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Clinical and treatment response differences according to age and gender in patients with acromegaly in Colombia: A retrospective study

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Abstract

Context: Acromegaly is a rare disease characterized by excessive growth of bones and soft tissues due to hypersecretion of the growth hormone (GH), usually associated with pituitary tumors. Timely diagnosis and treatment are essential to reduce chronic complications.

Objective: To determine if there are clinical differences and differences in the treatment response according to age and gender in patients with acromegaly in Colombia.

Methods: Observational, analytical, multicenter, retrospective cohort study based on a national registry of patients with acromegaly in Colombia.

Results: A total of 201 patients were included (of whom 60% were women and 75% were under 60 years old). The average weight was 75.1 kg ± 12.9 and the height was 1.63 m ± 0.08, with men and those under 60 years old tending to be taller. The average time of evolution of the disease until diagnosis was 6.9 ± 4.4 years, however, older adults had a longer time of 8.6 ± 5.7 years, with no differences with respect to gender. The most common type of tumor was macroadenoma in 78% of cases. In addition to the

Highlights

- Patients diagnosed with acromegaly under 60 years old exhibited higher anthropometric parameters and were primarily treated with surgery. In those over 60, depression, cardiomyopathy, hypertension, and bone disease were the most common comorbidities.
- The average time to acromegaly diagnosis was 6.9 years, with a longer delay in patients over 60 years old (8.6 years), suggesting a more significant diagnostic lag in this group.

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classic symptoms of the disease, decreased libido was found more frequently in men, and depression was predominant in those over 60 years old. Arterial hypertension, colonic and hepatobiliary pathology were more common in women. Cardiomyopathy, hypertension and bone pathology (osteoporosis and osteopenia) were more frequent among people over 60 years old. Surgical intervention, combined with medical management, was the preferred treatment approach for individuals aged 18 to 60 and was associated with improved clinical outcomes.

Conclusion: The combined treatment of surgery and medical management was associated with better clinical control of acromegaly, with no significant differences in disease control by gender or age group.

Keywords: Acromegaly, Gender, Age groups, Surgery, Medical therapy, Radiation.

- Approximately 78% of patients had macroadenomas, the most common tumor type in acromegaly, with no significant differences by gender or age.
- The combined treatment of surgery and medical management was associated with better clinical control of acromegaly, with no significant differences in disease control by gender or age group.

Diferencias clínicas y en la respuesta al tratamiento según edad y género en pacientes con acromegalia en Colombia: un estudio retrospectivo

Resumen

Contexto: la acromegalia es una enfermedad rara caracterizada por el crecimiento excesivo de los huesos y tejidos blandos debido a una hipersecreción de hormona de crecimiento (GH), generalmente asociada con tumores hipofisarios. Su diagnóstico y tratamiento oportunos son fundamentales para reducir las complicaciones crónicas.

Objetivo: determinar si existen diferencias clínicas y en la respuesta al tratamiento según la edad y el género en pacientes con acromegalia en Colombia.

Métodos: estudio observacional, analítico, multicéntrico, de cohorte retrospectiva, basado en un registro nacional de pacientes con acromegalia en Colombia.

Resultados: se incluyeron un total de 201 pacientes (de los cuales 60 % eran mujeres y 75 % eran menores de 60 años). El peso promedio fue de 75.1 kg ± 12.9 y la estatura fue de 1.63 m ± 0.08, siendo mayor en hombres y en menores de 60 años. El tiempo promedio de evolución de la enfermedad hasta el diagnóstico fue de 6.9 ± 4.4 años, sin embargo, los adultos mayores tuvieron un tiempo mayor de 8.6 ± 5.7 años, sin diferencias con respecto al género. El tipo de tumor más común fue el macroadenoma en el 78 % de los casos. Además de los síntomas clásicos de la enfermedad, la disminución del libido fue más frecuente en hombres, mientras que la depresión predominó en los mayores de 60 años. La hipertensión arterial así como la patología colónica y hepatobiliar, fueron más comunes en mujeres. La cardiomiopatía, la hipertensión y la patología ósea (osteoporosis y osteopenia) fueron más frecuentes entre las personas mayores de 60 años. El enfoque de tratamiento preferido fue la intervención quirúrgica y la orientación médica para individuos de entre 18 y 60 años. La combinación de manejo médico e intervención quirúrgica fue la opción asociada con un mayor control clínico.

Conclusión: el tratamiento combinado de cirugía y manejo médico se asoció con un mayor control clínico de la acromegalia, sin diferencias significativas en el control de la enfermedad según género o grupo etario.

Palabras clave: acromegalia, género, grupos etarios, cirugía, tratamiento médico, radiación.

Destacados

- Los pacientes con diagnóstico de acromegalia menores de 60 años presentaron mayores parámetros antropométricos y fueron tratados principalmente con cirugía. En los mayores de 60 años, la depresión, cardiomiopatía, hipertensión y patología ósea fueron las comorbilidades más comunes.
- El tiempo promedio hasta el diagnóstico de la acromegalia fue de 6.9 años, siendo mayor en los pacientes mayores de 60 años (8.6 años), lo que sugiere un retraso diagnóstico más significativo en este grupo.
- El 78 % de los pacientes presentaron macroadenomas, el tipo de tumor más común en la acromegalia, sin diferencias significativas por género o edad.
- El tratamiento combinado de cirugía y manejo médico se asoció con un mayor control clínico de la acromegalia, sin diferencias significativas en el control de la enfermedad según género o grupo etario.

Introduction

Acromegaly is a progressive disease resulting from an increase in the release of growth hormone (GH), and as a consequence of insulin-like growth factor 1 (IGF-1), it is induced in most cases by a GH-producing pituitary tumor, and less frequently by pituitary hyperplasia, ectopic secretion of GH or growth hormone-releasing hormone (GHRH) [1, 2].

The overall annual incidence is 1.1 cases per 100,000 individuals [3, 4]. While frequency by gender does not vary widely between men and women, however, several studies have reported a slight predominance in women [5–10]. The mean age at presentation ranges between 40 and 50 years, with a mean time from symptom onset to diagnosis of <5 years [11].

The most common form of presentation is sporadic, occurring in at least 95% of cases, which is secondary to a GH-producing adenoma derived from somatotrophic cells, or mixed by secreting GH and prolactin (PRL) by anterior pituitary cells [12, 13]. These tumors are usually benign and do not metastasize; however, they can grow locally and become injurious by compressing neighboring structures [14].

Prolonged exposure to GH induces somatic changes and metabolic alterations that lead to the appearance of the typical clinical findings of acromegaly, along with an increase in morbidity and mortality. These outcomes vary depending on the time of disease onset, gender, and age [15]. Key manifestations and associated comorbidities include the growth of the hands, feet and face (prognathism), soft tissue hypertrophy, hyperhidrosis, carpal tunnel syndrome, sleep apnea, osteoarthritis, colonic polyps, and finally reproductive, metabolic and cardiac disorders, such as arterial hypertension (HTN) and cardiac arrhythmias [16].

Diagnosis requires the integration of a detailed clinical history, aimed at searching for the characteristic features of the disease, associated with elevated serum concentrations of IGF- 1 and GH [17, 18]. Once the hormonal alteration is documented, the use of conventional imaging, especially magnetic resonance imaging (MRI), allows the identification of the adenoma at the pituitary level, distinguishing between those smaller than 10 mm (microadenomas) and more than 10 mm (macroadenomas), as well as invasion of neighboring structures [19].

Whenever feasible, the treatment of choice for acromegaly —and the only potentially curative option— is transsphenoidal surgery performed at an expert center. However, since many patients are diagnosed with invasive macroadenomas, surgical success is limited to approximately 50% of cases, requiring a multimodal therapeutic approach [2, 20 ,21].

Gender and age have been described as factors that influence acromegaly presentation, severity, response to treatment, and disease control. The demographic, clinical, and paraclinical characteristics, treatment offered, and response to it vary among each individual diagnosed with this entity. The purpose of this study was to determine whether there is an association between clinical differences and response to treatment, according to age and gender, in patients with acromegaly in Colombia.

Materials and methods

Study Design

Observational, analytical, multicenter, retrospective single cohort study.

Participants

A total of 201 patients were included, based on a national registry (RAPACO) created in 2018 by 9 endocrinologists in the country in a joint effort to group the largest number of patients with this rare clinical entity. Patients with a confirmed diagnosis of acromegaly aged 16 years or older were included, while those with incomplete medical records were excluded.

Defining Variables

Data were collected retrospectively from the RAPACO registry. The following variables were included:

- **Sociodemographic:** Gender, age at diagnosis and origin.
- Clinical variables: Weight, height, body mass index (BMI), cervical circumference, waist circumference, hip circumference, waist-to-hip ratio, type of tumor by magnetic resonance imaging (MRI) (microadenoma <10 mm, macroadenoma >10 mm), and time of evolution until diagnosis.
- **Clinical manifestations:** Enlargement of the hands, feet and face, headache, fatigue, arthralgias, menstrual disturbances, palpitations, visual disturbances, erectile dysfunction, depression, hyperhidrosis, constipation, decreased libido, hand dysesthesia, dyspnea, snoring, blindness, and galactorrhea. Symptoms were documented based on the medical history, patient-reported outcomes, and physical examination findings recorded in the registry.
- **Comorbidities:** Diagnoses of cardiomyopathy, diabetes, prediabetes, hypertension, arrhythmias, sleep apnea, colonic pathology, carpal tunnel syndrome, renal lithiasis, thyroid pathology, osteopenia, osteoporosis, hepatobiliary pathology, and hypopituitarism were recorded based on documented diagnoses in the patients' medical records and corresponding treatments (e.g., antihypertensive or antidiabetic medications).
- **Treatment variables (at registry entry and 6 months of follow-up):** Type of surgery (transsphenoidal or transcranial), number of surgeries, pathology and immunohistochemistry markers (Ki67 [%], P53 [%], GH [Growth Hormone], FSH [Follicle-Stimulating Hormone], ACTH [Adrenocorticotropic Hormone], TSH [Thyroid Stimulating Hormone], LH [Luteinizing Hormone], PRL [Prolactin]), radiotherapy type (holocranial or radiosurgery), medical management (cabergoline, lanreotide, octreotide, pasireotide, combination therapy), GH and IGF-1 levels, and disease control status.
- **Biochemical control of disease:** Biochemical control was defined as achieving both GH levels below 1 ng/mL and IGF-1 levels within the age- and sex-adjusted normal reference range established by the laboratory.

All variables were collected retrospectively from patient medical records, as documented by the treating physicians in the RAPACO registry. This approach ensured standardization and reliability in data collection, facilitating accurate analysis of the clinical and therapeutic characteristics of patients with acromegaly.

Statistical analysis

A quality control of the information was carried out through an exploratory analysis of the Excel database where the variables to be studied were recorded, and subsequently a general scheme of analysis was designed by gender (men and women) and age groups (under 60 and 60 or older), using the cut-off point defined by the Colombian Ministry of Health in 2020 (Figure 1).

A bivariate analysis was carried out in order to select statistically significant variables ($P \leq 0.05$) by both gender and age. This was followed by a multivariate analysis using the multiple binary logistic regression model and discriminant analysis model for categorical and numerical variables respectively, which showed that the original grouped cases of the bivariate analysis were correctly classified. Non-parametric tests were applied, and a tree diagram was developed to calculate conditional probabilities, aiming to assess treatment response and disease control.

Measures of central tendency and dispersion, percentage distribution, prevalence, and confidence intervals were used for the descriptive analysis. The statistical association was determined for categorical variables using the Chi-square test and Fisher and McNemar's exact test, while numerical variables were analyzed using the T student, ANOVA, and Wilcoxon's test. All analyses were performed using IBM-SPSS version 25.0.

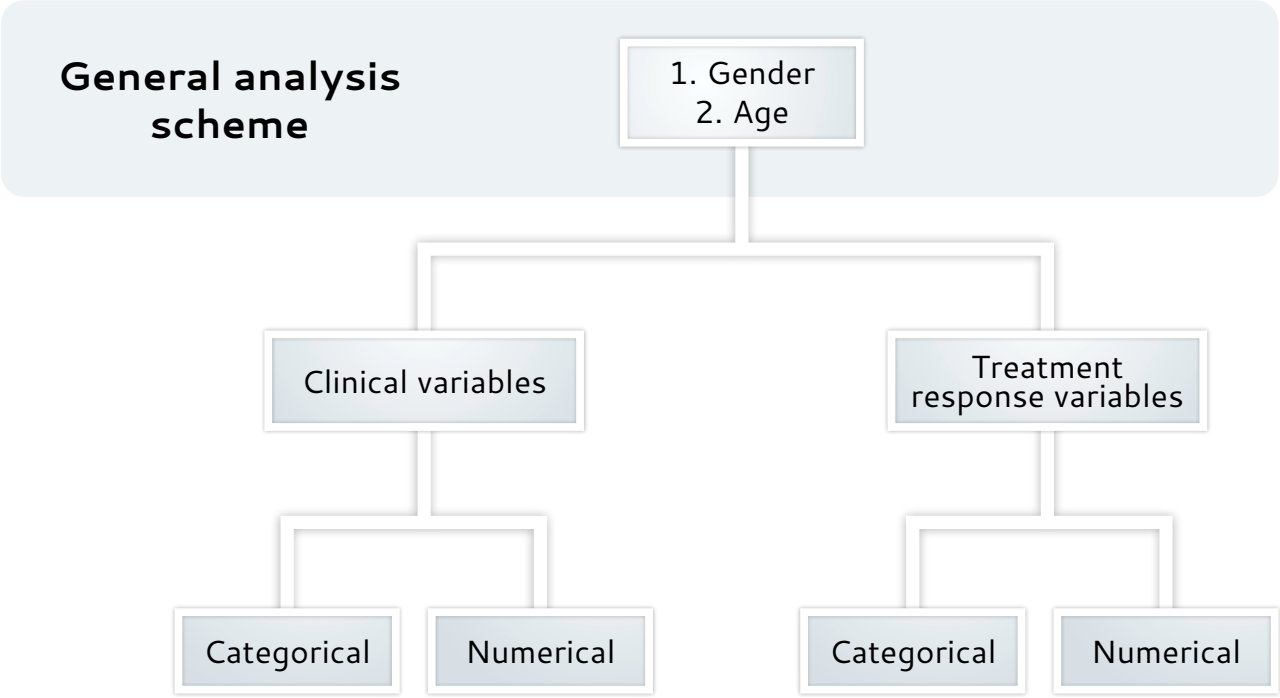


Figure 1. General outline of analysis
Source: own elaboration

Results

Demographic characteristics

A total of 201 patients were included in the study, of whom 60% were women and 75% were under the age of 60. The age of the population at the time of the study ranged from 16 to 89 years, with a mean of 49.4 ± 14.5 years (Table 1).

Table 1. General characteristics of the population studied by gender and age

Characteristics	GENDER		P-value	AGE		P-value	Total
	Men	Women		< 60 years	≥60 years		
Age (years) n	80	121	0,068	150	51	0,000(*)	201
Mean ± SD	47,1 ± 13,1	50,9 ± 15,2		43,3 ± 10,7	67,6 ± 7,1		49,4 ± 14,5
Rank	16 – 77	17 – 89		16 – 59	60 – 89		16 – 89
Median	47,5	52		44	66		51
Interquartile Range	38-57	40-61		35-52	62-69		39-60

Weight (Kg) n	80	121	0,000(*)	150	51	0,013(*)	201
Mean ± SD,	81,5 ± 14,4	70,8 ± 9,8		76,4 ± 13,1	71,2 ± 11,8		75,1 ± 12,9
Rank	48 – 131	47 – 98		50 – 131	47 – 99		47 – 131
Median	80	69		74	70		72
Interquartile Range	72-91	64-77		68-82	63-78		67-82
Height (m) n	80	121	0,000(*)	150	51	0,013(*)	201
Mean± SD	1,69 ± 0,07	1,59 ± 0,05		1,64 ± 0,08	1,60 ± 0,08		1,63 ± 0,08
Rank	1,47 – 1,90	1,47 – 1,79		1,47 – 1,90	1,47 – 1,87		1,47 – 1,90
Median	1,69	1,60		1,63	1,60		1,63
Interquartile Range	1,65-1,76	1,55-1,63		1,58-1,69	1,55-1,65		1,58-1,68
Body mass index n	80	121	0,738	150	51	0,221	201
Mean ± SD	28,2 ± 4,5	28 ± 4,2		28,3 ± 4,4	27,4 ± 4,0		28,1 ± 4,3
Rank	21,3 – 41,6	18,6 – 43,7		18,6 – 41,6	20,8 – 43,7		18,6 – 43,7
Median	27	28		28	27		28
Interquartile Range	25-31	26-30		25-31	25-29		26-30
Cervical circumference (cm) n	69	107	0,000(*)	132	44	0,107	176
Mean ± SD	39,2 ± 3,3	35 ± 3,1		36,9 ± 3,9	35,8 ± 3,3		36,6 ± 3,8
Rank	29 – 46	27 – 44		27 – 46	29 – 44		27 – 46
Median	39	35		36	36		36
Interquartile Range	37-41	33-37		35-39	33-37		34-39
Waist circumference (cm)	66	101	0,000(*)	125	42	0,345	167
n	90,8 ± 14,2	83,4 ± 11,6		86,9 ± 14,0	84,7 ± 10,3		86,3 ± 13,2
Mean± SD	69 – 130	60 – 112		60 – 130	63 – 112		60 – 130
Rank	87	84		86	85		86
Median	80-100	74-92		78-96	79-91		78-94
Interquartile Range							
Hip circumference (cm) n	66	101	0,268	125	42	0,752	167
Mean± SD	101,6 ± 15,6	98,7 ± 16,2		100,1 ± 16,3	99,2 ± 15,1		99,9 ± 16
Rank	70 – 139	66 – 134		68 – 139	66 – 126		66 – 139
Median	100	98		100	100		100
Interquartile Range	91-113	86-110		90-113	86-110		89-113

Waist-to-hip ratio n	66	101	0,001(*)	125	42	0,485	167
Mean ± SD	0,90 ± 0,1	0,85 ± 0,08		0,87 ± 0,09	0,86 ± 0,09		0,87 ± 0,09
Rank	0,72 – 1,2	0,6 – 0,99		0,60 – 1,2	0,68 – 1,1		0,6 – 1,2
Median	0,87	0,85		0,86	0,86		0,86
Interquartile Range	0,84-0,94	0,80-0,91		0,82-0,92	0,78-0,93		0,81-0,92
Evolution time (years) n							
Mean ± SD	80	121	0,586	150	51	0,001(*)	201
Rank	7,1 ± 5,1	6,7 ± 3,9		6,3 ± 3,7	8,6 ± 5,7		6,9 ± 4,4
Median	1 – 32	1 – 27		1 – 32	1 – 27		1 – 32
Interquartile Range	6,5	6		6	7		6
	4-9	4-8		4-8	4-11		4-9

Note. (*) Statistically significant differences.
Source: own elaboration.

Anthropometric measurements

The average weight was 75.1 ± 12.9kg, with a height of 1.63 ± 0.08m and BMI of 28.1 ± 4.3Kg/m2. The mean cervical, waist and hip circumference were 36.6 ± 3.8 cm, 86.3 ± 13.2 cm and 99.9 ± 16 cm, respectively, with a waist-to-hip ratio of 0.87 ± 0.09. Statistically significant differences (P value ≤ 0.05) were found in the analysis by gender in weight, height, cervical and waist circumference, and waist-to-hip ratio, which were higher in men than in women. In the analysis by age group, weight and height were equally significant, being higher in patients under the age of 60 years (as seen on Table 1).

Type of tumor and time of disease progression

The average time to diagnosis in years was 6.9 ± 4.4, and 8.6 ± 5.7 in those over 60 years old (P=0.001). Regarding the type of tumor (macro or microadenoma), no statistically significant differences were found by gender or age, however, 78.6% of the included population had a macroadenoma (Tables 1 and 2).

Table 2. Tumor type (%) by gender and age

Type of tumor	Gender		P-value	Age		P-value	Total (n=201)
	Men (n=80)	Women (n=121)		<60 years (n=150)	≥60 years (n=51)		
Macroadenoma	83,8	75,2	0,148	80,7	72,5	0,222	78,6
Microadenoma	16,3	24,8		19,3	27,5		21,4

Source: own elaboration.

Clinical manifestations and comorbidities

The most commonly reported clinical manifestations at diagnosis were the growth of hands (68.7%), feet (62.7%), and face (54.2%). Less frequent symptoms include snoring (2.5%), blindness (1.5%) and galactorrhea (1.0%). Statistically significant differences were found in the analysis by gender in the decrease in libido (P=0.017), which was reported more frequently in men than in women. In terms of age group, depression was the predominant symptom in those over 60 years old (P=0.002) (Table 3).

Table 3. Clinical manifestations (%) by gender and age

Clinical manifestations	Gender		P-value	Age		P-value	Total (n=201)
	Men (n=80)	Women (n=121)		<60 years (n=150)	≥60 years (n=51)		
Hand growth	67,5	69,4	0,774	70,7	62,7	0,292	68,7
Foot growth	61,3	63,6	0,732	66,0	52,9	0,096	62,7
Face growth	55,0	53,7	0,858	56,7	47,1	0,234	54,2
Headache	10,0	17,4	0,146	14,7	13,7	0,869	14,4
Fatigue	11,3	8,3	0,479	8,0	13,7	0,244	9,5
Arthralgias	8,8	5,8	0,419	5,3	11,8	0,139	7,0
Menstrual disturbances	-	9,9	0,009	8,0	2,0	0,091	5,9
Palpitations	6,3	5,0	0,695	6,0	3,9	0,560	5,5
Visual disturbances	7,5	4,1	0,310	5,3	5,9	0,882	5,5
Erectile dysfunction	13,8	-	0,000	6,7	2,0	0,159	5,5
Depression	3,8	5,8	0,509	2,0	13,7	0,002(*)	5,0
Hyperhidrosis	6,3	4,1	0,503	5,3	3,9	0,681	5,0
Constipation	1,3	6,6	0,050	4,0	5,9	0,585	4,5
Decreased libido	8,8	1,7	0,017(*)	5,3	2,0	0,275	4,5
Dysesthesias in the hands	2,5	4,1	0,528	2,7	5,9	0,305	3,5
Dyspnea	3,8	1,7	0,375	3,3	0,0	0,085	2,5
Snore	5,0	0,8	0,063	2,0	3,9	0,468	2,5
Blindness	1,3	1,7	0,816	0,7	3,9	0,130	1,5
Galactorrhea	0,0	1,7	0,153	0,7	2,0	0,453	1,0

Note. (*) Statistically significant differences
Source: own elaboration.

Hypertension was the most common comorbidity within the study population, occurring in 50.2%, followed by cardiomyopathy in 25.8%, with left ventricular hypertrophy being the most frequently reported in the echocardiogram, which was performed in 96% of the patients (n=193). Additionally, biventricular hypertrophy and valvular heart disease (tricuspid, mitral and aortic regurgitation) were observed, while less frequent findings (5.8%) included aortic dilatation, diastolic dysfunction, contractility disorder, dilation of the right chambers, and global heart disease.

A history of diabetes mellitus was reported in 21.9% of patients, while 4.5% had prediabetes. Polysomnography was performed in 40.2% (n =81) of patients, where sleep apnea was found in 55.5% (n=45), mostly classified as severe in 20.7% (n=17).

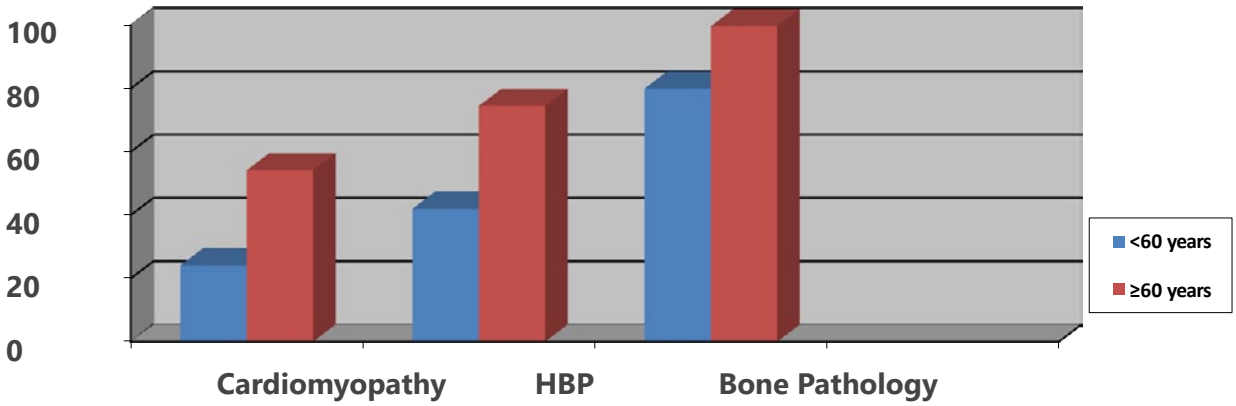
The presence of colonic pathology was evaluated through colonoscopy in 77.6% of patients, which was normal in more than half of them. Among the remaining cases, adenomatous polyps (12.1%) and hyperplastic polyps (11.5%) were reported as the main finding, followed by less frequent hemorrhoids, diverticular disease, cancer and colitis.

Electromyography was performed in 78.6% and carpal tunnel syndrome was confirmed in 19.6%. Thyroid ultrasound performed in 68% (n=137) of patients, identified multinodular goiter in 14.6% (n=20), diffuse goiter in 10.9% (n=15) and uninodular goiter in 10.2% (n=14).

Bone densitometry was performed on 18% (n=36) of the population, finding osteoporosis in 63.9% and osteopenia in 27.8%. Hypopituitarism was documented in 27.9% (n=56) of patients. Finally, the main finding was reported through hepatobiliary ultrasound indicating the presence of fatty liver in 29.6% (n=8), cholelithiasis in 25.9% (n=7) and biliary polyp in 3.7% (n=1), out of a total of 27 examinations performed.

In the bivariate analysis by gender, statistically significant differences were found for hypertension (P=0.038), colonic pathology (P=0.046), and hepatobiliary conditions (P=0.021), all of which were more common in women. In contrast, hypopituitarism (P=0.013) was higher in men. In the analysis by age groups, cardiomyopathy (P=0.001), hypertension (P=0.000) and bone pathology (osteoporosis and osteopenia) (P=0.025) were comorbidities found more frequently in the population over 60 years old (Figure 2).

2a. Gender



Comorbidity	Women (%)	Men (%)	P-value
High blood pressure	56,2	41,3	0,038
Colonic pathology	10,2	9,5	0,046
Hepatobiliary pathology	70	28,6	0,021
Hypopituitarism	21,5	37,5	0,013

2b. Age groups

Comorbidity	*< 60 years(%)*	*≥ 60 years(%)*	
Cardiomyopathy	24,1	54,2	0,001
HBP	42	74,5	0,000
Bone pathology	80	99,7	0,025

Figure 2. Comorbidities according to gender and age
Source: own elaboration

Types of treatment

Surgery

At the time of registration 62.2% (n=124) of the total study population had previously undergone surgery, with a transsphenoidal approach in 89.6% of cases. A second surgical intervention was required in 3% of patients, with the transsphenoidal route being the most common (83.3%), while the remaining cases underwent the transcranial procedure.

Surgery was prescribed after admission to the registry in 48.8% of the cases, and 96.9% were performed transsphenoidally. Statistically significant differences were found in the analysis by age group, as this type of treatment was more frequently prescribed in patients under the age of 60 years (P=0.001).

Radiotherapy

A total of 16% of the patients were admitted to the registry with previous radiotherapy treatment, most of which was holocranial, with radiosurgery used to a lesser extent. After joining the registry, radiotherapy was given to 11.5% of the population. The holocranial strategy being the most commonly used. When the gender analysis was performed, statistically significant differences were found, with this management strategy being prescribed more frequently to females (P=0.005) and to those under 60 years of age (P=0.042).

Medical Treatment

At the time of entry into the registry, 46.5% of the population had been receiving medical management, with lanreotide being the most frequently formulated medication in 63% of cases, and to a lesser extent octreotide in 20.7%, cabergoline in 10.9% and combined management in 5.4%, however, no statistically significant differences were found by gender or age groups. After entering the registry, medical management was prescribed as a new treatment strategy in 81.6% of cases, especially in the population over 60 years of age (P=0.024). Regarding the most formulated type of medication, lanreotide was again in first place at 60.4%, followed by octreotide, combined management, cabergoline, and finally pasireotide which was formulated to 3 patients (Table 4).

Immunohistochemistry

Immunohistochemistry information was obtained prior to entry into the registry in 60.7% of patients (n= 125), of whom the initial mean Ki-67 was 3.35 ± 3.0 and p53 was 1.36 ± 2.07. Of the 98 patients who underwent prescribed surgery after entering the registry, 100% of immunohistochemistry reports were obtained, with an average Ki-67 of 1.59 ± 1.79 and p53 of 0.44 ± 0.93. No statistically significant differences were found by gender or age group, however, there were significant differences when performing the global analysis (P=0.001).

Regarding immunohistochemistry stains, 99.2% of patients in the pre-registration group and 100% in the post-registration group were GH positive, associated or not with positivity in conjunction with other stains such as prolactin. In addition, higher expression of LH (P=0.027) and

ACTH (P=0.022) was found in women compared to men, with no significant differences by age group. Figure 3 summarizes the expression of stains by immunohistochemistry.

Table 4. Types of treatment by age and gender
4a. Previous types of treatment

Previous treatment	Gender		P-value	Age		P-value	Total
	Men	Women		<60 years	≥60 years		
Surgery (1)	65,0 (80)	60,3 (121)	0,504	63,3 (150)	58,8 (51)	0,566	62,2 (201)
Type of Surgery	(52)	(73)	0,725	(95)	(30)	0,106	(125)
1. Transesfenoidal	88,5	90,4		87,4	96,7		89,6
1. Transcranial	11,5	9,6		12,6	3,3		10,4
Surgery (2)	2,5 (80)	3,3 (121)	0,740	4,0 (150)	0,0 (51)	0,059	3,0 (201)
Type of Surgery	(2)	(4)	0,105	(6)			(6)
1. Transesfenoidal	50,0	100,0		83,3	-		83,3
1. Transcranial	50,0	0,0		16,7			16,7
Radiotherapy			0,330			0,042(*)	
1. Holocranial	(80)	(121)		(150)	(51)		(201)
Radiation	13,8	7,4		12,0	3,9		10,0
Therapy	5,0	6,6		4,0	11,8		6,0
2. Radiosurgery							
Medical Management	47,5 (80)	44,6 (121)	0,689	42,7 (150)	54,9 (51)	0,130	45,6 (201)
Type of Medical Management	63,3	63,0	0,464	65,6	57,1	0,130	63,0
Lanreotide	26,3	16,7		17,2	28,6		20,7
Octeotride	7,9	13,0		14,1	3,6		10,9
Cabergolina	2,6	7,4		3,1	10,7		5,4
Combined							

Note. (*) Statistically significant differences.
Source: own elaboration.

4b. Current types of treatment

Current treatment	Gender		P-value	Age		P-value	Total
	Men	Women		<60 years	≥60 years		
Surgery	46,3 (80)	50,4 (121)	0,563	55,3 (150)	29,4 (51)	0,001(*)	48,8 (201)
Type of Surgery Transesfenoidal Transcranial	(37) 97,3 2,7	(61) 96,7 3,3	0,871	(83) 96,4 3,6	(15) 100,0 0,0	0,314	(98) 96,9 3,1
Radiotherapy Holocranial Radiation Therapy Radiosurgery	(80) 5,0 5,0	(121) 0,0 12,4	0,005(*)	(150) 2,7 8,0	(51) 0,0 13,7	0,180	(201) 2,0 9,5
Medical Management	78,8 (80)	83,5 (121)	0,398	78,0 (150)	92,2 (51)	0,024(*)	81,6 (201)
Type of Medical Management Lanreotide Octeotride Cabergolina Combined Pasireotide	63,5 14,3 4,8 14,3 3,2	58,4 22,8 6,9 10,9 1,0	0,508	61,5 16,2 7,7 12,8 1,7	57,4 27,7 2,1 10,6 2,1	0,351	60,4 19,5 6,1 12,2 1,8

Note. (*) Statistically significant differences
Source: own elaboration.

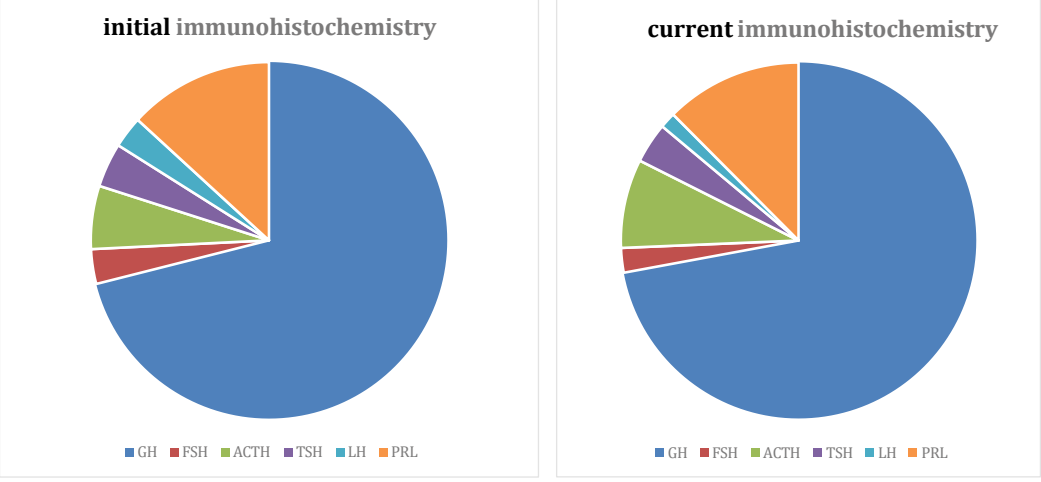


Figure 3. Initial and current immunohistochemistry expression
Note. (*) 99.2% and 100% of patients in baseline and current immunohistochemistry, respectively, were GH positive, associated or not with positivity in conjunction with other stains.
Source: own elaboration

Disease control

The levels of IGF-1 and GH were reported at the time of registration in a 100% of the patients, and at six months of control in 200 patients, due to the death of one patient. The mean baseline IGF-1 was 810 ± 383 (ng/ml) and GH was 16.12 ± 14.96 (ng/ml), the latter being higher in men (P=0.041). The mean control IGF-1 value was 256 ± 127 (ng/ml) and GH was 2.37 ± 2.56 (ng/ml), with statistically significant differences according to gender when higher IGF-1 levels were found in men compared to women (P=0.000). We evaluated whether there was a change in IGF-1 and GH values at both baseline and control, finding a 67% and 87% decrease in IGF-1 and GH levels respectively, with a (P=0.000). However, no differences by gender or age groups were observed (Figure 4).

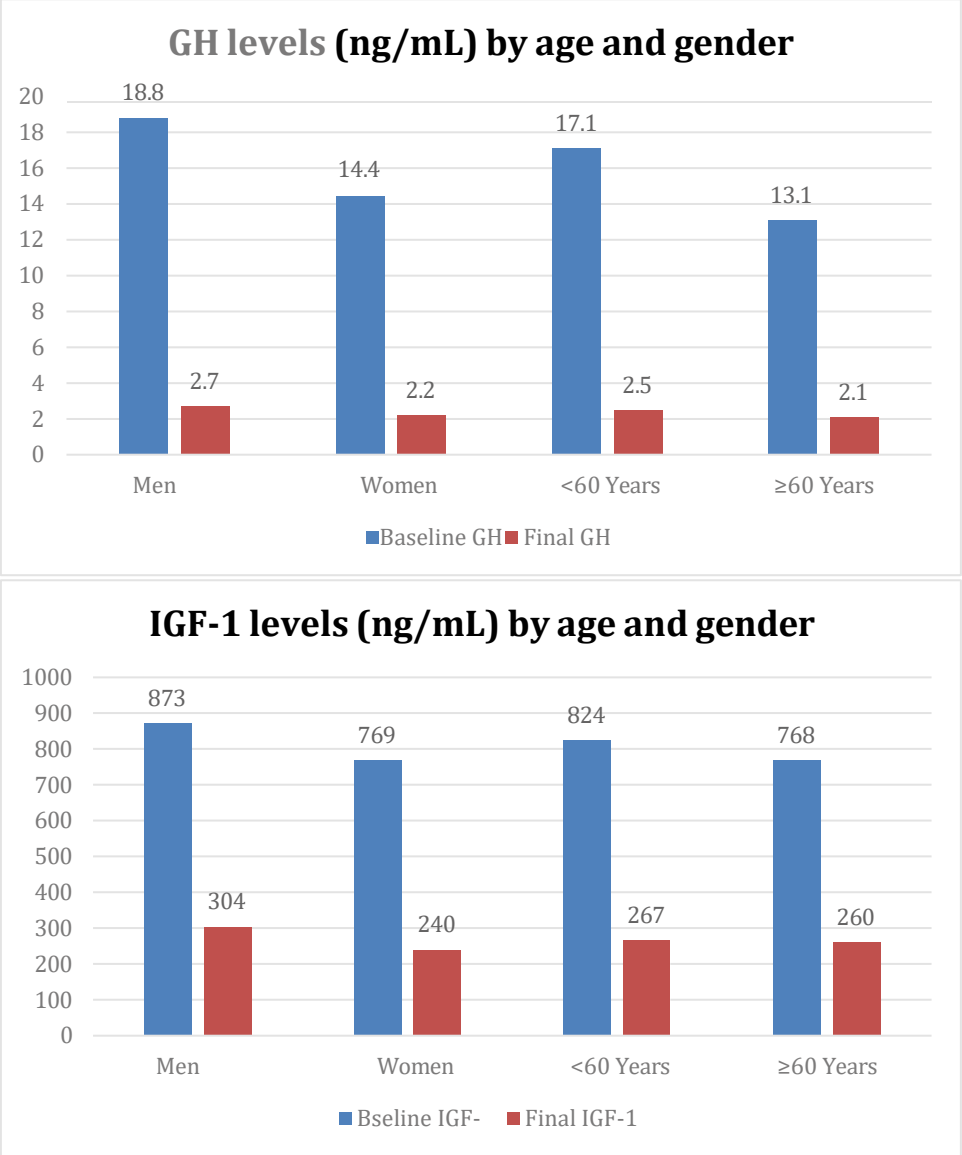


Figure 4. Baseline and final GH and IGF-1 levels
Source: own elaboration

At the time of entry into the registry, only 2% of the population was in control of the disease. Six months later, after each treating endocrinologist instituted a new treatment, readjusted the previous therapeutic management or continued with the same therapy, disease control was achieved in 30.5% of patients, with a P=0.000 in the overall analysis. However, no statistically significant differences were found in the analysis by gender or age groups.

Finally, a tree diagram was created to determine which type of treatment was associated with greater or lesser disease control. The analysis revealed that medical management, either in monotherapy or in combination with surgery, was associated with greater control of the disease, as opposed to less control with radiotherapy alone or in combination with surgery (Table 5).

Table 5. Type of treatment associated with greater and lesser control of the disease

Disease control (%)	Categorical variable			
	Men (n=80)	Women (n=121)	<60 years (n=150)	≥60 years (n=51)
Mayor control				
Surgery + Medical Medical treatment	32,7 38,0	36,8 36,2	38,5 31,1	23,3 56,1
Less control				
Radio + Surgery Radiotherapy	0,9 1,1	1,0 1,0	1,3 1,0	0,3 0,7

Source: own elaboration

Discussion

This study is the first analytical report of acromegaly in Colombia. Of the 201 patients included, female were predominant, a finding that correlates with 19 population registries where up to 68.4% of the population were women [9]. The mean age at registration was similar to the age range reported in several series, which varies between 41 and 50 years, placing the largest number of acromegalic patients under 60 years of age [8, 10, 22].

In most population registries, anthropometric measurements are not reported, and there are currently no measurements with which to compare. However, alterations in the regulation of body composition and a decrease in ghrelin levels have been described in patients with disease activity [23]. This finding could explain the high percentage of overweight people in this study, which correlates with the changes at the body level described in acromegaly [24, 25]. The findings revealed that weight, height, cervical and males, as well as in individuals under the age of 60, a finding that has not been reported in other registries, but resembles the behavior suggested in the literature [26].

The average time of evolution of the disease was 6.9 ± 4.4 years, however, in those patients over 60 years of age, a longer time was reported, which correlates with what was found in a French registry that compared a population with

acromegaly, where the time of evolution of the disease was 11 years vs. 7 years in those over and under 70 years of age, respectively [27]. The majority of patients presented a pituitary macroadenoma, with no differences by gender or age. This finding is consistent with a study of an Italian cohort that evaluated the impact of age and gender on the severity of acromegaly, where it was found that tumor size does not differ between men and women, although it tends to be greater in the young population under 40 years of age [28].

Acral overgrowth was the most frequently reported clinical manifestation, comparable to the findings usually described in the literature [16]. However, a decrease in libido was more commonly mentioned by men compared to women, similar to results found in a systematic review and meta-analysis conducted in Brazil [29] and the United States [30]. In addition, adults over 60 years of age reported greater depression compared to the younger population, a finding that could be explained by the association of acromegaly with decreased cognitive functions such as learning, planning, and attention [31], as well as the demonstrated increase in hippocampal gray and white matter [32]. These factors, combined with the aging process, social support and others, may predispose the elderly to experience depression [33].

Multiple comorbidities have been described in patients with acromegaly, among the most prevalent of which is hypertension, which represents the most frequent cardiovascular complication, secondary to the increase in peripheral vascular resistance attributed to the excess of GH and IGF-1, with a prevalence between 11% and 54.7% [34, 35], similar to the one found in this study. The most common metabolic disorder is diabetes mellitus, occurring in 30% to 50% of cases at the time of diagnosis, a higher percentage observed in this study [36]. Obstructive sleep apnea can be detected in more than 80% of patients diagnosed with acromegaly, which is a result of soft tissue hypertrophy at the pharyngeal level [37]. However, polysomnography was performed in less than 50% of the included population, which may lead to an underdiagnosis of this comorbidity.

The occurrence of carpal tunnel syndrome is correlated with disease duration and IGF-1 levels, with a prevalence ranging between 19% and 64% among those patients who underwent electromyography in this registry [36]. Finally, the excess of GH and IGF-1 translates into greater bone turnover along with deterioration of cortical and trabecular bone structure, which predisposes to the development of osteopenia and osteoporosis especially in the elderly [38]. On the other hand, it is also associated with a greater risk of the appearance of epithelial transformation of the colon, polyposis and cell differentiation in the thyroid gland [39], which explains the presence of these pathologies in the included population. Significant differences in comorbidities between gender and age groups were found in the study population. Women more frequently reported the presence of hypertension, as well as colonic and hepatobiliary pathology, while hypopituitarism was more prevalent in men. Additionally, adults older than 60 years old reported cardiomyopathy, hypertension, and bone pathology more frequently, findings that correlate with those reported worldwide [40–43].

The main goals of treatment in acromegaly are the normalization of GH and IGF-1 levels, associated with tumor size control and reduction of systemic complications derived from this disease [44]. Transsphenoidal surgery represents the main pillar of management of GH- producing pituitary tumors in patients without high surgical risk, and was the most frequently prescribed treatment option, especially in patients under 60 years of age, comparable to that described by Dupuy et al. [25], who reported surgical maneuvering in 90% of patients under 70 years of age and only in 44% of older patients. The choice of surgical management should be individualized, as comorbidities and increased risk in elderly patients may limit its use in this population [45].

Radiation therapy is indicated after failed surgery, medical therapy that is not available, not tolerated, or lack of control with it [17]. At the time of entry into the registry, 16% of patients had previously received radiotherapy, and it was newly prescribed as a management strategy for 11.5%. This percentage varies by country, which is why there is a wide range of use of radiotherapy

ranging from 9% to 87% [9]. In this study, it was more frequently prescribed in women and those under 60 years of age, similar to what was reported in the Swedish registry [46].

Medical therapy is the first-line of treatment, either as an alternative to surgery or as a second-line management [47]. At the time of registration, 46.5% of cases received medical management, and 81.6% were prescribed it as new therapy, with lanreotide being the most formulated drug. This therapeutic option was preferred in patients over 60 years of age, likely due to the ease of medical management in the elderly compared to invasive procedures, which may pose a higher risk in this age group [44]. Worldwide, the prevalence of use of this therapy varies between 0% and 78%, however, it is estimated that 60% of patients have a medical formulation in the course of their disease, which correlates with what is described in this registry [9].

Information concerning immunohistochemistry prior to registration was collected in 60.7% and in 100% of new post-registration reports. The mean levels of Ki-67 were similar and those of p53 were lower than those described in the literature [48]. Regarding immunohistochemical stains, 100% of patients were positive for GH associated or not with other types of stains, especially prolactin, which was an expected finding. However, greater expression of LH and ACTH was found in women, a finding that has not been described in other series [48]. There were no differences with respect to Ki67 values in terms of gender or age, which is consistent with what was described by Alimohamadi et al. [48].

Finally, disease control was assessed by the presence of normal age- and gender-adjusted IGF-1 associated with GH <1 ng/mL [49]. The levels of IGF-1 and GH at the time of registration were higher than those reported in the Mexican [10] and German [22] registries, as well as in the case series of 24 patients from a Colombian hospital [50], reflecting the low initial disease control. However, these levels showed a decrease in the follow-up evaluation at 6 months. This could be explained by the effect of the readjustment of the initial treatment in those who did not have adequate control. Both GH and IGF-1 levels were higher in men, comparable to what was found in a cohort study by Dal et al. [51], where IGF-1 levels were lower in women. However, neither GH nor tumor size differed between genders, in contrast to the findings of Colao et al. [28], where both markers were lower in women. Similarly, there were no differences with respect to age groups in both measurements, contrary to what was described by Taminoto et al. [52], who reported decreased GH and IGF-1 levels with increasing age.

Disease control was achieved in only 2% of the population at the time of registration and in 30.5% when re-evaluated 6 months later. This rate remains lower than those reported in various studies, where disease control ranges from 37% to 76% [9]. The combination of treatment that was associated with enhanced control was medical management, either in monotherapy or in conjunction with surgery. In contrast, radiotherapy alone or in conjunction with surgery was associated with lower control. This finding can be attributed to the higher prescription of surgery and medical management compared to the low percentage of patients who received radiotherapy, and the expected late effect of up to 10 years in the control of the disease in patients undergoing radiation [7]. The insufficient biochemical oversight of our registry can be attributed to the inability to obtain timely medical care and follow-up from a multidisciplinary team capable of undertaking a comprehensive intervention, which in turn necessitates the adoption of public health guidelines to lessen the obstacles to care for this group.

Limitations

This study brings together patients who have been evaluated by endocrinologists from fourteen departments in Colombia. However, it is noteworthy that the inclusion of other departments of significant importance in the country is lacking. Relevant information such as data concerning some comorbidities and initial immunohistochemistry was lost when data collection was carried out retrospectively.

Strengths

This is the first multicenter analytic study to compare gender and age in relation to patients

with acromegaly in Colombia, which favors local knowledge of the behavior of this rare clinical entity. The sample of patients is larger than other registries and includes anthropometric parameters that are not reported in other series. This allows us to set cut-off points for these measurements in this specific population group. Based on the information found and described, it is possible to open the field of research to other types of studies that respond to new gaps in knowledge that have not yet been studied, the integration of new patients from other regions of the country, and in the future, achieve the construction of a population registry with a greater number of variables.

Impact on public health

Acromegaly is a rare condition; however, it is associated with significant morbidity and mortality. The behavior of the disease in Colombia and the disparities between gender and age are largely unknown, due to the absence of studies that include our population. Using the results of this study, important clinical variables and the response to treatment are revealed, which contribute to a better medical examination of this entity in the country, allowing a timely diagnosis and initiation of treatment.

Recommendations

Considering the aforementioned findings and the insufficient control of the disease in Colombia, it is recommended that patients with acromegaly be enrolled in centers that facilitate interdisciplinary management and timely access to a therapeutic approach, with the ultimate objective of enhancing the management of the disease, which goes along with fewer medical complications and a better quality of life.

Conclusion

According to gender, men had higher anthropometric parameters and a predominance of decreased libido, while women had a higher frequency of medical comorbidities such as hypertension, and colonic and hepatobiliary pathology. Patients under 60 years of age had higher anthropometric parameters and the therapeutic strategy of choice was surgery. In people over 60 years of age, after acral changes and headache, depression was the main clinical manifestation, standing out for its significance in people over 60 years of age. The frequency of medical complications such as cardiomyopathy, hypertension and bone pathology was relevant. The study found no disparities in the degree of illness control across gender or age groups, but it does suggest that surgical management and medical intervention are associated with greater disease management.

Ethics

This study was approved by the ethics committee of all participating centers (RAPACO) and was conducted in accordance with the Declaration of Helsinki and good clinical practice. For the registry, all patients were informed about its characteristics and purpose, and all signed an informed consent. In addition, the study protocol was sent to the health research department of the Universidad Libre de Cali, where document #002 was issued, which was considered according to resolution 8430 of 1993, article 11, as a risk-free study.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

Authors' contributions

Alin Abreu Lomba: conceptualization, formal analysis, investigation, methodology, writing (peer review and editing corrections); Marcela Patiño Arboleda: conceptualization, formal analysis, investigation, methodology, writing (original draft); Natalia Buitrago Gómez: conceptualization, formal analysis, investigation, methodology, writing (original draft), writing (peer review and editing corrections); Reynaldo

Carvajal Ortiz: conceptualization, formal analysis, investigation, methodology, writing (peer review and editing corrections); Alejandro Pinzón Tovar: conceptualization, formal analysis, investigation, methodology, writing (peer review and editing corrections); David Alexander Vernaza Trujillo: formal analysis, investigation, methodology, writing (peer review and editing corrections); Rafael Castellanos Bueno: conceptualization, formal analysis, investigation, methodology, writing (peer review and editing corrections); Doly Pantoja Guerrero: conceptualization, formal analysis, investigation, methodology, writing (peer review and editing corrections); Henry Mauricio Arenas: conceptualization, formal analysis, investigation, writing (peer review and editing corrections); Alejandro Castellanos Pinedo: conceptualization, formal analysis, writing (peer review and editing corrections).

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