Treatable glomerular hyperfiltration in patients with active acromegaly

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Abstract

Objective: The glomerular filtration rate (GFR) is increased in patients with active acromegaly. The aim of this study is to elucidate whether renal function deteriorates in patients with acromegaly and whether this deterioration is reversible after surgical remission.

Design/methods: A case–control study of 48 acromegalic patients who were surgically cured (cases) and 48 patients with nonfunctioning pituitary adenomas (NFomas, controls) was conducted. We performed clinical and biochemical examinations before surgery and 3 months post-surgery. The GFR of each patient was estimated (estimated GFR, eGFR) using their serum creatinine, age, sex, and body surface area, and postoperative changes in the eGFR were assessed.

Results: The preoperative eGFR was significantly higher in patients with acromegaly than in those with NFoma (99.8 vs 75.1 mL/min respectively, \(< 0.01\)). In acromegalic patients, surgical remission was accompanied by a significant decline in the eGFR (from 99.8 to 86.2 mL/min, \(\< 0.01\)). Conversely, in patients with NFoma, the postoperative eGFR did not change significantly (from 75.1 to 81.9 mL/min, \(\approx 0.12\)). Among the acromegalic patients, the postoperative decreases in the eGFR were more prominent in patients with a preoperatively high or normal versus low eGFR.

Conclusions: Our data demonstrated a significant post-surgical eGFR decrease in patients with acromegaly, but not in patients with NFomas. This change in the eGFR was reversible in acromegalic patients with a high/normal preoperative eGFR, but not in those with a low preoperative eGFR. This suggests that the reversible pathophysiological change in some patients is functional but not organic.

Introduction

Acromegaly is caused by hypersecretion of growth hormone (GH) and subsequent increases in the serum and local concentrations of insulin-like growth factor (IGF) 1, and is most commonly caused by GH-secreting pituitary adenomas (1). The clinical symptoms of acromegaly are manifold, including acral overgrowth, arthralgias, jaw prognathism, diabetes mellitus, hypertension, respiratory and cardiac failure, and visceromegaly (1). Kidneys are one of the target organs for GH/IGF1 action (2). GH affects renal function both directly and indirectly through serum or local IGF1 (3, 4, 5). In healthy volunteers, administration of exogenous GH induces glomerular hyperfiltration (6). Hypersecretion of GH in patients with acromegaly also increases the glomerular filtration rate.
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(GFR) (7, 8). These findings suggest that the reduction in GH and IGF1 associated with the treatment of acromegaly may affect renal function.

To elucidate the effect of GH hypersecretion on renal function, we evaluated changes in the GFR in acromegalic patients who have achieved surgical remission, and compared these changes with the GFR of patients who underwent a similar surgery for other types of pituitary tumours.

This study was conducted to: (i) assess changes in the GFR in patients with acromegaly before surgery and after surgical remission, (ii) compare differences in the GFR between patients with acromegaly and those with nonfunctioning pituitary adenomas (NFomas), (iii) investigate the factors affecting GFR before and after surgery, and (iv) investigate the effect of GH/IGF1 normalization in patients with preoperatively low GFR.

Subjects and methods

Patients

Between 2006 and 2014, 70 patients with newly diagnosed acromegaly were treated with transsphenoidal surgery (TSS) by a senior neurosurgeon (K Arita). Among these 70 cases, 81.4% (57/70) achieved remission by surgery alone, as judged by the Cortina consensus criteria (nadir GH level during postoperative oral glucose tolerance test (OGTT) <1 µg/L and normal levels of IGF1) (9). Among these 57 patients, pre- and post-surgical hormonal levels were measured in 53 patients, and four patients were lost to follow-up. We excluded three patients who had received preoperative medical therapy, such as somatostatin analogues and dopamine agonists for acromegaly, and two patients who had been taking diuretics for congestive heart failure; thus, 48 patients were finally included in this study. One patient received treatment with prednisolone for rheumatoid arthritis, but none of the patients had overt central hypothyroidism, hypocortisolism, or diabetes insipidus requiring replacement therapy. Patients with pre- or postoperative central hypothyroidism, hypocortisolism, or diabetes insipidus requiring replacement therapy were excluded when we selected the control subjects.

Methods

Clinical and biochemical examinations were performed before surgery and 3 months post-surgery. The GFR of each patient was estimated using the new Japanese equation which incorporates patient’s age and serum creatinine value (SCr) as follows: estimated GFR (mL/min/1.73 m²) = 194 × Age−0.287 × SCr−1.094 (if female × 0.739) (10). Commonly, ‘eGFR’ means estimated GFR calculated by the above formula. However, to avoid the influence of differences in body surface area (BSA) among patients, we used the formula: eGFR (mL/min) = estimated GFR × body surface area/1.73. BSA was calculated according to the DuBois formula: BSA (m²) = 0.007184 × height (cm)0.725 × weight (kg)0.425.

We compared pre- and postoperative eGFRs in patients with acromegaly and in those with NFoma. In acromegalic patients, we assessed the correlation between preoperative eGFR and disease duration, preoperative GH, IGF1 standard deviation score (SDS), blood pressure, glycosylated haemoglobin (HbA1c), and plasma glucose (PG). We also assessed the correlation between postoperative eGFR and postoperative GH, IGF1 SDS, and nadir GH during OGTT, blood pressure, HbA1c, and PG.

We divided patients with acromegaly into two groups (low eGFR and high/normal eGFR groups), according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for chronic kidney disease (11). The ‘low-eGFR’ group comprised patients with preoperative eGFR <90 mL/min, and the ‘high/normal eGFR’ group comprised those with preoperative eGFR >90 mL/min. We compared clinical and biochemical features and postoperative changes in the eGFR between both groups.

Assays

Creatinine was measured using an enzymatic method (2006: Labo Research CRE, A&T, Kanagawa, Japan, coefficient of variation (C.V.) was 1.00 %; 2007–2012: Liquitech Creatinine PAP II Roche Diagnostics, Rotkreuz, Switzerland, C.V. was 1.12 %; 2013: Cygnus auto CRE, Shino-Test, Tokyo, Japan, C.V. was 0.29 %). The levels were rounded to the nearest one decimal place until May 2010 and to the nearest two decimal places thereafter. The GH concentration was measured...
by an electrochemiluminescence (ECL) immunoassay (Immulite 2000 hGH; Siemens, C.V. was 3.32 %) that uses recombinant human GH as a standard. The sensitivity of this assay was 0.1 µg/L. The IGF1 concentration was measured by an immunoradiometric assay (IGF1 IRMA ‘Daiichi’, TFB, Tokyo, Japan, C.V. was 1.80 %). Raw IGF1 concentrations were quantified according to IGF1 SDSs and calculated by the standard IGF1 values of each gender and age group of the Japanese population (12).

**Statistical analysis**

All statistical analyses were performed using Starflex version 6.0 (Artech Co, Ltd, Osaka, Japan). The data were analysed using the Wilcoxon signed-rank test, Mann–Whitney’s U test, χ² test, and Fisher’s exact test, according to the characteristics of the dataset. We assessed the correlation between preoperative eGFR and disease duration, preoperative GH, IGF1 SDS, blood pressure, HbA1c, and PG. Additionally, we also assessed the correlation between postoperative eGFR and postoperative GH, IGF1 SDS, and nadir GH during OGTT, blood pressure, HbA1c, and PG. The Spearman’s rank-correlation coefficient was used to assess these correlations. A two-sided P-value <0.05 was considered statistically significant.

**Ethical considerations**

This study was approved by the Kagoshima University Hospital Ethics Committee (Reference no. 27-499). Data were routinely obtained and were essential for proper management of the pituitary disease. The need for an informed consent was waived because this study was retrospective. In addition, we anonymized the data to protect patients’ privacy.

**Results**

**Baseline characteristics of patients with acromegaly vs nonfunctioning pituitary adenomas**

Data were expressed as median and range. A comparison of the preoperative clinical and biochemical features of patients who had acromegaly and NFoma is presented in Table 1. Patients with acromegaly had a higher BSA than those with NFoma (1.67 m² vs 1.57 m², P=0.04). Serum creatinine of acromegal patients was lower than in patients with NFoma (45.1 µmol/L vs 55.7 µmol/L, P<0.01). The rate of diabetes mellitus in patients with acromegaly was higher than in patients with NFoma (31.3% vs 12.5%, P=0.03). The pre- and postoperative clinical and biochemical features of the acromegalic patients are presented in Table 2. GH, IGF1, and the IGF1 SDS all significantly decreased, and serum creatinine increased after the operation. We observed significant decreases in the systolic and diastolic blood pressure (from 128 to 123 mmHg, P<0.01, and from 79 to 74 mmHg, P<0.01 respectively), in HbA1c (from 5.9 to 5.6%, P<0.01) and in plasma glucose (from 5.9 to 5.2 mmol/L, P<0.01).

### Table 1  Baseline characteristics of patients with acromegaly vs nonfunctioning pituitary adenomas. Data are presented as median (range) unless otherwise specified.

<table>
<thead>
<tr>
<th></th>
<th>Acromegaly</th>
<th>NFoma</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.5 (18–75)</td>
<td>54.5 (19–80)</td>
<td>0.69a</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>17/31</td>
<td>17/31</td>
<td>–</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.1 (141.8–190.4)</td>
<td>159.0 (139.7–180.7)</td>
<td>0.05a</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.2 (41.0–102.9)</td>
<td>58.5 (44.1–98.7)</td>
<td>0.07a</td>
</tr>
<tr>
<td>BMI</td>
<td>24.3 (17.9–32.0)</td>
<td>23.3 (17.2–37.4)</td>
<td>0.23a</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.67 (1.30–2.25)</td>
<td>1.57 (1.36–2.07)</td>
<td>0.04a</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>10.8 (1.6–85.0)</td>
<td>0.1 (0.1–3.9)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>IGF1 (µg/L)</td>
<td>564 (262–1320)</td>
<td>107 (57–332)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>SD score of IGF1</td>
<td>6.4 (3.0–12.6)</td>
<td>−0.9 (−4.0 to 3.1)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>45.1 (26.5–84.0)</td>
<td>55.7 (36.2–95.5)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>19/29</td>
<td>14/34</td>
<td>0.28b</td>
</tr>
<tr>
<td>ACE inhibitor/ARB (yes/no)</td>
<td>12/36</td>
<td>8/40</td>
<td>0.31b</td>
</tr>
<tr>
<td>Diabetes mellitus (yes/no)</td>
<td>15/33</td>
<td>6/42</td>
<td>0.03b</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>128 (85–166)</td>
<td>125 (90–170)</td>
<td>0.51a</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79 (55–100)</td>
<td>78 (45–100)</td>
<td>0.53a</td>
</tr>
</tbody>
</table>

*a*Wilcoxon signed-rank test; *b*χ² test.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BSA, body surface area; GH, growth hormone; IGF1, insulin-like growth factor 1; NFoma, nonfunctioning pituitary adenomas; s.d., standard deviation.
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Pre- and postoperative changes in the estimated glomerular filtration rate

Both pre- and postoperative eGFRs were significantly higher in acromegalic patients than in patients with NFoma (preoperative: 99.8 mL/min vs 75.1 mL/min, P<0.01; postoperative: 86.2 mL/min vs 81.9 mL/min, P=0.03 respectively; Fig. 1). eGFR decreased significantly in acromegalic patients after surgery (from 99.8 to 86.2 mL/min, P<0.01; Fig. 1A), whereas it did not decrease after surgery in patients with NFoma (from 75.1 to 81.9 mL/min, P=0.12; Fig. 1B).

Correlation of the estimated glomerular filtration rate with pre- and postoperative factors

In patients with acromegaly, the preoperative IGF1 SDS positively correlated with preoperative eGFR (r=0.32, P=0.03; Fig. 2), whereas none of the postoperative factors correlated with the postoperative eGFR.

Comparison between groups with low and high/normal estimated glomerular filtration rates

The study included 13 patients with a low preoperative eGFR (<90 mL/min) and 35 patients with high/normal preoperative eGFR (>90 mL/min). The clinical and biochemical features of these groups are presented in Table 3. Patients in the high/normal eGFR group were significantly younger (P<0.01) and had a significantly higher BSA (P=0.01) and IGF1 SDS (P=0.02) than those in the low-eGFR group. The prevalence of hypertension and the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers tended to be higher in the low-eGFR group, but without statistical significance (P=0.06). In the low-eGFR group, no significant change was observed in the eGFR group (from 67.8 to 71.9 mL/min, P=0.35; Fig. 3A), whereas

### Table 2 Pre- and postoperative clinical and biochemical features of patients with acromegaly. Data are presented as median (range) unless otherwise specified.

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>63.2 (41.0–102.9)</td>
<td>61.6 (41.2–101.7)</td>
<td>0.18a</td>
</tr>
<tr>
<td>BMI</td>
<td>24.3 (17.9–32.0)</td>
<td>24.1 (17.8–32.5)</td>
<td>0.26a</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.67 (1.30–2.25)</td>
<td>1.66 (1.31–2.24)</td>
<td>0.19a</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>10.8 (1.6–85.0)</td>
<td>1.2 (0.1–6.7)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>IGF1 (µg/L)</td>
<td>564 (262–1320)</td>
<td>164 (63–364)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>SD score of IGF1</td>
<td>6.4 (3.0–12.6)</td>
<td>0.8 (–1.4 to 2.0)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>45.1 (26.5–84.0)</td>
<td>52.2 (33.6–88.4)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>19/29</td>
<td>19/29</td>
<td>–</td>
</tr>
<tr>
<td>ACE inhibitor/ARB (yes/no)</td>
<td>12/36</td>
<td>12/36</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes mellitus (yes/no)</td>
<td>15/33</td>
<td>9/39</td>
<td>0.16b</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>128 (85–166)</td>
<td>123 (90–153)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79 (55–100)</td>
<td>74 (52–92)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.9 (5.3–11.1)</td>
<td>5.6 (4.9–9.4)</td>
<td>&lt;0.01a</td>
</tr>
<tr>
<td>PG (mmol/L)</td>
<td>5.9 (4.6–14.7)</td>
<td>5.2 (4.3–12.8)</td>
<td>&lt;0.01a</td>
</tr>
</tbody>
</table>

*Wilcoxon signed-rank test; †χ² test.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BSA, body surface area; GH, growth hormone; HbA1c, glycosylated haemoglobin; IGF1, insulin-like growth factor 1; PG, plasma glucose; s.d., standard deviation.

![Figure 1](https://www.eje-online.org)
Figure 1
Changes in the estimated glomerular filtration rate in patients with acromegaly or nonfunctioning pituitary adenomas. Both pre- and postoperative estimated glomerular filtration rates (eGFR) were significantly higher in acromegalic patients than in patients with NFoma (preoperative: 99.8 mL/min vs 75.1 mL/min, P<0.01; postoperative: 86.2 mL/min vs 81.9 mL/min, P=0.03 respectively; Fig. 1). eGFR decreased significantly in acromegalic patients after surgery (from 99.8 to 86.2 mL/min, P<0.01; Fig. 1A), whereas it did not decrease after surgery in patients with NFoma (from 75.1 to 81.9 mL/min, P=0.12; Fig. 1B).
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Among the 38 acromegalic patients whose pre- and postoperative urinalyses were available, four patients showed preoperative proteinuria, which resolved in 3/4 postoperatively and was sustained in one patient. The changes in eGFR of these patients before and after the surgery were 62.2–56.9 mL/min, 113.0–99.3 mL/min, 93.3–83.7 mL/min, and 96.3–107.9 mL/min respectively.

Discussion

Kidneys are one of the target organs for GH/IGF1 (1). Genes of the GH receptor, IGF1, IGF1 receptor, and IGF1-binding proteins are constitutively expressed in the human adult kidneys. These proteins are variably expressed in anatomically and functionally different segments of the nephron, suggesting that GH and IGF1 may have diverse roles in different kidney segments (5). In animals, chronic administration of exogenous GH or IGF1 was reported to induce selective hypertrophy of the kidneys (13, 14). In humans, kidney volume is increased by GH hypersecretion (15, 16, 17). GH/IGF1 affects not only the structure of the kidney but also its function. Some reports have shown that GH administration to healthy subjects increases GFR and renal plasma flow (RPF) (4, 6, 18, 19). Luft and Sjogren reported that the mean GFR of patients with acromegaly was 26% higher than that of control subjects (7). In our study, we observed that the preoperative eGFR was significantly higher in patients with acromegaly than in patients with NFoma, matched by gender and age group.

Several reports have offered hypotheses on the mechanism of hyperfiltration induced by GH/IGF1 excess. Auriemma et al. hypothesized that the increase in kidney size might lead to an increase in GFR, RPF, and tubular reabsorption, which may enhance renal filtration and reabsorption processes (20). Ikkos et al. hypothesized that the increased GFR in acromegaly could be attributed to primary increases in extracellular fluid volume without any changes in the filtered fraction (8). Tönshoff et al. reported that the increase in the GFR by GH administration to healthy subjects was completely ablated by indomethacin, a cyclooxygenase inhibitor (6). This finding suggests that GH/IGF1-induced glomerular hyperfiltration is mediated by or is due to a mechanism involving vasodilatory prostanoids. Future studies are necessary to fully understand the mechanism of glomerular hyperfiltration in patients with acromegaly.

In our study, the preoperative IGF1 SDS correlated with preoperative eGFR, but not with other factors, including disease duration, preoperative GH, blood pressure, HbA1c, or PG. Transient GH administration is reported to induce a delayed rise in GFR and RPF in association with increased plasma IGF1 levels, at which time the plasma GH level had fallen to the baseline level (4). Thus, GH-induced IGF1 production may be responsible for the increase in GFR, which also explains the association between preoperative IGF1 SDS and eGFR in our study.
We demonstrated a significant post-surgical decrease in the eGFR among patients with acromegaly, but not in patients with NFomas who underwent a similar operation, suggesting that the cure of GH/IGF1 overproduction is responsible for the decrease in the eGFR. Dullaart et al. reported a decline in GFR after 3 months of treatment with octreotide, a somatostatin analogue (21). Somatostatin receptors are expressed in many organs and the effect of somatostatin analogues is not confined to the GH/IGF1 system (22). For example, somatostatin receptors are located in the atrioventricular node (23), and administration of somatostatin analogue sometimes lowers heart rate (24) and reduces GFR in some patients. This is the reason why we evaluated changes in the GFR in acromegalic patients who have achieved remission by surgery alone. This reduction in the GFR after hypophysectomy in patients with acromegaly was reported as early as 1965 (25). Recently, Sze et al. reported a decrease in the GFR after transsphenoidal surgery in 20 cured and four non-cured patients with acromegaly (26). Neidert et al. showed that postoperative GFR decreased in 14 patients with acromegaly, whereas postoperative GFR increased in 13 and nine patients with NFoma and prolactinoma respectively (27).

Using the formula, we employed to calculate eGFR, when the serum creatinine is decreased and the calculated eGFR is increased. In healthy population, serum creatinine significantly correlates with muscle mass (28). Brummer et al. reported that muscle mass of acromegalic patients decreased after successful treatment (29). Therefore, when the muscle mass is decreased after surgical cure of acromegaly, serum creatinine concentration is expected to decrease. The reduction in serum creatinine concentration is reflected in the increased calculated eGFR. In acromegalic patients, however, eGFR was decreased after the surgical cure; therefore, we postulate that the mechanisms underlying this phenomenon are not related to the change in muscle mass.

Despite postoperative normalization of GH/IGF1, there was a significant difference in the changes in the eGFR between patients with low preoperative eGFR and those with high/normal eGFR. A similar phenomenon was observed in patients with diabetes mellitus. The hyperfiltration observed in patients with a short history of type 1 diabetes mellitus is reversible and normalizes after the glucose profile is controlled, whereas the impaired renal function in patients with long-standing diabetes mellitus is not significantly changed by controlling the glucose profile. Organic changes in the glomerulus, such as glomerular sclerosis, are suggested to be responsible for this irreversibility (30). The difference observed in patients with acromegaly may also be related to such glomerular changes.

Table 3  Baseline characteristics of patients with acromegaly grouped according to preoperative estimated glomerular filtration rate. Data are presented as median (range) unless otherwise specified.

<table>
<thead>
<tr>
<th>Low eGFR group (eGFR &lt; 90 mL/min)</th>
<th>High/normal eGFR group (eGFR &gt; 90 mL/min)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.0 (40–73)</td>
<td>53.0 (18–75)</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>3/10</td>
<td>14/21</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>7 (2–20)</td>
<td>6 (1–24)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.8 (141.8–167.9)</td>
<td>161.3 (142.3–190.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.3 (41.0–73.7)</td>
<td>66.7 (43.2–102.9)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.2 (17.9–32.0)</td>
<td>24.5 (19.8–30.8)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.59 (1.34–1.83)</td>
<td>1.74 (1.30–2.25)</td>
</tr>
<tr>
<td>GH (ng/mL)</td>
<td>9.6 (2.5–43)</td>
<td>11.4 (1.6–85)</td>
</tr>
<tr>
<td>IGF1 (μg/L)</td>
<td>410 (262–808)</td>
<td>586 (312–1320)</td>
</tr>
<tr>
<td>SD score of IGF1</td>
<td>5.4 (3.0–11.7)</td>
<td>6.9 (3.1–12.6)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>53.0 (44.2–84.0)</td>
<td>44.2 (26.5–70.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>126 (85–159)</td>
<td>129 (101–166)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71 (60–92)</td>
<td>80 (55–100)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.8 (5.3–7.7)</td>
<td>6.0 (5.3–11.1)</td>
</tr>
<tr>
<td>PG (mmol/L)</td>
<td>5.6 (4.6–11.2)</td>
<td>6.1 (4.8–14.7)</td>
</tr>
</tbody>
</table>

\*Mann–Whitney U test; \(^{\circ}\)Fisher’s exact test; \(^{\chi^2}\) test.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; GH, growth hormone; HbA1c, glycosylated haemoglobin; IGF1, insulin-like growth factor 1; PG, plasma glucose; s.d., standard deviation.
Preoperative proteinuria resolved in 3/4 patients and was sustained in one patient, suggesting that treatment of GH hypersecretion may ameliorate the renal damage in some patients. It was not possible to elucidate the mechanism of how GH oversecretion induces reversible hypersecretion in some patients and irreversible renal dysfunction in others. In the animal model of GH hypersecretion (transgenic mice overexpressing GH or GHRH) reported by Doi et al. (31), progressive glomerulosclerosis was observed. This paper gives us a speculation that long-standing GH oversecretion may induce organic change (glomerulosclerosis) in acromegalic patients. Irreversible change in renal function may be explained by glomerular hyperfiltration, glucose dysregulation, hypertension, or some other mechanism (32).

Previous reports suggest a reduction in GH action in patients with compromised renal function. Patients with chronic renal failure (CRF) may show resistance to GH (33, 34). No significant increases in the GFR were noted after GH administration in patients with CRF (33). However, the renal function in the low preoperative eGFR group was mostly above 60mL/min (Fig. 3A), which is above the range of chronic renal failure.

The IGF1 SDS score was extremely higher in patients with acromegaly compared with the level in patients with GH deficiency treated with GH replacement. Therefore, kidney injury induced by GH replacement should not be of concern.

Our study has some limitations. First, some of the patients with NFoma might have been GH deficient (GHD) because preoperative IGF1 SDS was relatively low. Growth hormone deficiency in these patients may have influenced the eGFR. Secondly, we measured serum creatinine and body weight only once before and once after 3 months of surgery, although these parameters change daily. Mean values of serial measurements over a period of time are necessary to increase the validity of the individual body weight and eGFR measurements. Thirdly, there was no significant correlation between the eGFR and blood pressure, HbA1c, or PG in our study. However, we could not collect data related to the duration of hypertension and diabetes mellitus from all the patients. Future studies are necessary to understand how these comorbidities affect the renal function and postoperative changes in the eGFR.

Lastly, we used eGFR in acromegalic patients; however, it is not guaranteed that whether eGFR calculated from serum creatinine, age, sex, and body surface area is applicable to acromegalic patients and is proportional to GFR. We did not measure the RPF and compare it with the calculated eGFR in this study. This basic limitation should be addressed in future studies.

Conclusions

We found that the preoperative eGFR was significantly higher in patients with acromegaly than in patients with NFomas. There was a significant decrease in the eGFR after surgical remission in patients with acromegaly, but not in those with NFomas who underwent similar surgery.
Among patients with acromegaly, postoperative decreases (normalization) in the eGFR were more often observed in patients with preoperatively high/normal eGFR than in those with low eGFR. Our findings suggest that in patients with a preoperatively high/normal eGFR, surgical remission achieves normalization of hyperfiltration, whereas in patients with low eGFR, surgical remission does not significantly influence eGFR.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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