Persistence of Diabetes and Hypertension After Multimodal Treatment of Acromegaly

Baldomero González,[1]* Guadalupe Vargas,[1]* Ana Laura Espinosa de los Monteros,[1] Victoria Mendoza,[1] and Moisés Mercado[1]

[1]Endocrinology Service and the Experimental Endocrinology Unit, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City 01120, Mexico

Context: Diabetes and hypertension are frequent comorbidities of acromegaly.

Objective: To analyze the course of diabetes and hypertension at diagnosis and after multimodal therapy in a large cohort of patients with acromegaly.

Design and Setting: Retrospective study at a tertiary care center.

Patients and Methods: A total of 522 patients with acromegaly treated according to a preestablished protocol.

Main Outcome Measures: Prevalence of diabetes and hypertension and its relationship with biochemical indices of acromegalic control.

Results: The cohort was stratified according to disease activity upon last visit to clinic: (1) surgical remission (n = 122), (2) pharmacologically controlled (n = 92), (3) active disease (n = 148), (4) insulinlike growth factor (IGF)-1 discordance (n = 64), and (5) growth hormone (GH) discordance (n = 96). The prevalence of diabetes and hypertension at diagnosis was 30% and 37%, respectively, and did not change upon the last visit (30.6% and 38%). Both comorbidities were more prevalent at diagnosis and on the last visit than in the general population. Diabetes was less prevalent on the last visit in patients who achieved surgical remission than in those who persisted with active disease (25% vs 40%, $P = 0.01$). Upon multivariate analysis, diabetes was associated with an IGF-1 at diagnosis $>2\times$ upper limit of normal, with the persistence of active acromegaly, the presence of hypertension upon the last visit, with the presence of a macroadenoma, and with female sex.

Conclusion: Our findings underscore the importance of an integral approach when managing these patients, focusing not only on the control of GH and IGF-1 levels but also on the timely diagnosis and the specific treatment of each comorbidity. (***J Clin Endocrinol Metab*** **103: 2369–2375, 2018)**

Acromegaly is a chronic and systemic disease whereby the long-term growth hormone (GH) and insulinlike growth factor (IGF)-1 excess results in a series of complications and comorbidities that eventually lead to a substantial compromise of quality of life and a reduced life expectancy (1). Conditions such as diabetes and hypertension are significantly more prevalent among patients with acromegaly than in the general population (1). Although the frequency rate of these conditions is similar among the different epidemiological studies, it seems likely that specific ethnogenetic and environmental factors of the background population without acromegaly may also play a role in determining their prevalence and severity (1–7). Such comorbidities can be present at diagnosis of the disease or may become apparent during the lifespan of the patient and may be affected by the different therapeutic interventions used to control hypersomatotropinemia (8–10). Evidence from both

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 8 February 2018. Accepted 26 March 2018.
First Published Online 30 March 2018

*These authors contributed equally to this study.

Abbreviations: BMI, body mass index; CI, confidence interval; CV, coefficient of variation; GH, growth hormone; IGF, insulinlike growth factor; IQR, interquartile range; OR, odds ratio; ULN, upper limit of normal.

countrywide registries and large single-center studies shows that the key to a successful reduction of the increased mortality rate in acromegaly is a multimodal intervention aimed not only at controlling GH and IGF-1 levels, but also at carefully diagnosing and treating these comorbidities individually (11).

With the currently available therapeutic interventions, most patients with acromegaly can achieve, if not an absolute normalization of the somatotropic axis, an unprecedented strict control of the GH and IGF-1 excess (12). Yet, little is known to what extent these therapeutic interventions modify the course and severity of acromegalic comorbidities. The purpose of this study was to analyze in detail the course of diabetes and hypertension in a large cohort of patients with acromegaly uniformly treated according to a preestablished protocol.

Patients and Methods

The study analyzed data from patients enrolled in the Acromegaly Clinic of the Hospital de Especialidades, Centro Médico Nacional Siglo XXI in Mexico City, between 2000 and 2015. This is a highly specialized, multidisciplinary clinic in which patients are diagnosed, treated, and followed according to a preestablished protocol. All subjects signed an informed consent on enrollment, and the protocol was approved by our local ethics and scientific committees. The main inclusion criterion was a minimum follow-up of 12 months. The main objective was to evaluate the prevalence and clinical characteristics of diabetes mellitus and hypertension on diagnosis and after multimodal treatment of acromegaly.

Definitions

Acromegaly was diagnosed based on the finding of a glucose-suppressed GH >1 ng/mL and an IGF-1 >1.2× the upper limit of normal (ULN) in a patient with the classical symptoms and signs of the disease. In most operated patients, the diagnosis was confirmed by a positive GH immunohistochemistry of the adenoma. Diabetes mellitus was defined as the presence of a fasting hyperglycemia ≥126 mg/dL (7 mmol/L) and/or a blood glucose level >200 mg/dL (11.1 mmol/L) 120 minutes after a 75 g-glucose load. Hypertension was considered to be present if the systolic or diastolic values exceeded 140 and 90 mm Hg, respectively. Blood pressure was measured using a standard sphygmomanometer in the seating position every time the patient attended clinic. Hypertension and diabetes at the last visit was defined by the persistent need for antihypertensive and antidiabetic medications, respectively.

For the purpose of this study patients were grouped according to the disease activity status upon their last visit to clinic as follows:

1. Patients in remission: Surgically treated patients with postoperative glucose-suppressed GH <1 ng/mL and an IGF-1 <1.2× ULN. None of these patients had received radiation therapy.
2. Patients with controlled disease: Patients adequately controlled with first-generation somatostatin analogs (basal GH <1 ng/mL and IGF-1 <1.2× ULN), the majority of them on a secondary basis, after failed transsphenoidal surgery.
3. Patients with active disease: Surgically treated patients with persistent acromegalic biochemical activity (glucose-suppressed GH >1 ng/mL and IGF-1 >1.2× ULN) who at the time of the last visit were not receiving any adjuvant treatment and patients treated with somatostatin analogs who had not achieved control (basal GH >1 ng/mL and IGF-1 >1.2× ULN).
4. Patients with IGF-1 discordance: IGF-1 >1.2× ULN along with a glucose suppressed GH <1 ng/mL.
5. Patients with GH discordance: Glucose-suppressed GH >1 ng/mL, along with an IGF-1 <1.2× ULN.

Hormonal measurements

From 2000 to 2008, GH was measured by means of the Immulite two-site chemiluminescent assay (Diagnostic Products Corporation, Los Angeles, CA), with a sensitivity of 0.01 ng/mL and intra- and interassay coefficients of variation (CVs) of 6%. As of 2009, GH was determined using the Diasorin-Liaison assay (Salugia, Italy), which has a detection limit of 0.009 ng/mL and intra- and interassay CV of 2.5% and 5.8%, respectively. The International Reference Preparation used in these GH assays is the World Health Organization second 95/574.

IGF-1 was separated from its binding proteins by acid-ethanol extraction before immunoassay. From 2000 to 2008, we used the Diagnostic Systems Laboratory 2-site chemiluminescent assay (DSL, Webster, TX) with intra- and interassay CVs of 2.6% and 4.4%, respectively. Since 2009, IGF-1 has been determined by the Diasorin-Liaison chemiluminescent assay. The International Reference Preparation in these IGF-1 assays is World Health Organization second 02/254. We established our own normative IGF-1 data analyzing serum samples from 400 healthy individuals.

Statistical analysis

The prevalence of diabetes and hypertension was compared against the figures of the 2016 National Health and Nutrition Survey (Encuesta Nacional de Salud y Nutrición), which evaluates a representative sample (n = 29,795) of the Mexican population ages 3 to >80 years (13). More specifically, hypertension was directly assessed by blood pressure measurement of 8054 adults, whereas the prevalence of diabetes was estimated from a sample of 9500 individuals ages 20 to 80 years (13).

Quantitative variables are presented either as means ± standard deviations or as medians with interquartile ranges (IQRs), according to their distribution. Data distribution was determined by means of the Shapiro-Wilks test. Quantitative variables were analyzed using Student *t*, Mann-Whitney *U*, or Wilcoxon test, whereas for qualitative variables we used either χ^2 or Fisher's exact tests. Cox proportional hazard analysis was used for multivariate analysis. $P < 0.05$ was considered statistically significant. We used as statistical software SPSS, version 17, and STATA, version 11.2.

Results

The studied population consisted of 522 patients (mean age, 44 ± 12.8 years; 64% women) who had complete

clinical and biochemical information upon diagnosis of the disease and after treatment. Median follow-up time was 7.4 years (IQR, 3 to 12). The cohort was stratified according to disease activity status as (1) patients in remission (n = 122, 23.6%), (2) patients with controlled disease (n = 92, 17.8%), (3) patients with active disease (n = 148, 28.6%), (4) patients with IGF-1 discordance (n = 64, 12.4%), and (5) patients with GH discordance (n = 96, 18.6%). Table 1 depicts the clinical, biochemical, and tumor size characteristics at diagnosis of the patients and the frequency of pituitary hormone deficiencies at the last visit. Median GH at diagnosis was significantly higher in those patients who, at the last visit, persisted with active disease [18.8 ng/mL (IQR, 8 to 40)] than in those who achieved surgical remission [9.05 ng/mL (IQR, 3.7 to 19.7), $P = 0.01$] or pharmacological control [13.2 ng/mL (IQR, 5.1 to 27), $P = 0.02$], or were IGF-1 discordant [9.3 ng/mL (IQR, 4.2 to 21), $P = 0.002$]. IGF-1 at diagnosis, on the other hand, was not different among the different disease activity status categories. Patients with active acromegaly on last visit harbored macroadenomas more frequently than those achieving remission (78% vs 61%, $P = 0.05$).

Upon diagnosis, diabetes and hypertension were present in 30% and 37% of the patients, respectively, and the prevalence of these comorbidities did not change when they were last seen in the clinic (30.6% and 38% for diabetes and hypertension, respectively) (Table 2). When the data were analyzed after stratifying for disease activity status, diabetes, but not hypertension, was significantly more prevalent on the last visit in patients who remained biochemically active (40%) or were IGF-1 discordant (37%) than in those who eventually achieved surgical remission (25%) ($P = 0.01$) (Table 2). The prevalence of these comorbidities, both at diagnosis and at the last visit, was significantly higher than that found in the general Mexican adult population (9.4% for diabetes, 25.4% for hypertension) (Table 2).

Because diabetes and hypertension are known to be significantly more frequent with advancing age, we analyzed their prevalence stratifying patients as younger and older than 30 years. At diagnosis and upon the last visit, both diabetes and hypertension were significantly more frequent among patients older than 30 years, regardless of the disease activity status eventually achieved by them (Table 3).

The prevalence of diabetes and hypertension on the last visit to the clinic was similar when we compared patients who achieved surgical remission with those who achieved biochemical control by means of pharmacological treatment. Patients who, at the last visit to clinic persisted with an IGF-1 above 1.2× ULN, had a significantly higher risk of having diabetes, regardless of the GH levels and the treatment modality [odds ratio (OR) 1.9; 95% confidence interval (CI), 1.27 to 2.85; $P = 0.001$]. Such an association was not found between IGF-1 and hypertension (OR, 1.19; 95% CI, 0.81 to 1.74; $P = 0.33$).

Upon multivariate analysis, the risk of having diabetes at the last visit to clinic was significantly associated with female sex, with harboring a macroadenoma, with an IGF-1 level >2× ULN at diagnosis, with the concomitant

Table 1. Baseline Characteristics of the Cohort

	Total	Remission	Controlled	Active	IGF-1 Discordance	GH Discordance
N	522	122	92	148	64	96
Age, y	44 ± 13	45.1 ± 12	41 ± 12	43 ± 12	47 ± 11	42 ± 15
Median BMI, kg/m^2	29.9 (26–33)	30.9 (27.5–35)	29.6 (27–34)	27.2 (24–31)	30.4 (27.3–34)	29.7 (27–32.6)
Female, %	64	56	68	67	44	77
Macro, %	71	61	71	78[a]	68	71
Median follow-up, y	7.4 (3–10)	6 (3–11)	9 (5–11)	5 (2–8)	8 (3–11)	6 (2–10)
Median Dx delay, y	5 (3–8)	5 (3–8)	5 (3–9)	5 (3–7)	6 (4–9)	5 (3–7)
Median GH at Dx, ng/mL	13.4 (5.2–29)	9.05 (3.7–19.7)	13.2 (5.1–27)	18.8 (8–40)[b]	9.3 (4.2–21)	14.2 (5–32)
Median IGF-1 at Dx, ×ULN	2.4 (1.7–3.2)	2.3 (1.7–2.9)	2.29 (1.6–2.6)	2.6 (1.8–3.7)[c]	2.33 (1.8–2.9)	2.38 (1.8–2.8)
PO XRT, %	20.1	0	17.4	30.4	12.5	16.6
Hypopituitarism on last visit, %						
TSH	21	20	26.6	7.8	21.8	19.3
ACTH	2.1	1.7	1.1	2.8	1.5	3.2
LH/FSH	1.7	3.3	0	2.1	3.1	0

To convert IGF-1 to SI units (nmol/L), multiply by 0.131. To convert GH to SI units (mU/L), multiply by 3.

Abbreviations: Dx, diagnosis; LH/FSH, luteinizing hormone/follicle-stimulating hormone; PO XRT, postoperative radiation therapy; TSH, thyrotropin.

[a] Active vs remission, $P = 0.01$; active vs controlled, $P = 0.02$; active vs IGF-1 discordant, $P = 0.002$.

[b] Active vs remission, $P = 0.05$.

[c] Active vs remission, $P = 0.08$.

Table 2. Prevalence of Diabetes and Hypertension at Dx and Upon Last Visit in Patients With Acromegaly Compared With Rates Observed in the General Mexican Population

	Total (N = 522), %	Remission (N = 122), %	Controlled (N = 92), %	Active (N = 148), %	IGF-1 Discordant (N = 64), %	GH Disccordant (N = 96), %	ENSANUT (N = 9500)[a]
Diabetes							
At diagnosis	30	27	29	36	35	25	9.4% (OR, 4.05;
Last visit	30.6	25[b]	29	40	37	22	95% CI, 3.29-4.97; $P < 0.001$)
Hypertension							25.5% (OR, 1.74;
At diagnosis	37	39	28	40	44	31	95% CI, 1.44-2.11;
Last visit	38	48	30	38	45	29	$P < 0.001$)

[a] ENSANUT-2016: Encuesta Nacional de Salud y Nutrición, National Health and Nutrition Survey.

[b] $P = 0.01$ remission vs active and remission vs IGF-1 discordant.

presence of hypertension and with the persistence of acromegalic activity (Table 4). The risk of having hypertension, on the other hand, was only significantly associated with an IGF-1 at diagnosis >2× ULN, the coexistence of diabetes, and the persistence of biochemical acromegalic activity (Table 4).

At the last visit, 160 patients had diabetes and 198 had hypertension. Median follow-up time was the same for subjects with and without diabetes or hypertension. Metformin was used in all patients as the main antidiabetic medication; glyburide and insulin were used in 50% and 20% of the patients, respectively. Median glycosylated hemoglobin was 6% (IQR, 5.7 to 6.2) and did not differ between groups. Losartan was the most commonly prescribed antihypertensive medication and it was used alone or combined with metoprolol, hydrochlorothiazide, or amlodipine. Neither the presence of diabetes nor of hypertension was associated with a higher body mass index (BMI). Diabetes control, as judged from glycosylated hemoglobin levels did not correlate with BMI. Similarly, blood pressure control, as judged by the number of antihypertensive medications required to maintain a normal reading, did not correlate with BMI.

Discussion

Type 2 diabetes mellitus and hypertension are among the most common comorbidities of acromegaly and potentially contribute to the increased cardiovascular risk of these patients (1). Despite being both pathophysiologically linked to the GH and IGF-1 excess, several other genetic as well as environmental factors contribute to their pathogenesis (14). The GH excess in acromegaly leads to an increased insulin resistance with a substantial reduction in peripheral glucose uptake but also results in increased hepatic glucose production, mostly from enhanced gluconeogenesis (15, 16). Although in most patients with acromegaly, the euglycemic state is maintained at the expense of an increased insulin secretion, fasting hyperglycemia appears in some of them upon exhaustion of the β-cell secretory capacity (17). The pathophysiology of hypertension in acromegaly includes a GH-induced increment in renal tubular reabsorption of sodium and water, which in turn results in an increased plasma volume and perhaps also an increment in cardiac output and peripheral vascular resistance (18). Although one would expect a higher prevalence of

Table 3. Prevalence of Diabetes and Hypertension According to Age and Disease Activity Status at Diagnosis and at Last Visit

	Remission			Controlled			Active		
	<30 (n = 17)	>30 (n = 105)	P^a	<30 (n = 22)	>30 (n = 70)	P^a	<30 (n = 27)	>30 (n = 121)	P^a
Diabetes									
At diagnosis	14%	29%	0.05	10%	33%	0.05	14%	40%	0.05
Last visit	14%	26%	0.05	20%	30%	0.06	32%	41%	0.01
P^b	0.6	0.8		0.5	0.6		0.6	0.5	
Hypertension									
At diagnosis	29%	44%	0.05	5%	38%	0.05	23%	43%	0.05
Last visit	29%	52%	0.02	15%	35%	0.05	14%	43%	0.001
P^b	0.96	0.80		0.45	0.6		0.56	0.86	

[a] P younger than 30 vs older than 30 y.

[b] P at diagnosis vs upon last visit.

Table 4. Multivariate Analysis (Cox Proportional Hazard Ratio) Using Diabetes and Hypertension at the Last Visit as End Points

	Diabetes at Last Visit		Hypertension at Last Visit	
	HR (95% CI)	*P*	HR (95% CI)	*P*
At diagnosis				
Age, y	1.01 (0.99–1.03)	0.05	1.02 (1.01–1.03)	0.01
Female	1.53 (1.04–2.27)	0.03	0.96 (0.69–1.34)	0.84
BMI	1.01 (0.99–1.02)	0.1	0.99 (0.99–1.01)	0.59
Macroadenoma	1.56 (1.03–2.36)	0.03	1.29 (0.91–1.84)	0.15
GH >10 ng/mL	0.78 (0.54–1.13)	0.19	0.61 (0.44–0.85)	0.4
IGF-1 >2× ULN	1.67 (1.17–2.39)	0.004	1.81 (1.30–2.52)	0.000
At last visit				
Active acromegaly	1.82 (1.15–3.03)	0.01	1.61 (1.02–2.55)	0.04
Hypopituitarism	0.93 (0.83–1.05)	0.3	0.90 (0.80–1.01)	0.08
Diabetes	—	—	1.42 (1.03–1.96)	0.028
Hypertension	1.68 (1.19–2.37)	0.003	—	—

these conditions in populations genetically more prone to develop them, data from several single-center studies (9, 10, 14, 19, 20) as well as from acromegaly registries (2–7) reveal a rather consistent rate among populations of different ethnic backgrounds from different countries. Upon the diagnosis of acromegaly, diabetes has been reported to be present in 20% to 35% of the patients, whereas hypertension occurs in 30% to 40%. To our knowledge, the current study is the largest-scale, single-center study evaluating the prevalence of hypertension and diabetes in acromegaly at diagnosis and on long-term follow-up after multimodal therapy. Although the principal limitation of our study is its retrospective nature, this weakness is at least partially overcome by the fact that all patients were followed according to a preestablished protocol. We have demonstrated that these comorbidities persist after many years of follow-up and that their prevalence remains above the rate found in the general population without acromegaly. We can speculate that after several years of GH and IGF-1 excess, some of the changes in insulin secretion and sensitivity become irreversible. Similarly, the long-term exposure to excessive amounts of GH may result in irreversible changes in vascular endothelial function. Whereas the prevalence of diabetes at the last visit was clearly higher in patients who persisted biochemically active than in those achieving either surgical remission or pharmacological control, the prevalence of hypertension did not seem to be modified by the successful treatment of acromegaly. It is noteworthy that metabolic control of our patients with diabetes was exceptional, as reflected by their near-normal glycosylated hemoglobin levels. This is in sharp contrast to what occurs in patients with diabetes without acromegaly in Mexico and is likely the result of the close surveillance of the patients enrolled in our Acromegaly Clinic. We have previously postulated that such a tight control of comorbidities is the reason why neither diabetes nor hypertension has a substantial effect on mortality rate (11).

Our results are in general agreement with the few, smaller scale published studies that have addressed this issue. Jonas *et al.* (21) evaluated 57 patients with acromegaly and found that the prevalence of diabetes was very similar at diagnosis (25%) and upon the last visit (32%), independently of whether patients were surgically cured (n = 20), pharmacologically controlled (n = 28), or biochemically active (n = 9). More important perhaps was their finding of a greater loss of β-cell function in pharmacologically controlled patients than in surgically cured patients (21). Carmichael *et al.* (22) also found the same degree of persistence of diabetes and hypertension when comparing the prevalence found at diagnosis with that found upon the last visit to the clinic after a median follow-up of 5.8 years. Interestingly, similar to our results, the authors found the prevalence for diabetes and hypertension to be somewhat lower in the patients achieving biochemical control than in those who remained biochemically active (22). More recently, Rochette *et al.* (23) evaluated the prevalence of glucose and lipid metabolism abnormalities as well as hypertension in 130 patients with acromegaly at diagnosis and after surgical or medical treatment and compared them with the prevalence figures found in the general French population (23). In this series, the prevalence of both diabetes and hypertension remained unchanged upon follow-up and, in the case of diabetes, still higher than in the general French population.

The relationship between GH and IGF-1 levels and glucose homeostasis or hypertension in acromegaly is rather controversial (16). Studies in untreated patients with acromegaly reveal conflicting results as to whether GH, IGF-1, or both correlate with diabetes or hypertension (9, 10, 14). We have previously found in a smaller

but still very substantial group of patients with acromegaly (n = 257) that subjects with diabetes at diagnosis had significantly higher IGF-1 levels than those with normal glucose metabolism or with glucose intolerance (9). Such an association between diabetes and IGF-1 was more recently confirmed by data from the Mexican Acromegaly Registry, in which all of our patients are included (6). Although in the current study we found the same prevalence of diabetes and hypertension at diagnosis and upon the last visit to clinic, a stratified analysis revealed that, at the last visit, diabetes but not hypertension was indeed associated with an abnormally elevated IGF-1 level. Furthermore, a multivariate analysis revealed that the risk of having diabetes at the last visit was significantly associated with an IGF-1 at diagnosis >2× ULN and with the persistence of acromegalic activity when the patient was last seen in the clinic.

Other independent risk factors for diabetes upon the last visit were female sex and the presence of a macroadenoma. We have previously reported a higher prevalence of diabetes in women than in men and in patients harboring macroadenomas than in those with microadenomas; however, these associations have not been documented in other studies (9). Regarding the sex difference, it may be simply the reflection of what occurs in the population without acromegaly because in Mexico the prevalence of diabetes is higher in women than in men (13). The reason larger adenomas are associated with an increased risk of diabetes may be that patients harboring macroadenomas usually have higher GH and IGF-1 levels and are less likely to achieve surgical remission or pharmacological control than those with microadenomas.

As in the general population, diabetes and hypertension frequently coexist in patients with acromegaly (4). We had previously reported that almost 60% of the patients with acromegaly and diabetes also had hypertension, compared with only 30% to 35% of subjects with acromegaly and normal glucose tolerance, glucose intolerance, or impaired fasting glucose (9). In the current study, the multivariate analysis showed that hypertension was an independent risk factor for the presence of diabetes, which in turn was itself significantly associated with the presence of hypertension upon the last visit.

We conclude that the general prevalence of diabetes and hypertension among patients with acromegaly remains higher than in the population without acromegaly several years after multimodal therapy. The frequency of diabetes but not of hypertension appears to be related to the biochemical control of acromegaly, particularly to IGF-1 concentrations. Our findings underscore the importance of an integral approach when managing patients with acromegaly, focusing not only on the control of GH and IGF-1 levels, but also on the timely diagnosis and the specific treatment of each comorbidity.

Acknowledgments

Correspondence and Reprint Requests: Moisés Mercado, MD, Sur 132, #142, Suite 210, Colonia las Américas, Mexico City 01120, Mexico. E-mail: mmercadoa@yahoo.com.

Disclosure Summary: The authors have nothing to disclose.

References

1. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev*. 2004;**25**(1):102–152.
2. Alexopolou O, Bex M, Abs R, T'Sjoen G, Velkariers B, Maiter D. Divergence between growth hormone and insulin-like growth factor-1 concentrations in the follow-up of acromegaly. *J Clin Endocrinol Metab*. 2008;**93**(4):1324–1330.
3. Sesmilo G, Gaztambide S, Venegas E, Picó A, Del Pozo C, Blanco C, Torres E, Álvarez-Escolà C, Fajardo C, García R, Cámara R, Bernabeu I, Soto A, Villabona C, Serraclara A, Halperin I, Alcázar V, Palomera E, Webb SM, Investigators REA; REA investigators. Changes in acromegaly treatment over four decades in Spain: analysis of the Spanish Acromegaly Registry (REA). *Pituitary*. 2013;**16**(1):115–121.
4. Petersenn S, Buchfelder M, Gerbert B, Franz H, Quabbe HJ, Schulte HM, Grussendorf M, Reincke M; Participants of the German Acromegaly Register. Age and sex as predictors of biochemical activity in acromegaly: analysis of 1485 patients from the German Acromegaly Register. *Clin Endocrinol (Oxf)*. 2009;**71**(3):400–405.
5. Arosio M, Reimondo G, Malchiodi E, Berchialla P, Borraccino A, De Marinis L, Pivonello R, Grottoli S, Losa M, Cannavò S, Minuto F, Montini M, Bondanelli M, De Menis E, Martini C, Angeletti G, Velardo A, Peri A, Faustini-Fustini M, Tita P, Pigliaru F, Borretta G, Scaroni C, Bazzoni N, Bianchi A, Appetecchia M, Cavagnini F, Lombardi G, Ghigo E, Beck-Peccoz P, Colao A, Terzolo M; Italian Study Group of Acromegaly. Predictors of morbidity and mortality in acromegaly: an Italian survey. *Eur J Endocrinol*. 2012;**167**(2):189–198.
6. Portocarrero-Ortiz LA, Vergara-López A, Vidrio-Velázquez M, Uribe-Díaz AM, García-Dominguez A, Reza-Albarrán AA, Cuevas-Ramos D, Melgar V, Talavera J, Rivera-Hernández AJ, Valencia-Méndez CV, Mercado M; Mexican Acromegaly Registry Group. The Mexican Acromegaly Registry: clinical and biochemical characteristics at diagnosis and therapeutic outcomes. *J Clin Endocrinol Metab*. 2016;**101**(11):3997–4004.
7. Maione L, Brue T, Beckers A, Delemer B, Petrossians P, Borson-Chazot F, Chabre O, François P, Bertherat J, Cortet-Rudelli C, Chanson P; French Acromegaly Registry Group. Changes in the management and comorbidities of acromegaly over three decades: the French Acromegaly Registry. *Eur J Endocrinol*. 2017;**176**(5):645–655.
8. Vitale G, Pivonello R, Auriemma RS, Guerra E, Milone F, Savastano S, Lombardi G, Colao A. Hypertension in acromegaly and in the normal population: prevalence and determinants. *Clin Endocrinol (Oxf)*. 2005;**63**(4):470–476.
9. Espinosa-de-los-Monteros AL, González B, Vargas G, Sosa E, Mercado M. Clinical and biochemical characteristics of acromegalic patients with different abnormalities in glucose metabolism. *Pituitary*. 2011;**14**(3):231–235.
10. Dreval AV, Trigolosova IV, Misnikova IV, Kovalyova YA, Tishenina RS, Barsukov IA, Vinogradova AV, Wolffenbuttel BHR.

Prevalence of diabetes mellitus in patients with acromegaly. *Endocr Connect*. 2014;**3**(2):93–98.
11. Mercado M, Gonzalez B, Vargas G, Ramirez C, de los Monteros AL, Sosa E, Jervis P, Roldán P, Mendoza V, López-Félix B, Guinto G. Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. *J Clin Endocrinol Metab*. 2014;**99**(12): 4438–4446.
12. Espinosa E, Ramirez C, Mercado M. The multimodal treatment of acromegaly: current status and future perspectives. *Endocr Metab Immune Disord Drug Targets*. 2014;**14**(3):169–181.
13. National Institute of Health, Ministry of Health. National Health and Nutrition Survey, halfway results 2016 [in Spanish]. Available at: https://www.gob.mx/cms/uploads/attachment/file/209093/ENSANUT.pdf. Accessed 20 April 2018.
14. Colao A, Baldelli R, Marzullo P, Ferretti E, Ferone D, Gargiulo P, Petretta M, Tamburrano G, Lombardi G, Liuzzi A. Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. *J Clin Endocrinol Metab*. 2000;**85**(1):193–199.
15. Møller N, Jørgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev*. 2009;**30**(2):152–177.
16. Frara S, Maffezzoni F, Mazziotti G, Giustina A. Currents and emerging aspects of diabetes mellitus in acromegaly. *Trends Endocrinol Metab*. 2016;**27**(7):470–483.
17. Kasayama S, Otsuki M, Takagi M, Saito H, Sumitani S, Kouhara H, Koga M, Saitoh Y, Ohnishi T, Arita N. Impaired beta-cell function in the presence of reduced insulin sensitivity determines glucose tolerance status in acromegalic patients. *Clin Endocrinol (Oxf)*. 2000;**52**(5):549–555.
18. Kamenický P, Mazziotti G, Lombès M, Giustina A, Chanson P. Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications. *Endocr Rev*. 2014; **35**(2):234–281.
19. Biering H, Knappe G, Gerl H, Lochs H. Prevalence of diabetes in acromegaly and Cushing syndrome [in German]. *Acta Med Austriaca*. 2000;**27**(1):27–31.
20. Alexopoulou O, Bex M, Kamenicky P, Mvoula AB, Chanson P, Maiter D. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a study in 148 patients. *Pituitary*. 2014;**17**(1):81–89.
21. Jonas C, Maiter D, Alexopoulou O. Evolution of glucose tolerance after treatment of acromegaly: a study on 57 patients. *Horm Metab Res*. 2016;**48**(5):299–305.
22. Carmichael JD, Broder MS, Cherepanov D, Chang E, Mamelak A, Said Q, Neary MP, Bonert V. The association between biochemical control and cardiovascular risk factors in acromegaly. *BMC Endocr Disord*. 2017;**17**(1):15.
23. Rochette C, Graillon T, Albarel F, Morange I, Dufour H, Brue T, Castinetti F. Increased risk of persistent glucose disorders after control of acromegaly. *J Endocr Soc*. 2017;**1**(12):1531–1539.