Growth hormone control and cardiovascular function in patients with acromegaly

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Abstract

Background: Acromegaly is associated with cardiovascular alterations. Up to 50% acromegalic patients suffered from treatment failure after multiple modalities. We investigated correlation between cardiovascular function and control of growth hormone (GH) in acromegalic patients following transsphenoidal adenomectomy (TSA).

Methods: We recruited acromegalic patients who had undergone TSA between 2006 and 2014 in this cross-sectional study. Patients were assigned to group 1, controlled acromegaly (GH <1.0 ng/mL and normalized insulin-like growth factor-1 [IGF-1]); group 2, partially controlled acromegaly (either GH >1.0 ng/mL or non-normalized IGF-1); or group 3, uncontrolled acromegaly (GH >1.0 ng/mL and non-normalized IGF-1). Echocardiography evaluated the left ventricular mass index, left ventricular ejection fraction, and the early transmitral filling velocity (E)-to-late transmitral filling velocity (A) and the E-to-the early diastolic mitral annular velocity (E′) ratios. Carotid tonometry evaluated the intima-media thickness of the carotid artery, carotid-femoral pulse wave velocity, augmentation index, aortic characteristic impedance (*Zc*), and pulse pressure amplification.

Results: Thirty-three patients participated in this study. Fourteen of the 33 patients were males (42%). Mean age at diagnosis was 50.33 years (SD 18.45). Compared to patients in group 1, patients in group 3 had younger age and shorter years after operation, without statistical significance. Cumulative GH levels were progressively higher from group 1 to group 3, without statistical significance. The groups did not differ with respect to cardiovascular structure and function evaluated by echocardiography and carotid tonometry. Only *Zc* value had a difference that was of borderline significance (group 1: 109.13 ± 32.99; group 2: 129.30 ± 32.27; group 3: 159.56 ± 77.4 dynes × s/cm^5; ANOVA $p = 0.088$; $p = 0.086$ for group 1 vs group 3).

Conclusion: In the patients with acromegaly who had undergone TSA, cardiac structure and vascular stiffness did not differ among the groups with different levels of GH control.

Keywords: Acromegaly; Cardiovascular function; Growth hormone; Insulin-like growth factor-1

1. INTRODUCTION

Acromegaly is a chronic debilitating disorder caused by a growth hormone (GH)-producing pituitary adenoma, and it is characterized by increases in the serum levels of GH and insulin-like growth factor (IGF-1).[1] Active acromegaly is associated with a 2–4-fold increase in the risk of mortality, mainly from cardiovascular diseases and cancer.[2] Elevated GH and IGF-1 levels are thought to stimulate cardiomyocyte hypertrophy, which is most commonly characterized by concentric biventricular hypertrophy.[3] Other cardiac changes include left ventricular (LV) hypertrophy, diastolic dysfunction, systolic dysfunction during exercise, arrhythmias, and heart failure.[4,5]

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Acromegaly is also associated with vascular alterations[5]; however, inconsistent findings have been described. Smith et al[6] reported that the augmentation index (AI) was significantly increased in patients with active acromegaly, which was suggestive of high levels of arterial stiffness. Moreover, the AI was reduced in acromegalic patients who responded to treatment.[6] The aortic pulse wave velocity (PWV) was reported to be higher in acromegalic patients.[7] Treating acromegaly with a somatostatin receptor ligand reduced the aortic PWV and improved endothelial function, which was measured by low flow-mediated dilatation (FMD).[8] In contrast, Matsuda et al[9] used the cardio-ankle vascular index to assess arterial stiffness, and reported that patients with active acromegaly had lower levels of arterial stiffness than patients with controlled acromegaly.

In routine clinical practice, the fasting serum GH and IGF-1 levels are used to monitor disease activity in patients with acromegaly. A normal age-matched serum IGF-1 level and a fasting GH level <1.0 ng/mL are the accepted criteria used to define biochemical control in patients with acromegaly in this cohort.[10] Although, studies demonstrated that compared to untreated acromegaly, treatment of the disease resulted in improvements of cardiovascular function,[6,8] 10%–50% of acromegalic patients remained biochemically uncontrolled despite the use of multiple treatment modalities, including transsphenoidal adenomectomy

(TSA), medical treatment, and radiosurgery.[11] The impact of different GH levels on cardiovascular function is unknown in treated acromegalic patients. In this study, we aimed to undertake a detailed assessment of cardiovascular structure and function in patients with acromegaly who had undergone TSA and who had different levels of GH control.

2. METHODS

2.1. Subjects

Acromegalic patients who had undergone TSA for at least 1 year at a tertiary medical center between 2006 and 2014 were recruited to participate in this study. The patients' post-TSA acromegaly was considered active if the plasma GH nadir following a glucose load was >1 ng/mL. The patients with active acromegaly were treated with radiosurgery or long-acting somatostatin, or both, or neither of two. All of the patients underwent complete metabolic and endocrine screening. The patient exclusion criteria included hemodynamic instability, a previous myocardial infarction, thyrotoxicosis, rheumatic fever, endocarditis, anorexigen use, or connective-tissue disease. Based on previous study of Varadhan et al,[12] cumulative GH exposure is related to vascular comorbidities, years after operation and cumulative GH levels (defined as a sum of average GH in consecutive years between operation and cardiovascular examination) were recorded.

2.2. Study design

Echocardiography and carotid tonometry were performed, and the patients' blood pressures were measured in their right arms using a mercury sphygmomanometer while they were seated. Fasting blood samples were collected on the same morning to measure the levels of IGF-1, GH, glucose, hemoglobin A1c (HbA1c), total cholesterol, high-density lipoprotein-cholesterol, triglycerides, and creatinine. The clinical practice guideline applying for the cohort of present study was based on the consensus published in 2010.[10] The patients were assigned to group 1 that comprised those with controlled acromegaly (fasting GH ≤ 1.0 ng/mL and normalized IGF-1), group 2 that comprised those with partially controlled acromegaly (fasting GH >1.0 ng/mL or non-normalized IGF-1), or group 3 that comprised those with uncontrolled acromegaly (fasting GH >1.0 ng/mL and non-normalized IGF-1). Informed consents were obtained from all of the patients. The present study complied with the principles of the Helsinki Declaration, and was approved by Taipei Veterans General Hospital's Institutional Ethics Committee.

2.3. Cardiovascular examinations

One independent cardiologist analyzed all of the acromegalic subjects' cardiac and vascular parameters, and a second cardiologist reviewed these parameters. Echocardiographic measurements were obtained by observers in a blind manner. The echocardiographic studies were performed in the morning with the subjects in a supine left lateral decubitus position after resting for 15 minutes. The two-dimensional imaging of the longitudinal parasternal view was checked to avoid angulation of the ultrasonic beam and subsequent changes in the shape of the left ventricle. The LV internal dimensions, posterior LV wall thickness, and the interventricular septum thickness were measured in accordance with the recommendations from the American Society of Echocardiography.

The LV volumes were calculated using the cube formula. The LV mass (LVM) was calculated according to the Penn Convention,[13] and it was indexed to the patient's body surface area, which was calculated using the formula developed by Dubois and Dubois.[14] All echocardiographic tracings will be digitally stored and examined by one expert reader in a reading center to remove echocardiographic tracings of poor quality by uniform criteria and recalculate the data blindly. The LVM index (LVMI) provided by the control analysis will be used for calculations of mean data and correlations with blood pressure values.

Pulse-Doppler recordings with the sample volume positioned between the mitral leaflets were obtained from an apical four-chamber view to assess the LV filling dynamics. For each Doppler profile analyzed, the peak early (E) and late (A) transmitral filling velocities, the early diastolic mitral annular velocity (E′), the E/A ratio, and the E/E′ ratio were computed on-line. The brachial blood pressure was monitored and recorded during the echocardiographic examinations using an automated noninvasive blood pressure monitor that employed an oscillometric device.

Carotid tonometry was performed using a pencil-type tonometer that incorporated a high-fidelity strain-gauge transducer in a 7-mm-diameter flat tip (SPC-350; Millar Instruments Inc., Houston, Texas). The tonometric carotid pressure signal was digitized instantly at a rate of 250 Hz for off-line analysis. The right common carotid artery was scanned using a 7.5 MHz vascular probe that was incorporated into the echocardiographic unit. The carotid systolic diameter, diastolic diameter, and the intima-media thickness (IMT) of the posterior wall of the right carotid artery (i.e., the distance from the leading edge of the lumen-intimal interface to the leading edge of the media-adventitia interface) were measured on-line from digitized frozen longitudinal images.

Sequential non-directional Doppler flow (Parks Model 802 Doppler; Parks Medical Electronics, Inc., Aloha, OR) measurements and the simultaneous collection of electrocardiography data from the right carotid artery and right femoral artery determined the carotid-femoral PWV (cfPWV). The propagation time of the arterial pulse wave was obtained by measuring the time delay between the feet of the flow waveforms, which represents the difference in the time intervals between the peak of the R wave of the QRS complex and the foot of each flow wave. The cfPWV was calculated by dividing the measured external distance from the suprasternal notch to the right femoral pulse by the calculated time delay. The carotid AI, which was defined as the amplitude of the pressure wave above the systolic shoulder-to-the total pulse pressure (PP) ratio, was calculated using custom-designed software that locates the inflection point of the wave reflection on the upwards- or downwards-stroke of the pressure wave.

The aortic characteristic impedance *(Zc)* was estimated as $\Delta P/\Delta Q$, which represents the pressure change associated with an increase in flow from 0% to 95% peak flow in the time domain. The PP amplification was obtained by measuring the brachial and carotid blood pressures, and it was calculated as follows: PP amplification = (brachial pulse pressure – carotid pulse pressure)/brachial pulse pressure.

2.4. Assays

The standards for the GH immunoradiometric assay contain the 22K recombinant human GH, and they are calibrated to the World Health Organization reference preparation 88/624. In our laboratory, the intra-assay coefficient of variation (CV) is 3.1%, the inter-assay CV is 5.9%, and the assay's sensitivity is 0.05 ng/mL. The IGF-1 levels were measured using a radioimmunoassay and a polyclonal rabbit antibody to human IGF-1 (Nichols Institute Diagnostics, San Juan Capistrano, CA). The intra-assay CV is 4%, the inter-assay CV is 11%, and the assay's sensitivity is 13.5 ng/mL. The patients' IGF-1 levels were compared with age-appropriate normal ranges.

2.5. Statistical analyses

The statistical analyses were performed using PASW software, version 19.0 for Windows (IBM, Armonk, NY). Unless stated otherwise, all of the data are presented as the means and SDs or median and interquartile range. The variables were compared to determine the significance of any differences among the groups by using the analysis of variance (ANOVA) and post hoc testing using Fisher's multiple comparison tests. A two-tailed $p < 0.05$ was considered statistically significant. Continuous data were subjected to the Kolmogorov-Smirnov test to determine their distribution and differences between means were assessed by Mann-Whitney U test. Chi-square statistics test was used to assess differences between categorical variables.

3. RESULTS

Thirty-three patients with acromegaly who had undergone TSA participated in this study. Table 1 presents the treatment modalities, and the fasting GH and IGF-1 levels for each patient. Fourteen of the 33 patients were males (42%), and the mean ± SD age of the patients was 50.33 ± 18.45 years. The patients were assigned to three groups based on their fasting GH and IGF-1 levels, namely, group 1: the controlled acromegaly group, group 2: the partially controlled acromegaly group, and group 3: the uncontrolled acromegaly group, as described previously.

3.1. Patients' clinical characteristics and biochemical data

Table 2 summarizes the clinical characteristics of and the biochemical data from the three patient groups. The mean ± SD fasting GH and IGF-1 levels were significantly higher in group 3 compared with those in group 1 and group 2 ($p < 0.05$). The fasting GH level in group 2 was higher than that in group 1, but there was no difference between these groups in relation to the IGF-1 level. The mean ± SD age of the patients in group 3 was lower (41.5 ± 16.5 years) than those in groups 1 and 2 (56.4 ± 18.1 years and 59.7 ± 16.5 years, respectively), a difference that was not significant. Years after operation were progressively shorter while cumulative GH levels were progressively higher from group 1 to group 3, but without statistical significance ($p = 0.2$ and 0.12, respectively). The three groups were similar with respect to the body mass index and blood pressure. The biochemical parameters, including the fasting plasma glucose, HbA1c, total cholesterol, high-density lipoprotein-cholesterol, triglyceride, and creatinine levels, did not differ among the groups.

3.2. Cardiac structure and function

The three groups of acromegalic patients did not differ with respect to the LVMI, LV ejection fraction (LVEF), E/A ratio, or the E/E′ ratio (Table 3).

Table 1

Baseline characteristics of acromegalic patients status post-trans-sphenoidal adenomectomy

No.	Age	Sex	Years after operation	Radio surgery	Somatostatin analogs	Fasting GH (ng/mL)	Fasting IGF-1 (ng/mL)	IGF-1 normalized	Group
1	30	M	11	Yes	Yes	0.80	296	Yes	1
2	18	F	2	Yes	Yes	4.64	766	No	3
3	65	F	22	No	Yes	0.55	263	No	2
4	62	M	13	No	Yes	0.46	178	Yes	1
5	74	F	32	No	No	0.25	157	Yes	1
6	58	F	4	Yes	Yes	3.32	386	No	3
7	70	F	24	Yes	Yes	2.23	258	No	3
8	65	F	16	Yes	Yes	2.12	54.3	Yes	2
9	87	F	18	No	No	0.46	54.2	Yes	1
10	42	M	4	Yes	Yes	0.83	138	Yes	1
11	38	F	6	No	Yes	1.85	621	No	3
12	75	F	12	No	No	0.9	134	Yes	1
13	39	F	14	No	Yes	0.47	192	Yes	1
14	23	F	3	Yes	Yes	1.71	422	No	3
15	74	F	3	No	No	1.96	97	Yes	2
16	44	M	3	Yes	Yes	0.42	466	No	2
17	51	M	25	Yes	No	0.17	163	Yes	1
18	38	M	15	No	Yes	0.48	196	Yes	1
19	28	F	2	No	No	10.1	695	No	3
20	57	F	6	No	No	0.8	152	Yes	1
21	19	M	1	No	No	10.3	742	No	3
22	48	F	9	No	No	2.17	308	No	3
23	62	M	2	No	No	5.74	744	No	3
24	49	F	5	Yes	Yes	1.75	193	Yes	2
25	32	M	1	No	No	6.22	841	No	3
26	38	M	1	No	No	0.8	391	No	2
27	83	M	32	No	No	2.16	196	Yes	2
28	63	F	26	No	No	5.76	328	No	3
29	65	F	16	No	No	0.30	208	Yes	1
30	38	M	1	No	No	2.74	941	No	3
31	50	M	1	Yes	No	2.50	1232	No	3
32	40	F	3	No	No	29.0	520	No	3
33	36	M	1	No	No	8.23	933	No	3

Table 2

Clinical characteristics and biochemical data of acromegalic patients status post-trans-sphenoidal adenomectomy by different levels of fasting GH and IGF-1

	Group 1	Group 2	Group 3
	GH ≤ 1.0 ng/mL and normalized IGF-1	Either GH > 1.0 ng/mL or non-normalized IGF-1	GH > 1.0 ng/mL and non-normalized IGF-1
Number	11	7	15
Age (years)	30 to 87	38 to 83	18 to 70
Years after operation	14 (11 to 18)	5 (3 to 22)	2 (1 to 6)
Radiosurgery (yes/no)	3/8	3/4	5/10
Somatostatin analogs (yes/no)	5/6	4/3	5/10
Neither radiosurgery nor somatostatin analogs	5	3	9
Fasting GH (ng/mL)	0.54 ± 0.25	1.39 ± 0.77	5.29 ± 3.70[a]
Cumulative GH levels	6.58 (4.80 to 8.28)	8.75 (1.26 to 33.92)	10.3 (6.22 to 20.2)
Fasting IGF-1 (ng/mL)	169.8 ± 59.0	237.2 ± 149.1	647.8 ± 278.1[a]
SD score of IGF-1	–0.15 (–0.3 to 0.19)	0.78 (–0.70 to 2.22)	4.11 (2.67 to 8.17)[a]
Body height (cm)	168.2 ± 17.6	164.1 ± 11.1	167.1 ± 9.6
Body weight (Kg)	77.7 ± 22.4	71.3 ± 22.5	72.9 ± 16.4
BMI (Kg/m^2)	26.95 ± 3.66	25.95 ± 5.37	26.01 ± 4.99
Systolic blood pressure (mmHg)	125.9 ± 11.7	120.6 ± 12.9	121.9 ± 16.8
Diastolic blood pressure (mmHg)	78.7 ± 5.9	67.4 ± 5.7[b]	73.7 ± 11.8
Fasting plasma glucose (mg/dL)	125.3 ± 34.7	104.4 ± 4.8	102.8 ± 14.8
HbA1c (%)	6.82 ± 1.26	5.82 ± 0.43	6.20± 0.63
Total cholesterol (mg/dL)	173.0 ± 30.1	162.2 ± 39.6	170.4 ± 49.8
High density cholesterol (mg/dL)	48.6 ± 10.9	53.8 ± 12.5	58.6 ± 14.0
Triglyceride (mg/dL)	146.3 ± 77.1	79.0 ± 48.8	105.0 ± 49.8
Serum creatinine (mg/dL)	0.85 ± 0.27	0.74 ± 0.16	0.62 ± 0.15

BMI = body mass index; GH = growth hormone.

[a]$p < 0.05$ compared between group 3 vs 2 and group 3 vs 1. Ages are presented as ranges, other data are expressed in mean ± SD or median (interquartile range).

[b]$p < 0.05$ compared with group 1.

3.3. Vascular structure and function

Table 4 presents the data from the assessments of the acromegalic patients' vascular structure and function. Group 3 had the highest mean ± SD *Zc* value and group 1 had the lowest mean ± SD *Zc* value, a difference that was of borderline significance (group 1: 109.13 ± 32.99 dynes × s/cm^5; group 2: 129.30 ± 32.27 dynes × s/cm^5; group 3: 159.56 ± 77.4 dynes × s/cm^5; ANOVA $p = 0.088$; $p = 0.086$ for group 1 vs group 3). The other vascular function parameters assessed, including the carotid IMT, PP amplification, cfPWV, and AI, did not differ among the groups.

4. DISCUSSION

In this study of detailed assessment by using echocardiography and carotid tonometry, we demonstrated that following TSA for acromegaly, the different levels of GH control had no influence on cardiovascular structure and function. We also observed that patients who were not biochemically controlled are younger and had shorter disease duration.

The findings from an observational case-controlled study carried out by Colao et al,[15] showed that acromegalic patients

Table 3

Cardiac structure and function of acromegalic patients at least 1-year after trans-sphenoidal adenomectomy

	Group 1	Group 2	Group 3
	GH ≤ 1.0 ng/mL and normalized IGF-1	Either GH > 1.0 ng/mL or non-normalized IGF-1	GH > 1.0 ng/mL and non-normalized IGF-1
LVM index	100.5 ± 36.2	100.6 ± 19.4	88.5 ± 28.2
LVEF	63.9 ± 19.6	66.0 ± 11.3	65.6 ± 5.9
E/A ratio	0.99 ± 0.27	1.24 ± 0.60	1.30 ± 0.32
E/E′ ratio	10.33 ± 5.17	9.10 ± 1.75	8.95 ± 3.90

Data are expressed in mean ± SD.

E/A ratio = peak early (E) and late (A) trans-mitral filling velocities ratio; E/E′ ratio = peak early filling (E) to early diastolic mitral annular velocity (E′) ratio; LVEF = left ventricle ejection fraction; LVM index = left ventricle mass index.

Table 4

Vascular structure and function of acromegalic patients at least 1-year after trans-sphenoidal adenomectomy

	Group 1	Group 2	Group 3
	GH ≤ 1.0 ng/mL and normalized IGF-1	Either GH > 1.0 ng/mL or non-normalized IGF-1	GH > 1.0 ng/mL and non-normalized IGF-1
Carotid IMT (cm)	0.64 ± 0.21	0.62 ± 0.10	0.49 ± 0.15
bSBP (mmHg)	122.0 ± 17.7	116.7 ± 15.2	120.3 ± 18.8
bDBP (mmHg)	73.77 ± 13.46	68.86 ± 9.08	74.20 ± 14.03
bPP (mmHg)	48.18 ± 9.06	47.86 ± 11.47	46.13 ± 12.27
cSBP (mmHg)	113.8 ± 16.0	106.5 ± 16.0	113.2 ± 18.6
cDBP (mmHg)	75.14 ± 13.48	70.13 ± 8.98	73.94 ± 13.54
cPP (mmHg)	38.69 ± 7.32	36.38 ± 12.44	39.25 ± 12.02
cfPWV (cm/sec)	890.2 ± 309.5	794.7 ± 363.8	864.5 ± 395.9
AI	0.24 (0.14 to 0.31)	0.07 (–0.13 to 0.20)	0.14 (–0.10 to 0.33)
Zc (dynes × s/cm^5)	109.13 ± 32.99	129.30 ± 32.27	159.56 ± 77.4[a]
PP amplification	0.24 (0.18 to 0.32)	0.35 (0.24 to 0.43)	0.17 (–0.29 to 0.29)

Data is expressed in mean ± SD or median (interquartile range).

AI = augmentation index; bDBP = brachial diastolic blood pressure; bPP = brachial pulse pressure; bSBP = brachial systolic blood pressure; cDBP = central diastolic blood pressure; cfPWV = carotid-femoral pulse wave velocity; cPP = central pulse pressure; cSBP = central systolic blood pressure; IMT = intima-media thickness; PP amplification = pulse pressure amplification; *Zc* = aortic characteristic impedance.

[a]ANOVA $p = 0.088$, $p = 0.086$ group 1 vs group 3.

had lower LVEFs and E/As, and higher LVMIs compared with those in control individuals. In addition, diastolic dysfunction is a major complication in acromegalic patients, with a prevalence of approximately 29% in untreated patients, and this increases in patients with coexisting hypertension or glucose intolerance.[16] Successful TSA has been shown to markedly reduce the LVM and blood pressure, but only half of the patients show increases in diastolic filling.[17] The findings from several studies have shown that treating acromegalic patients with somatostatin analogs improves cardiac structure and function.[18–20] Although it is evident that cardiac function improves in treated acromegalic patients, our study's results showed that among the acromegalic patients who had undergone TSA and were grouped according to their level of GH control, cardiac function did not differ with respect to the LVMI, LVEF, E/A ratio, or the E/E´ ratio. Our study individuals all received TSA soon after acromegaly were diagnosed. Patient age could be taken as a surrogate of disease duration which plays a pivotal role in the acromegalic cardiomyopathy suggesting a potential cumulative effect of the exposure to chronic hormone excess.[12] Although our study cohort is too small in size to show significant difference in age and years after TSA between groups, the younger age and the shorter years after TSA of the uncontrolled group compared with the controlled group could have protective effect on heart and be the possible explanations.

The incidence of vascular alterations is higher in acromegalic patients compared with that in healthy individuals. This can be attributed to coexisting metabolic abnormalities, including hypertension and glucose intolerance, but the direct effects of excessively high GH levels on vascular function should also be considered. Carotid artery B-mode ultrasonography can be used to measure the IMT and FMD, and, hence, endothelial dysfunction. Patients with active acromegaly had lower FMD values and higher IMT than those in patients whose acromegaly were cured.[21] There are several other ways to evaluate arterial stiffness.[22–24] These studies concluded the level of arterial stiffness was higher in acromegalic patients compared with that in healthy individuals,[22,23] but no significant differences were noted between patients with active acromegaly and those whose acromegaly was in remission.[23] The PWV is a more frequently used parameter to evaluate arterial stiffness, but previous studies' results have shown inconsistent association.[7,24] Matsuda et al[9] also reported that the cardio-ankle vascular index was unexpectedly lower in 21 acromegalic patients compared with that in matched control individuals, indicating a reduction in arterial stiffness. In this study, there were no differences among the three groups with respect to vascular function. Of note, over half of the patients in the uncontrolled group (9/13, 69.2%) had not undergone radiosurgery nor received somatostatin analog therapy after TSA. The uncontrolled group also had the highest cumulative GH level. The uncontrolled group had the highest *Zc* value and the controlled group had the lowest *Zc* value, a difference that was of borderline significance. The *Zc* value provides an indication of the vascular stiffness of the proximal aortic root, which could be regarded as the earliest abnormality presented, whereas the cfPWV provides an evaluation of the spatially-averaged properties of the descending thoracic and abdominal aorta and the iliac artery, and is elevated at the more advanced stages of disease by a previous study of type 1 diabetic patients.[25]

This study had several limitations. First, the sample size is small which could have led to a type-2 statistical error and is unable to make solid conclusions. Second, in this retrospective observation study, multiple confounding factors, including pituitary hormone insufficiency is lacking, which may have impact on cardiovascular function. Third, the young age and short disease duration in uncontrolled patients may have protective effect on cardiovascular function but the outcomes remained statistically non-significant after multivariate logistic regression of the two factors (data not shown). However, in this study, we demonstrated the rigorous evaluations of the patients' cardiovascular structure and function in a real-world scenario of patients with different levels of GH control after TSA.

In conclusion, cardiac structure and vascular stiffness did not differ among different levels of GH control in patients with acromegaly, who had undergone TSA followed by treatments with somatostatin analogs and/or radiosurgery. Further large-scale studies maybe warranted to confirm these findings.

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REFERENCES

1. Barkan AL. Acromegaly. Diagnosis and therapy. Review guidelines for acromegaly management: an update. *Endocrinol Metab Clin North Am* 1989;**18**:277–310.
2. Melmed S. Acromegaly pathogenesis and treatment. *J Clin Invest* 2009;**119**:3189–202.
3. Pivonello R, Auriemma RS, Grasso LF, Pivonello C, Simeoli C, Patalano R, et al. Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities. *Pituitary* 2017;**20**:46–62.
4. Clayton RN. Cardiovascular function in acromegaly. *Endocr Rev* 2003;**24**:272–7.
5. Mosca S, Paolillo S, Colao A, Bossone E, Cittadini A, Iudice FL, et al. Cardiovascular involvement in patients affected by acromegaly: an appraisal. *Int J Cardiol* 2013;**167**:1712–8.
6. Smith JC, Lane H, Davies N, Evans LM, Cockcroft J, Scanlon MF, et al. The effects of depot long-acting somatostatin analog on central aortic pressure and arterial stiffness in acromegaly. *J Clin Endocrinol Metab* 2003;**88**:2556–61.
7. Paisley AN, Banerjee M, Rezai M, Schofield RE, Balakrishnannair S, Herbert A, et al. Changes in arterial stiffness but not carotid intimal thickness in acromegaly. *J Clin Endocrinol Metab* 2011;**96**:1486–92.
8. Annamalai AK, Webb A, Kandasamy N, Elkhawad M, Moir S, Khan F, et al. A comprehensive study of clinical, biochemical, radiological, vascular, cardiac, and sleep parameters in an unselected cohort of patients with acromegaly undergoing presurgical somatostatin receptor ligand therapy. *J Clin Endocrinol Metab* 2013;**98**:1040–50.
9. Matsuda Y, Kawate H, Matsuzaki C, Sakamoto R, Abe I, Shibue K, et al. Reduced arterial stiffness in patients with acromegaly: non-invasive assessment by the cardio-ankle vascular index (CAVI). *Endocr J* 2013;**60**:29–36.
10. Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, et al.; Acromegaly Consensus Group. A consensus on criteria for cure of acromegaly. *J Clin Endocrinol Metab* 2010;**95**:3141–8.
11. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, et al; Acromegaly Consensus Group. Guidelines for acromegaly management: an update. *J Clin Endocrinol Metab* 2009;**94**:1509–17.
12. Varadhan L, Reulen RC, Brown M, Clayton RN. The role of cumulative growth hormone exposure in determining mortality and morbidity in acromegaly: a single centre study. *Pituitary* 2016;**19**:251–61.
13. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977;**55**:613–8.
14. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989;**5**:303–11; discussion 312–3.
15. Colao A, Pivonello R, Grasso LF, Auriemma RS, Galdiero M, Savastano S, et al. Determinants of cardiac disease in newly diagnosed patients with acromegaly: results of a 10 year survey study. *Eur J Endocrinol* 2011;**165**:713–21.
16. Colao A, Baldelli R, Marzullo P, Ferretti E, Ferone D, Gargiulo P, et al. Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. *J Clin Endocrinol Metab* 2000;**85**:193–9.

17. Minniti G, Moroni C, Jaffrain-Rea ML, Esposito V, Santoro A, Affricano C, et al. Marked improvement in cardiovascular function after successful transsphenoidal surgery in acromegalic patients. *Clin Endocrinol (Oxf)* 2001;**55**:307–13.
18. Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Della Morte AM, et al. Is the acromegalic cardiomyopathy reversible? Effect of 5-year normalization of growth hormone and insulin-like growth factor I levels on cardiac performance. *J Clin Endocrinol Metab* 2001;**86**:1551–7.
19. Lombardi G, Colao A, Marzullo P, Biondi B, Palmieri E, Fazio S; Multicenter Italian Study Group on Lanreotide. Improvement of left ventricular hypertrophy and arrhythmias after lanreotide-induced GH and IGF-I decrease in acromegaly. A prospective multi-center study. *J Endocrinol Invest* 2002;**25**:971–6.
20. Hradec J, Kral J, Janota T, Krsek M, Hana V, Marek J, et al. Regression of acromegalic left ventricular hypertrophy after lanreotide (a slow-release somatostatin analog). *Am J Cardiol* 1999;**83**:1506–9, A8.
21. Brevetti G, Marzullo P, Silvestro A, Pivonello R, Oliva G, di Somma C, et al. Early vascular alterations in acromegaly. *J Clin Endocrinol Metab* 2002;**87**:3174–9.
22. Dassie F, Grillo A, Carretta R, Fabris B, Macaluso L, Bardelli M, et al. Ambulatory arterial stiffness indexes in acromegaly. *Eur J Endocrinol* 2012;**166**:199–205.
23. Topaloglu O, Sayki Arslan M, Turak O, Ginis Z, Sahin M, Cebeci M, et al. Three noninvasive methods in the evaluation of subclinical cardiovascular disease in patients with acromegaly: epicardial fat thickness, aortic stiffness and serum cell adhesion molecules. *Clin Endocrinol (Oxf)* 2014;**80**:726–34.
24. Sakai H, Tsuchiya K, Nakayama C, Iwashima F, Izumiyama H, Doi M, et al. Improvement of endothelial dysfunction in acromegaly after transsphenoidal surgery. *Endocr J* 2008;**55**:853–9.
25. Sweitzer NK, Shenoy M, Stein JH, Keles S, Palta M, LeCaire T, et al. Increases in central aortic impedance precede alterations in arterial stiffness measures in type 1 diabetes. *Diabetes Care* 2007;**30**:2886–91.