma underwent transsphenoidal adenectomy. In a study of 115 patients with acromegaly by Anagnostis et al., it was reported that 79% of the patients underwent surgery during follow-ups [15].

In the literature, post-surgical remission rates in acromegaly patients vary due to the adenoma size. In our study, our postoperative remission rate was 36.8% in microadenomas and 39.5% in macroadenomas. In the study on 134 patients with acromegaly by Kim et al., the surgical remission rate was reported as 86.7% in patients with microadenoma and 72.3% in patients with macroadenoma [16]. In a study on 56 acromegaly patients by Yıldırım et al., it was reported that surgical remission was achieved in 80% of microadenomas and 64.7% of macroadenomas [17]. Postoperative remission rates in our study were significantly lower than in the literature, especially in patients with microadenoma. This may be based on the lack of a surgical center experienced in the pituitary in our region. However, some patients are operated on directly by neurosurgeons without being examined by an endocrinologist. Also, the rates of referral to a specialized center for surgery in patients with macroadenomas are higher than those with microadenomas.

There are many studies on medical treatments administered in the postoperative period for acromegaly treatment. In the study on 650 acromegaly patients by Mercado et al., 395 patients needed medical treatment. It was

reported that 67.6% of those who received medical treatment used somatostatin analogs, 25.4% used somatostatin analog + dopamine agonist, and 7% used only dopamine agonist [18]. In our study group, similar to the literature, 61.9% of the patients were treated with medical treatment, and somatostatin analogs were preferred most frequently.
Radiotherapy is another treatment method for treating residual mass and hormonal control in acromegaly patients who cannot be cured or controlled by surgical or medical treatment. Stereotactic radiotherapy was performed on 8.7% of our study group. In a study on 96 acromegaly patients by Can et al., it was stated that 30.2% of the patients received radiotherapy [19]. In the study on 442 acromegaly patients by Mercado et al., it was reported that 17% of the patients received radiotherapy [12]. Compared to the literature, the lower rate of patients who received radiotherapy in our study may be due to the differences in the success rate of the operation and the recommendations of the acromegaly guidelines, which recommend radiotherapy only for patients who are not in remission with surgical and medical treatment, published in the last ten years.
In our study group, a 49.3% remission rate was found with different treatment regimens. In the study on 93 acromegaly patients by Anagnostis et al., remission was reported in 51.6% after treatment [15]. In another study by Vandeva et al. involving 534 acromegaly patients, a 51.4% remission rate was reported [20]. In our study, post-treatment remission rates were within the rates with the literature.
During follow-up, hypopituitarism was 22.5% of the patients. Secondary adrenal insufficiency (12.5%) occurs most frequently. In the study on 442 patients by Mercado et al., hypogonadotropic hypogonadism was in 41%, panhypopituitarism in 28%, central hypothyroidism in 22%, and central hypercortisolism in 9% [12]. In the study on 271 acromegaly patients by Dutta et al., it was reported that hypercortisolism was in 55%, hypogonadism in 38.4%, and hypothyroidism in 34.2% after treatment [21]. In our study, the hypopituitarism frequency of our patients was significantly lower than in the literature. One of the reasons may be that we use radiotherapy less frequently in treatment. Another reason may be that extensive resection was not performed and so the normal pituitary tissue was not damaged much during the surgery.
Acromegaly and somatostatin analog drugs used for the treatment are known to be diabetogenic. We found that only 30.6% of the study group had normal glucose tolerance, and the remaining large patient group had varying degrees of glucose intolerance. In the study on 97 acromegaly patients by Dreval et al.; Overt DM was in 37% of patients, IGT in 34.1%, and normal glucose tolerance in 28.8% [22]. It suggests that good metabolic control with hormonal control will improve both life quality and survival in acromegaly patients.
Thyroid USG results of 65 patients in our study group were available. Pathologically proven thyroid malignancy occurred in 4 patients (5.6%) during their follow-ups. In a study involving 313 acromegaly patients by Keskin et al., it was reported that papillary thyroid carcinoma emerged in 6% of patients [23]. In a retrospective study on 160 acromegaly patients by Dağdelen et al., thyroid malignancy emerged in 10.6% of the patients [24]. In the study on 105 acromegaly patients by Gullu et al., thyroid malignancy was found in 4.7% [25]. Although there are studies in the literature showing an increased incidence of thyroid malignancies in acromegalic patients, it is considered that this increase is due to the more frequent screening of thyroid nodules in this patient group.
As a result of our study, it was seen that acromegaly disease was seen more frequently in men, the diagnosis age was 6 years earlier in men than in women, and they applied to a doctor most frequently because of physical changes and headaches. It was observed that glucose intolerance was very common in acromegaly patients, the hypertension prevalence was high, especially in female patients, and the malignancy incidence, especially in the thyroid and colon, was increased. In the preoperative pituitary magnetic resonance images, it was seen that the most common adenoma type was macroadenoma, and the remission rates after surgery were not different from the macroadenoma group in the microadenoma group. Similar to other studies on acromegaly treatment, it has been observed that transsphenoidal surgery is the most commonly used treatment method. New treatment agents and new studies are needed to increase remission rates.

Conflicts of interest

The author(s) declares that there is no conflict of interest conflict of interest.

In the preparation of this article, the data of Ali Pir's residency thesis 'Retrospective Evaluation of Acromegaly Patients Detected in the Endocrinology and Metabolic Diseases Polyclinic between 2010-2020', supervised by İrfan Nuhoğlu, were used.

Ethics approval

The study was accepted by the Institutional Ethics Committee of Karadeniz Technical University Trabzon, Turkey. (Decision no: 2020/217).

References

1. Dineen R, Stewart PM, Sherlock M. Acromegaly. QJM. 2017;110:411-420.
2. Bollerslev J, Heck A, Olarescu NC. Individualised management of acromegaly. Eur J Endoc. 2019;181:57–71.
3. Vilar L, Vilar CF, Lyra R, Naves LA. Acromegaly: clinical features at diagnosis. Pituitary. 2017; 20: 22-32.
4. Melmed S. Acromegaly. The Pituitary. 2017;1:423-466.
5. Katznelson L. Diagnosis and treatment of acromegaly. Growth Hor IGF-1 Res. 2005; 15:31-35.
6. Tilvawala M. Acromegaly:pathogenesis & treatment. J Clin Invest. 2009;119: 3189–3202.
7. Dal J, Feldt-Rasmussen U, Andersen MJ, et al. Acromegaly incidence, prevalence, complications and long- term prognosis: A nationwide cohort study. Eur J Endocrinol. 2016;175:181-190.
8. Maione L, Chanson P. National acromegaly registries. Best Pract Res Clin Endocrinol Metab. 2019;33101-264.
9. Petrossians P, Daly AF, Natchev E, et al. Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) Database. Endocr Relat Cancer. 2017;24:505-518.
10. Tseng FY, Huang TS, Lin JD, et al. A registry of acromegaly patients and one year following up in Taiwan. J Formos Med Assoc. 2019;118:1430–1437.
11. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998;83: 2730–2734.

12. Mercado M, Gonzalez B, Vargas G, et al. Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. J Clin Endocrinol Metab. 2014;99:4438-4446.
13. Terzolo M, Reimondo G, Berchialla P, et al. Acromegaly is associated with increased cancer risk: a survey in Italy. Endoc Relat Cancer. 2017;24:495–504.
14. Bonadonna S, Doga M, Gola M, et al. Diagnosis and treatment of acromegaly and its complications: Consensus guidelines. J Endocrinol Invest. 2005;28:43-7.
15. Anagnostis P, Efstathiadou ZA, Polyzos SA, et al. Acromegaly: Presentation, morbidity and treatment outcomes at a single center. Int J Clin Pract. 2011;65:896–902.
16. Kim JH, Hur KY, Lee JH, et al. Outcome of endoscopic transsphenoidal surgery for acromegaly. World Neurosurg. 2017;104:272–278.
17. Yildirim AE, Sahinoglu M, Divanlioglu D, et al. Endoscopic endonasal transsphenoidal treatment for acromegaly: 2010 consensus criteria for remission and predictors of outcomes. Turk Neurosurg. 2014;24:906–912.
18. Mercado M, Abreu C, Vergara-Lopez A, et al. Surgical and pharmacological outcomes in acromegaly: Real-life data from the Mexican acromegaly registry. J Clin Endocrinol Metab. 2020;105:1-25.
19. Can M, Kocabaş M, Çordan I, et al. Prevalence of comorbidities and associated factors in acromegaly patients in the Turkish population. Turkish J Med Sci. 2021:51:1–7.
20. Vandeva S, Elenkova A, Natchev E, et al. Treatment outcome results from the Bulgarian acromegaly database: Adjuvant dopamine agonist therapy is efficient in less than one fifth of non-irradiated patients. Exp Clin Endocrinol Diabetes. 2015;123:66–71.
21. Dutta P, Hajela A, Pathak A, et al. Clinical profile and outcome of patients with acromegaly according to the 2014 consensus guidelines: Impact of a multi-disciplinary team. Neurol India. 2015;63:360–368.
22. Dreval AV, Trigolosova IV, Misnikova IV, et al. Prevalence of diabetes mellitus in patients with acromegaly. Endocr Connect. 2014;3:93–98.
23. Keskin FE, Ozkaya HM, Ferahman S, et al. The role of different molecular markers in papillary thyroid cancer patients with acromegaly. Exp Clin Endocrinol Diabetes. 2019;127:437-444.
24. Dagdelen S, Cinar N, ErbasT. Increased thyroid cancer risk in acromegaly. Pituitary. 2014;17:299-306.
25. Gullu BE, Celik O, Gazioglu N, Kadioglu P. Thyroid cancer is the most common cancer associated with acromegaly. Pituitary. 2010;13:242-8.