Changes in cardiovascular risk factors in patients with acromegaly after trans-sphenoidal adenomectomy

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Abstract. The surgical treatment of acromegaly reduces mortality, however its impact on cardiovascular risk factors is unclear. This study was carried out to determine the changes in cardiovascular risk factors in patients with acromegaly who received trans-sphenoidal surgery. We recruited 127 patients with acromegaly who received trans-sphenoidal adenomectomy between August 2003 and May 2014 and follow-up for 12 months. Fasting GH and IGF-1 levels were evaluated every 3 months, and cardiovascular risk factors were assessed before and 12 months after surgery. The main outcomes were changes in cardiovascular risk factors after surgery. One year after trans-sphenoidal adenomectomy, 68 patients (53.5%) had a fasting GH level <2.0 ng/mL, IGF-1 was normalized in 74 patients (58.3%), and both fasting GH and IGF-1 were under control in 51 patients (40.2%). Levels of glycated hemoglobin (HbA1c) (8.57 ± 3.19 vs. 6.66 ± 0.90%, p = 0.001) and triglycerides (130.6 ± 61.5 vs. 108.0 ± 47.5 mg/dL, p = 0.027) were significantly decreased and serum creatinine was significantly increased (0.665 ± 0.222 vs. 0.754 ± 0.223 mg/dL, p = 0.001) after trans-sphenoidal adenomectomy. However, there were no significant changes in body weight, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol and cardiovascular risk score after trans-sphenoidal adenomectomy. In the patient with high cardiovascular risk before surgery, systolic blood pressure, total cholesterol, fasting glucose, triglycerides and high-density lipoprotein cholesterol improved after trans-sphenoidal adenomectomy. In this study, HbA1c and triglycerides were significantly decreased after trans-sphenoidal adenomectomy in the patients with acromegaly irrespective of endocrinological outcomes. The other traditional cardiovascular factors might be improved after trans-sphenoidal adenomectomy in the patients with a high cardiovascular risk.

Key words: Acromegaly, Cardiovascular factors, Trans-sphenoidal adenomectomy

ACROMEGALY is characterized by an elevated GH level usually caused by a GH-producing pituitary adenoma. Active acromegaly is associated with a 2- to 4-fold increased risk of mortality, and cardiovascular disease (CVD) is a major contributor to this increased risk [1, 2]. The higher risk of mortality risk has also been associated with other factors, including serum GH and IGF-1 concentrations, and comorbidities at the time of diagnosis. Although cardiac hypertrophy typically occurs in the absence of other cardiovascular risk factors [3], several studies have reported that the coexistence of CV risk factors including hypertension, diabetes mellitus and dyslipidemia, can accelerate the onset and progression of cardiac complications [4].

Effective treatment of acromegaly has been reported to improve acromegalic cardiomyopathy, reduce left ventricular hypertrophy, and improve cardiac function, thereby reducing the risk of mortality [5-7]. Several recent studies have investigated the link between biochemical and other CVD risk factors. However, the normalization of GH/IGF-1 levels in acromegalic patients has been controversial with regards to its effect on CVD risk factors [8-10].

It has been well established that surgical treatment of acromegaly reduces mortality, however, few studies have investigated its impact on cardiovascular risk factors. Therefore, we conducted this study to evaluate the changes in cardiovascular risk factors in patients with acromegaly who received trans-sphenoidal surgery. We also investigated the relationships between hormone control and cardiovascular risk factors in acromegalic patients after surgery, and which patients would benefit the most after surgery.
Methods

Study population

Acromegalic patients aged between 20 and 100 years who received trans-sphenoidal surgery at our hospital were eligible to participate in this study. The diagnosis of acromegaly was based on clinical characteristics and confirmed by insufficient GH suppression during an oral glucose tolerance test (OGTT). Fasting GH and IGF-1 levels were evaluated every 3 months, and other pituitary hormone levels were evaluated every 6 months for at least 1 year. The new pituitary hormone deficiency was defined as normal hormones level at baseline, but low plasma target hormones level with normal or diminished tropic hormones after surgery. The patients who were treated with hormone replacement also defined as pituitary hormone deficiency. The pituitary hormone recovery were defined as low plasma target hormones level with normal or diminished tropic hormones, but recovery after surgery. Cardiovascular risk factors were assessed before and 12 months after surgery. Most patients also received repeat OGTT 12 months after surgery to assess GH control and glucose homeostasis. In cases of incomplete treatment, the patients may have received post-operative radiosurgery, treatment with somatostatin analogs, dopamine agonists, or no further management. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital, and written informed consent were obtained.

Cardiovascular risk factors evaluation

Cardiovascular risk factors were assessed through personal interviews and direct laboratory measurements. Patients were questioned about their history of diabetes, hypertension, dyslipidemia, and smoking habit. The use of cardiovascular medications (antihypertensive, lipid-lowering, and antidiabetic medications) was also recorded.

Blood pressure was measured in the right arm of each patient with an electric sphygmomanometer with the patient sitting in a relaxed position. Body height, body weight, sitting systolic and diastolic blood pressures, baseline serum glucose, glycated hemoglobin (HbA1c), cholesterol (total and high-density lipoprotein), and triglyceride levels were evaluated in each patient. These parameters and age were used to calculate the risk of a myocardial infarction (MI) within the next 10 years. We used the new Pooled Cohort Risk Assessment Equations developed by the Risk Assessment Work Group to estimate the 10-year risk of ASCVD (defined as the first-occurrence of nonfatal and fatal MI and nonfatal and fatal stroke) (see http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelinesand-Quality-Standards/2013-Prevention-Guideline-Tools.aspx#risk calculator) [11].

Blood samples and analysis

GH was measured using a two-site immunoradiometric assay obtained from Diagnostic Systems Laboratories, Inc. (Webster, TX). In our laboratory, the intraassay coefficient of variation is 3.1%, the interassay coefficient of variation is 5.9%, the assay sensitivity is 0.05 μg/L, and the upper limit of normal for nadir GH level after glucose is 0.14 μg/L. IGF-1 was measured by RIA using a polyclonal rabbit antibody generated against human IGF-1 (Nichols Institute Diagnostics, San Juan Capistrano, CA). The intraassay coefficient of variation is 4%, the interassay coefficient of variation is 11%, and the assay sensitivity is 13.5 ng/mL. The normal ranges for this assay are: age, 16–24 years, 182–780 ng/mL; 25–39 years, 114–492 ng/mL; 40–54 years, 90–360 ng/mL; and 55 years or older, 71–290 ng/mL. IGF-1 levels for all patients were compared with their age-appropriate normal ranges.

Plasma insulin levels were assayed using direct chemiluminescent technology with a two-site sandwich immunoassay (ADVIA Centaur, Bayer Corporation, Japan). A1C was measured using a high performance liquid chromatography system (HLC-723 GHB III, Tosoh, Japan) with a reference range of 4.5%–6.2%. Serum glucose was measured using the hexokinase method.

Statistical analysis

PASW for Windows version 19.0 (SPSS, Inc., Chicago, IL) was used to perform data analysis. All data are described as mean ± SEM unless otherwise stated. The paired t-test was used to compare parameters before and after trans-sphenoidal surgery. Nadir GH was defined as the lowest values at any time after oral glucose ingestion. Between-group differences were analyzed using ANOVA with post hoc testing using Fisher’s multiple comparison tests. Nonnormally distributed values were log transformed. Pearson’s correlation tests were used to assess the relationship between IGF-1 and GH. Differences among the groups of patients with acromegaly in the prevalence of diabetes, impaired fasting glucose, and treated hypertension were evaluated using the χ² test. A two-tailed p < 0.05 was considered to be statistically significant.

Results

We recruited 127 patients with acromegaly (mean age 46.2 ± 13.4 years), who received trans-sphenoidal adenomectomy (TSA) between August 2003 and May 2014. Table 1 shows their clinical characteristics and
biochemical data before and after TSA. After TSA, the fasting GH level decreased from 35.91 ± 68.74 ng/mL to 4.34 ± 9.47 ng/mL ($p < 0.001$) and the fasting IGF-1 level also decreased from 922.9 ± 249.7 ng/mL to 484.0 ± 280.5 ng/mL ($p < 0.001$). Of the uncontrolled cases, 7 patients received post-operative radiosurgery, 2 patients were treated with somatostatin analogs, and 4 patients received both treatments during 12 months of follow-up. Overall, 68 patients (53.5%) had a fasting GH level <2.0 ng/mL, IGF-1 was normalized in 74 patients (58.3%), and both fasting GH and IGF-1 were under control in 51 patients (40.2%).

Table 2 shows the other pituitary hormones change before and after trans-sphenoidal adenomectomy in patients with acromegaly. Serum ACTH and cortisol levels were significantly decreased after surgery. The new ACTH deficiency was found in 11 patients and recovery was found in 15 patients. The new thyrotropin deficiency was found in 6 patients and recovery was found in 12 patients. The new male gonadotropin deficiency was found in 1 patient and recovery was found in 8 patients. The new female gonadotropin deficiency was found in 4 patients and recovery was found in 5 patients. The patients with pituitary dysfunction were treated with hormone replacement accordingly.

The patients were followed for 12 months to investigate the influence of disease control on the CV risk factors. The results showed that after TSA, HbA1c (8.57 ± 3.19 vs. 6.66 ± 0.90%, $p = 0.001$) and triglycerides (130.6 ± 61.5 mg/dL vs. 108.0 ± 47.5 mg/dL, $p = 0.027$) significantly decreased, serum creatinine level significantly increased (0.665 ± 0.222 vs. 0.754 ± 0.223 mg/dL, $p = 0.001$), and the estimated glomerular filtrated rate significantly decreased (117.3 ± 37.1 vs. 102.8 ± 30.8 mL/min/1.73 m$^2$, $p = 0.001$). However, there were no significant changes in body weight, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol and cardiovascular risk score after

### Table 1 Clinical characteristics and biochemical data before and after trans-sphenoidal adenomectomy in 127 patients with acromegaly

|                      | Before TSA | After TSA | $p$ value |
|----------------------|------------|-----------|-----------|
| Male (%)             | 53 (41.7)  | NA        | NA        |
| Age (years)          | 46.2 ± 13.4| NA        | NA        |
| Medication for hypertension, N (%) | 14 (11.0)  | 18 (14.2) |           |
| Medication for diabetes, N (%) | 20 (15.7)  | 18 (14.2) |           |
| Medication for dyslipidemia, N (%) | 12 (9.4)   | 13 (10.2) |           |
| GH (ng/mL)           | 35.91 ± 68.74| 4.34 ± 9.47| <0.001    |
| IGF-1 (ng/mL)        | 922.9 ± 249.7| 484.0 ± 280.5| <0.001    |
| IGF-1 SD score       | 5.23 ± 2.81 | 2.13 ± 1.69| <0.001    |
| BW (Kg)              | 76.3 ± 14.6 | 76.2 ± 15.0 | 0.765     |
| BMI (kg/m$^2$)       | 27.00 ± 4.83| 26.98 ± 4.93| 0.771     |
| SBP (mmHg)           | 129.9 ± 21.2| 128.9 ± 16.6| 0.678     |
| DBP (mmHg)           | 79.3 ± 12.2 | 79.0 ± 12.8 | 0.832     |
| FPG (mg/dL)          | 130.5 ± 48.0| 112.1 ± 33.0| 0.007     |
| HbA1c (%)            | 8.57 ± 3.19 | 6.66 ± 0.90 | 0.001     |
| TC (mg/dL)           | 182.6 ± 33.6| 180.4 ± 29.6| 0.681     |
| HDL (mg/dL)          | 51.8 ± 14.1 | 54.2 ± 13.1 | 0.298     |
| Triglyceride (mg/dL) | 130.6 ± 61.5| 108.0 ± 47.5| 0.027     |
| Creatinine (mg/dL)   | 0.665 ± 0.222| 0.754 ± 0.223| 0.001     |
| eGFR (mL/min/1.73 m$^2$) | 117.3 ± 37.1| 102.8 ± 30.8| 0.001     |
| CVD score (10-year %) | 4.32 ± 6.63 | 4.32 ± 7.42 | 1.000     |

Abbreviations: TSA, trans-sphenoidal adenectomy; BW, body weight, BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GH, growth hormone; IGF-1, insulin-like growth factor-1; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, Triglyceride; eGFR, estimated glomerular filtrated rate; CVD, cardiovascular disease.
TSA (Table 1).

We divided the patients according to their GH control status after TSA. All of the results were the same as those of the overall study population regardless of whether they were based on GH alone (Tables 3 and 4), IGF-1 alone (data not shown), or GH and IGF-1 combined (Table 5).

We further used the median value of each cardiovascular risk factor before TSA to divide the patients into low or high cardiovascular risk groups. In the patients with a high risk of CVD, systolic blood pressure, total cholesterol, fasting glucose, triglycerides and high-density lipoprotein cholesterol improved after surgery (Fig. 1). However, there was no difference in CVD risk score

Table 2  Pituitary hormones change before and after trans-sphenoidal adenomectomy in 127 patients with acromegaly

|                      | Before TSA       | After TSA       | p value  |
|----------------------|------------------|----------------|----------|
| ACTH (pg/mL)         | 33.60 ± 20.49    | 21.08 ± 9.83   | <0.001   |
| Cortisol (ug/dL)     | 11.78 ± 5.20     | 9.32 ± 3.87    | <0.001   |
| TSH (ulU/mL)         | 1.09 ± 0.68      | 1.01 ± 0.64    | 0.237    |
| Free T4 (ng/dL)      | 1.18 ± 0.36      | 1.27 ± 0.37    | 0.100    |
| LH (mIU/mL)          | 6.95 ± 10.20     | 6.81 ± 7.01    | 0.931    |
| FSH (mIU/mL)         | 15.68 ± 28.86    | 15.00 ± 20.75  | 0.808    |
| Estrodiol (pg/mL)    | 52.60 ± 50.91    | 55.67 ± 61.44  | 0.835    |
| Testosterone (ng/mL) | 2.41 ± 1.44      | 3.33 ± 2.54    | 0.401    |

Abbreviations: TSA, trans-sphenoidal adenectomy; GH, growth hormone; IGF-1, insulin-like growth factor-1; SD, standard deviation; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; LH, Luteinizing Hormone; FSH, Follicle Stimulating Hormone.

Table 3  Clinical characteristics and biochemical data before and after trans-sphenoidal adenomectomy in 68 acromegalic patients with GH ≤2 ng/mL after TSA

|                      | Before TSA       | After TSA       | p value  |
|----------------------|------------------|----------------|----------|
| Male (%)             | 33 (49.3)        | NA             | NA       |
| Age (years)          | 48.2 ± 13.0      | NA             | NA       |
| GH (ng/mL)           | 19.89 ± 23.78    | 0.79 ± 0.65    | <0.001   |
| IGF-1 (ng/mL)        | 914.8 ± 242.3    | 354.6 ± 180.6  | <0.001   |
| BW (Kg)              | 76.4 ± 15.4      | 75.7 ± 15.9    | 0.372    |
| BMI (kg/m²)          | 27.45 ± 5.35     | 27.20 ± 5.52   | 0.418    |
| SBP (mmHg)           | 130.7 ± 25.5     | 129.8 ± 17.6   | 0.743    |
| DBP (mmHg)           | 78.8 ± 13.5      | 79.4 ± 12.7    | 0.813    |
| FPG (mg/dL)          | 124.2 ± 40.7     | 108.8 ± 24.3   | 0.080    |
| HbA1c (%)            | 7.98 ± 2.32      | 6.38 ± 0.79    | 0.010    |
| TC (mg/dL)           | 180.0 ± 29.0     | 182.8 ± 28.0   | 0.534    |
| HDL (mg/dL)          | 56.9 ± 12.6      | 55.9 ± 13.0    | 0.710    |
| Triglyceride (mg/dL) | 124.6 ± 66.8     | 107.2 ± 45.7   | 0.153    |
| Creatinine (mg/dL)   | 0.683 ± 0.220    | 0.787 ± 0.194  | 0.001    |
| eGFR (mL/min/1.73 m²)| 112.1 ± 38.0     | 96.5 ± 23.3    | 0.003    |
| CVD score (10-year %)| 4.65 ± 6.79      | 4.46 ± 6.44    | 0.594    |

Abbreviations: TSA, trans-sphenoidal adenectomy; BW, body weight; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GH, growth hormone; IGF-1, insulin-like growth factor-1; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, Triglyceride; eGFR, estimated glomerular filtrated rate; CVD, cardiovascular disease.
between the high and low risk groups. For the treatment of hypertension, there were 11 patients increasing medication and 7 patients decreasing medication after surgery. For the treatment of diabetes, there were 13 patients increasing medication and 15 patients decreasing medication after surgery. For the treatment of dyslipidemia, there were 11 patients increasing medication and 10 patients decreasing medication after surgery. There were many changes in medication for hypertension, diabetes, and hyperlipidemia. Therefore, we make a subgroup analysis (Supplemental Tables 1 and 2) to omit the influence by intensification of drug treatments during the observation period by deleting the cases with changes in these medications. The results were similar to our primary analysis.

### Discussion

Patients with acromegaly often have many cardiovascular risk factors including obesity, hypertension, dyslipidemia, and impaired glucose homeostasis. Several mechanisms have been proposed to explain the higher frequency of cardiovascular risk factors in these patients. An excess of GH in acromegaly leads to increased insulin resistance with a substantial reduction in peripheral glucose uptake accompanied with increased hepatic glucose production [12, 13]. The euglycemic state can be maintained at the expense of increased insulin secretion, and hyperglycemia occurs on exhaustion of beta-cell secretory capacity [14]. GH induces an expansion in plasma volume through a sodium retaining effect on the kidneys [15], and IGF-1 contributes to fluid retention by inhibiting atrial natriuretic peptide-induced natriuresis [16]. Furthermore, a chronic excess of GH and IGF-1 can lead to an increase in vascular resistance through stimulation of smooth muscle cell growth, which may explain the increase in diastolic blood pressure [17]. Total cholesterol levels have also been reported to be increased, normal or even decreased in patients with acromegaly in different studies [18]. Triglycerides have generally been reported to be increased [19], whereas normal or low high-density lipoprotein cholesterol levels have been reported [18, 20]. Effective surgical treatment of acromegaly is known to reduce mortality, however few studies have investigated its impact on cardiovascular risk factors. We conducted this study to investigate the changes in cardiovascular risk factors after TSA and follow-up for 1 year. Our data revealed that GH and

### Table 4 Clinical characteristics and biochemical data before and after trans-sphenoidal adenomectomy in 59 acromegalic patients with GH >2 ng/mL after TSA

|                          | Before TSA | After TSA | p value       |
|--------------------------|------------|-----------|---------------|
| Male (%)                 | 20 (33.3)  | NA        | NA            |
| Age (years)              | 43.9 ± 13.5| NA        | NA            |
| GH (ng/mL)               | 54.96 ± 95.35 | 8.59 ± 12.82 | <0.001       |
| IGF-1 (ng/mL)            | 932.3 ± 259.8 | 635.7 ± 301.4 | <0.001       |
| BW (Kg)                  | 76.2 ± 14.1 | 76.6 ± 14.4 | 0.584         |
| BMI (kg/m²)              | 26.58 ± 4.30| 26.72 ± 4.39 | 0.671         |
| SBP (mmHg)               | 129.1 ± 16.4| 128.1 ± 15.8| 0.593         |
| DBP (mmHg)               | 79.8 ± 11.0 | 78.6 ± 13.0 | 0.447         |
| FPG (mg/dL)              | 135.5 ± 53.3 | 114.7 ± 38.8 | 0.044         |
| HbA1c (%)                | 9.11 ± 3.85 | 6.92 ± 0.95  | 0.035         |
| TC (mg/dL)               | 185.0 ± 37.8 | 178.3 ± 30.6 | 0.470         |
| HDL (mg/dL)              | 45.3 ± 13.6 | 51.9 ± 13.4 | 0.059         |
| Triglyceride (mg/dL)     | 136.9 ± 56.6 | 108.9 ± 50.6 | 0.101         |
| Creatinine (mg/dL)       | 0.647 ± 0.217 | 0.720 ± 0.246 | 0.001         |
| eGFR (mL/min/1.73 m²)    | 123.2 ± 35.4 | 109.8 ± 36.4 | 0.008         |
| CVD score (10-year %)    | 4.03 ± 6.61  | 4.20 ± 8.32  | 0.757         |

Abbreviations: TSA, trans-sphenoidal adenomectomy; BW, body weight; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GH, growth hormone; IGF-1, insulin-like growth factor-1; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, Triglyceride; eGFR, estimated glomerular filtrated rate; CVD, cardiovascular disease.
IGF-1 levels were significantly decreased after TSA. In our primary analysis, there were no significant changes in most cardiovascular risk factors after TSA except for HbA1c, fasting plasma glucose and triglycerides. We further analyzed our results according to whether or not GH and/or IGF-1 normalization had been achieved, and all of the results were nearly the same as those of the overall study population. However, we found that most of these CVD risk factors were significantly improved after surgery in the patients with high risk of CVD before surgery. Therefore, we suggested that trans-sphenoidal surgery may provide more benefits in acromegalic patients at high risk, but may be no effects in patients with normal blood pressure, glucose and lipid.

Carmichael et al. investigate 121 patients with acromegaly to estimate the proportion of patients with various comorbidities and determine whether biochemical control was associated with a reduction in cardiovascular risk factors [21]. They found a much higher frequency of cases of hypertension, diabetes, and cardiomyopathy or heart failure in the biochemically controlled patients compared to controlled counterparts. Briet et al. retro-

**Table 5** Clinical characteristics and biochemical data after trans-sphenoidal adenectomy in acromegalic patients with different growth hormone control after TSA

|                       | GH normalized | G | GH elevated | G |
|-----------------------|---------------|---|-------------|---|
| **IGF-1 normalized**  | 25 (49.0)     | 8 (47.1) | 7 (30.4) | 13 (36.1) |
| Male (%)              | 25 (49.0)     | 8 (47.1) | 7 (30.4) | 13 (36.1) |
| Age (years)           | 49.8 ± 11.5   | 45.1 ± 15.7 | 46.5 ± 14.4 | 42.2 ± 12.8 |
| GH (ng/mL)            | 0.72 ± 0.63   | 1.01 ± 0.70 | 6.35 ± 10.21 | 9.89 ± 14.05 |
| IGF-1 (ng/mL)         | 274.1 ± 107.7 | 596.1 ± 132.9* | 346.0 ± 154.8 | 824.4 ± 203.9* |
| BW (Kg)               | 74.6 ± 16.3   | 81.2 ± 14.4 | 76.1 ± 15.3 | 76.8 ± 14.4 |
| BMI (kg/m²)           | 27.07 ± 5.68  | 29.07 ± 3.30 | 25.76 ± 2.95 | 27.13 ± 4.99 |
| SBP (mmHg)            | 130.9 ± 17.7  | 124.1 ± 16.4 | 124.5 ± 16.0 | 130.1 ± 15.7 |
| DBP (mmHg)            | 79.8 ± 11.8   | 75.1 ± 17.3 | 72.9 ± 12.5 | 81.9 ± 12.4 |
| FPG (mg/dL)           | 106.8 ± 26.4  | 116.8 ± 11.4 | 107.9 ± 35.2 | 118.0 ± 40.8 |
| HbA1c (%)             | 6.59 ± 1.60   | 6.53 ± 1.01 | 7.00 ± 1.37 | 6.94 ± 1.20 |
| TC (mg/dL)            | 182.8 ± 29.4  | 183.0 ± 18.8 | 201.7 ± 12.5 | 170.0 ± 6.5 |
| HDL (mg/dL)           | 55.8 ± 12.9   | 51.7 ± 16.0 | 60.0 ± 15.0 | 50.3 ± 13.2 |
| Triglyceride (mg/dL)  | 95.4 ± 36.4   | 170.0 ± 42.5 | 103.7 ± 40.0 | 107.9 ± 53.0 |
| Creatinine (mg/dL)    | 0.751 ± 0.143 | 0.928 ± 0.294 | 0.717 ± 0.224 | 0.722 ± 0.266 |
| eGFR (mL/min/1.73 m²) | 101.0 ± 21.3  | 77.5 ± 22.9 | 108.4 ± 36.7 | 110.9 ± 36.9 |
| CVD score (10-year %) | 4.83 ± 7.03   | 2.75 ± 2.36* | 3.29 ± 2.98 | 4.56 ± 9.70 |

*p < 0.05 compared with IGF-1 normalized.

Abbreviations: TSA, trans-sphenoidal adenectomy; BW, body weight; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GH, growth hormone; IGF-1, insulin-like growth factor-1; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, Triglyceride; eGFR, estimated glomerular filtrated rate; CVD, cardiovascular disease.
risk score, and decreased high-density lipoprotein. Moreover, these cardiovascular risk factors and Framingham risk score significantly decreased after 12 months of treatment with pegvisomant [8]. Akutsu et al. conducted a prospective study and compared 25 newly diagnosed acromegalic patients and 50 control subjects who were matched for age, sex, and CVD risk. The 10-year CVD risk was estimated, and the European Society of Cardiology risk score was higher in the acromegalic patients than in the matched controls. Therefore, the authors suggested that an excess of GH per se does not carry an additional CVD risk [9]. In our study, the calculated CVD risk factor score was nearly the same before and after surgery in all subgroup analyses. We calculated the CVD risk score from nine risk factors including sex, age, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, treatment for blood pressure, diabetes and smoking status, of which sex, age, race, diabetes and smoking status would not change after TSA, and the changes in cholesterol and systolic blood pressure were not large enough after TSA to change the CVD risk scores.

The GH/IGF-1 axis is physiologically involved in the regulation of electrolytes and water homeostasis by the kidneys, and enhances glomerular filtration through a decrease in renal vascular resistance, leading to increase glomerular perfusion [23]. Acromegalic patients were reported to have a remarkable increase in glomerular filtration and renal plasma flow several decades ago. Auriemma et al. reported that the creatinine clearance rate was higher in patients with acromegaly, and that the changes were not completely reversible after disease remission [24]. In addition, Kamenický et al. investigated 16 acromegalic patients before and after treatment, and found a consistent 15% increase in the glomerular filtrated rate in patients with active disease [25]. Our results revealed an increase in serum creatinine level accompanied with a 13% decrease in estimated glomerular filtrated rate after TSA. However, we did not have normal control subjects for comparison.

There were some limitations in this study. This was an observational study and the cardiovascular risk factors may have been treated by their physicians. For example, 29 of the acromegalic patients also had diabetes in this study. Six patients with diabetes were diagnosed during an OGTT, and another three patients with diabetes were not taking any medications before surgery. Patients with a high CVD risk before surgery are more likely to have been treated with medications. Another limitation is some non-remission patients were received additional treatments to control acromegaly during the follow of 12 months after surgery, which may lead the analysis more complex.

In conclusion, this study revealed that HbA1c and
triglycerides were significantly decreased after TSA in this large cohort of patients with acromegaly irrespective of endocrinological outcomes. However, there were no significant changes in body weight, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol and CVD risk score after TSA. We also found that these changes in cardiovascular risk factors were not associated with GH control status after TSA. In further analysis, systolic blood pressure, total cholesterol, fasting glucose, triglycerides and high-density lipoprotein cholesterol improved after surgery in the patients with a high risk of CVD before surgery. Therefore, the cardiovascular risk factors might be improved after TSA in the acromegalic patients with high risk of CVD.

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Contribution Statement

Y.S.Y. is a neurosurgery who cared these subjects, collect the data and contributed to the discussion. H.S.C. contributed to the study design, analyzed the researched data, and edited the manuscript and takes responsibility for content of the article.

Duality of Interest

Both authors declare they have received no support from any company for the submitted work, they have had no financial relationships with any companies that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

Disclosure Statement

The authors have nothing to disclose.
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