The kidney in acromegaly: renal structure and function in patients with acromegaly during active disease and 1 year after disease remission

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Abstract

Background: The GH/insulin-like growth factor 1 axis is physiologically involved in the regulation of electrolytes and water homeostasis by kidneys, and influences glomerular filtration and tubular re-absorption processes. The aim of the study was to investigate renal structure and function in acromegalic patients during active disease and disease remission.

Patients: Thirty acromegalic patients (15 males and 15 females), aged 32–70 years, were enrolled for the study. Ten de novo patients had active disease, whereas 20 patients showed disease remission 1 year after medical treatment with somatostatin analogs (SA) (ten patients) or surgery (ten patients). Thirty healthy subjects matched for age, gender, and body surface area were enrolled as controls.

Results: In both active (A) and controlled (C) patients, creatinine clearance \( P<0.001 \) and citrate \( P<0.05 \) and oxalate levels \( P<0.001 \) were higher, whereas filtered Na \( P<0.001 \) and K \( P<0.001 \) fractional excretions were lower than those in the controls. Urinary Ca \( P<0.001 \) and Ph \( P<0.05 \) levels were significantly increased compared with the controls, and in patients with disease control, urinary Ca \( P<0.001 \) levels were significantly reduced compared with active patients. Microalbuminuria was significantly increased in active patients \( P<0.05 \) compared with controlled patients and healthy control subjects. The longitudinal \( P<0.05 \) and transverse \( P<0.05 \) diameters of kidneys were significantly higher than those in the controls. In all patients, the prevalence of micronephrolithiasis was higher than that in the controls \( P<0.001 \), and was significantly correlated to disease duration \( r=0.871, P<0.001 \) and hydroxyproline values \( r=0.639, P<0.001 \).

Conclusions: The results of the current study demonstrated that acromegaly affects both renal structure and function. The observed changes are not completely reversible after disease remission.

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Introduction

GH and insulin-like growth factor 1 (IGF1) are physiologically involved in the regulation of renal growth and function (1). GH receptors, as well as IGF1, IGF2, IGF-binding proteins (IGFBPs) and IGF receptors, are expressed in adult rat kidney (2), where the GH/IGF1 system seems to exert an antidiuretic and antinatriuretic effect together with a decrease in K excretion, as mainly demonstrated after acute administration of recombinant GH (rGH) (2). In adult rats, GH, IGF1, and IGF2 receptors as well as IGFBPs have been detected in both glomerular and tubular structures (2, 3), and chronic administration of GH is associated with an increase in glomerular filtration rate (GFR), probably mediated by IGF1, and a transient decrease in urinary Na and K excretions (4).

Distinct from the cardiorespiratory and the gastrointestinal systems, kidney has only been superficially investigated in acromegalic patients, so that little data is available on renal structure and function in acromegaly presently. In acromegalic patients, the exposure to chronic GH and IGF1 levels has been found to induce an increase in renal plasma flow (RPF), GFR, and renal size, with the effects on RPF and GFR being mediated by IGF1 (5). Recently, Baldelli et al. reported a high prevalence of microalbuminuria (mA) in patients with acromegaly, particularly in those with diabetes mellitus or impaired glucose tolerance, and found a significant correlation of urinary albumin excretion with disease duration and insulin sensitivity and of urinary albumin/creatinine ratio with GH levels (6). No further study has investigated the effect of GH and IGF1 excess on kidney.

This cross-sectional study aimed at investigating renal structure and function in acromegalic patients during active disease and 1 year after disease remission, achieved by medical and/or surgical treatment.
Patients

Fifty-eight consecutive acromegalic patients (33 males and 25 females, aged 31–70 years, mean 48.7 ± 11.4 years) were admitted to our department from January 1st 2005 to December 31st 2007. The diagnosis of acromegaly was performed on the basis of the following criteria: i) mean integrated 24-h GH > 2.5 μg/l; ii) GH nadir > 1.0 μg/l after an oral glucose tolerance test (oGTT); and iii) IGF1 above the normal range adjusted for gender and age (7). Similarly, the achievement of biochemical control of acromegaly was considered when i) mean integrated 24-h GH was < 2.5 μg/l; ii) GH nadir was < 1.0 μg/l after oGTT; and iii) IGF1 was in the normal range adjusted for gender and age (7). Systemic arterial hypertension and diabetes mellitus were diagnosed in 22 (37.9%) and 6 (10.3%) patients respectively in line with the International Guidelines Criteria (8, 9). Inclusion criteria included written informed consent, age ≥ 18 years, diagnosis of active and/or controlled or cured acromegaly in line with the international criteria proposed by Giustina et al. (7). Treatment for arterial hypertension and diabetes mellitus (10, 11) was considered as an exclusion criterion, because it might interfere with renal filtration and re-absorption processes, so that all hypertensive and diabetic patients (28 patients, 48.3%) were excluded from the study. Acute or chronic renal disease was also considered as an exclusion criterion.

The remaining 30 patients were enrolled for the study. The patients’ profile at the study entry is reported in Table 1. Ten patients (33.3%) had active disease, whereas 20 patients (66.6%) showed clinical and biochemical control of acromegaly. All patients with active disease were evaluated at diagnosis; among patients with controlled disease, 10 patients were evaluated 12 months after transphenoidal selective adenomectomy and 10 patients were evaluated 12 months after the achievement of disease control with SA treatment, so that they were defined responders to medical therapy with SA. The characteristics of the patients in each subgroup are reported in Table 2. None of the patients showed secondary hormonal deficiencies or abnormal parathyromone (PTH) or calcitonin levels.

Thirty healthy subjects matched for gender (15 males and 15 females), age (47.2 ± 11.3 years), and BSA (1.91 ± 0.10 m²) were considered as the control group. In all patients, the spontaneous GH secretion (as six blood samples at 30-min intervals) and IGF1 levels were measured.

All subjects were enrolled for the study after their written informed consent had been obtained. The study was conducted in line with the Declaration of Helsinki for studies in human subjects.

Study protocol

This is a case–control cross-sectional study. All patients with acromegaly who were consecutively admitted to our department and met the inclusion criteria were enrolled for the study. All parameters were recorded at diagnosis in ten de novo patients, 12 months after the achievement of disease control by surgery in ten patients and 12 months after the achievement of disease control by medical treatment with SA in ten patients. At study entry, in both active and controlled patients, clinical parameters, including age, disease duration, height, weight and body mass index (BMI), and hemodynamic parameters, such as heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP), were recorded. The standard urine analysis, as well as the measurement of serum and urinary creatinine (Cr), urea (Ur), uric acid (UA), Na, K, Ca, and Ph levels, was performed. Urinary hydroxyproline (UHyd), citrate (UCit), bicarbonate (UBic) and oxalate (UOx), and mA were also evaluated. To investigate the glomerular filtration and tubular re-absorption function, creatinine clearance (CrC) and renal fractional excretion of electrolytes, Ur.

Table 1 Profile of patients and controls at the study entry.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Active patients (A)</th>
<th>Controlled patients (B)</th>
<th>Controls (C)</th>
<th>P value (A and B)</th>
<th>P value (A and C)</th>
<th>P value (B and C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.35 ± 9.93</td>
<td>47.90 ± 12.82</td>
<td>47.20 ± 11.30</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.59 ± 15.59</td>
<td>82.33 ± 30.47</td>
<td>82.30 ± 18.72</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>2.01 ± 0.30</td>
<td>1.98 ± 0.26</td>
<td>1.96 ± 0.10</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>124.86 ± 47.98</td>
<td>152.88 ± 42.89</td>
<td>152.88 ± 42.89</td>
<td>&lt; 0.05</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>127.06 ± 14.01</td>
<td>122.28 ± 15.86</td>
<td>121.33 ± 22.23</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>68.80 ± 10.99</td>
<td>68.14 ± 9.63</td>
<td>67.33 ± 7.98</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71.03 ± 8.97</td>
<td>69.15 ± 7.36</td>
<td>75.80 ± 9.86</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>91.07 ± 19.14</td>
<td>89.95 ± 26.81</td>
<td>88.13 ± 21.98</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.76 ± 0.19</td>
<td>0.83 ± 0.26</td>
<td>0.80 ± 0.10</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure.
and UA were also measured. In all patients, renal ultrasonography (US) was performed to evaluate kidney size, and to investigate the prevalence of nephrolithiasis (NL) and/or microlithiasis (mNL).

**Methods**

**Assays**

In all patients and control subjects, body surface area (BSA) was calculated in line with the DuBois formula: BSA = 0.007184 × [Height (cm)^0.725 × Weight (kg)^0.425]. Both serum GH and IGF1 levels were measured by chemiluminescent immunometric assay using commercially available kits (Immulite, DPC, Lhambers, UK). For GH assay, the sensitivity was 0.05 μg/l; the intra-assay and inter-assay coefficients of variation (CV) were 5.3–6.5 and 5.5–6.2% respectively. For IGF1 assay, the sensitivity was 20 ng/l; the intra-assay and inter-assay CV were 3.1–6.1 and 3.2–6.0% respectively.

In the urine analysis, serum and urinary Cr, electrolytes, UA and Ur, as well as UCit and Uox, and mA were measured by standard available procedures.

In order to guarantee a unique and repeatable method of urine collection and to minimize any possible interference of water and dietary protein intake, both patients and controls were accurately trained. According to the literature (12, 13) and taking into account that in acromegalic patients body composition and lean/fat mass ratio are different from those in healthy subjects (14), CrC was calculated using the following formula: (urinary Cr (mg/dl) × 24-h urinary volume (ml/min)/serum Cr (mg/dl)). In line with previous studies (15), electrolyte fractional excretions were calculated using the following formula: (UV (mmol/l) × serum Cr (mg/dl))/SV (mmol/l) × urinary Cr (mg/dl)) × 100, where UV indicates the urinary values and SV indicates the serum values. Similarly, Ur and UA fractional excretion was calculated using the following formula: (UV (mg/dl) × serum Cr (mg/dl))/SV (mg/dl) × urinary Cr (mg/dl)) × 100.

**Ultrasonographic study**

Renal US was performed using a commercially available real-time machine. Scans were obtained using a standard abdominal 7.5-MHz transducer. Multiple anatomic approaches, including supine and decubitus views obtained in transverse and longitudinal planes, were used to study kidney structure. The images were registered on magnetic supports and analyzed later. All US examinations were performed by a single operator, blinded with respect to patient or control study. According to Middleton et al. (16), overt NL and mNL were revealed by the presence of respectively hyperechoic areas ≥ 2.5 mm and hyperechoic spots detected in renal pelvis or calyces.

**Statistical analysis**

Data were analyzed using SPSS Software for Windows, version 13.0 (SPSS, Inc., Cary, NC, USA). Data are reported as mean ± S.D. The comparison between the numerical data was made by Kruskal–Wallis H test followed by Dunn’s test for the adjustment of multiple comparisons. The comparison between prevalence was performed by χ² test corrected by Fisher’s exact test when necessary. The correlation study was done by calculating Spearman’s correlation coefficients. Significance was set at 5%.

**Results**

The results of the present study are given in Table 3.

**Patients with active disease**

CrC (P < 0.001) was significantly increased, whereas Na (sodium fractional excretion (NaFE), P < 0.001) and K (potassium fractional excretion (KFE), P < 0.01) fractional excretions were significantly decreased compared with the controls (Fig. 1). UCa (P < 0.001) and UPh (P < 0.05) were significantly increased compared with the control subjects. UOx (P < 0.001), UCit (P < 0.05),
and mA (P < 0.05) levels were significantly increased compared with the controls. No significant difference was found in the remaining parameters between active patients and controls. The US examinations showed increased longitudinal (P < 0.05) and transverse (P < 0.05) renal diameters (Fig. 2), and an increased prevalence of mNL (P < 0.001, Fig. 3) compared with the controls.

**Patiens with controlled disease**

Compared with healthy control subjects, CrC (P < 0.001, Fig. 1), UCa (P < 0.05), UPh (P < 0.001), and UOx (P < 0.001) were significantly higher; NaFE (P < 0.05) and KFE (P < 0.001) were significantly lower in patients with controlled disease (Fig. 1), whereas UCit and mA levels were similar in the two groups of subjects. Compared with active patients, UCa (P < 0.001), UPh (P < 0.01), UCit (P < 0.05), and mA (P < 0.05) were significantly lower, whereas CrC was only slightly but not significantly reduced and NaFe and KFE were slightly but not significantly higher in patients with controlled disease. UOx levels were similar in the two groups of subjects. Among patients with controlled disease, no significant difference was found in any kidney function parameter between those treated by surgery and those treated by medical therapy with somatostatin analogs. The US examinations showed increased longitudinal (P < 0.05) and transverse (P < 0.05) renal diameters (Fig. 2), as well as an increased prevalence of mNL (P < 0.001, Fig. 3) compared with the controls, and no significant difference with the patients with active disease.

**Correlations**

In both active and controlled patients, the prevalence of micronephrolithiasis (μNL) was significantly correlated with disease duration (r = 0.871, P < 0.001) and UHyd values (r = 0.639, P < 0.001).

**Discussion**

The main result of this study is that acromegaly is characterized by significant modifications of renal structure and function.

Similar to cardiorespiratory and gastrointestinal systems, the kidney is a target organ in acromegaly. Kidneys have been reported to be heavier in acromegaly than in healthy control subjects (2). Moreover, the administration of recombinant human IGF1 to rats has been reported to reduce selective hypertrophy of kidney, whereas elevated levels of circulating GH also cause renal growth, inducing a gain in renal mass mediated by IGF1 (2). Many evidences in literature have clearly demonstrated in human and rodent models that the exposure to endogenous or exogenous
GH and IGF1 excess induces renal hypertrophy (17), causing the progressive enlargement of glomeruli until glomerulosclerosis (18) and modulating cellular growth in proximal tubule epithelia (19).

As expected, in patients with active disease, renal size was significantly increased, and it increased persistently also in patients with controlled disease. Together with the morphological changes, in patients with active acromegaly, several alterations, only partially reversible after disease remission, were found in functional parameters. This observation confirms that the morphological and functional abnormalities of kidney are only partially reversible after 1-year remission of acromegaly. However, it is noteworthy that this short time of observation after disease remission represents a clear limitation of the present study, and could explain the partial reversibility described in renal morphological and functional alterations. We cannot exclude that a longer time of observation after the achievement of disease control might be associated with a more significant reversibility of these changes in renal structure and function.

In the past, only few authors have investigated the effects of an increase in GH and IGF1 levels on the kidney. In previous studies, CrC has been found to be increased in patients with acromegaly and decreased in patients with GH deficiency compared with healthy subjects (20, 21). In line with the previous reports, the results of the present study demonstrated a significant increase in CrC in both active and controlled patients compared with healthy subjects. We hypothesized that the increase in kidney size might induce consequently an increase also in RPF and GFR and tubular re-absorption, and so that might enhance renal filtration and re-absorption processes. These data could also explain the alterations observed in renal clearance and in electrolyte fractional excretions.

In particular, it is noteworthy that NaFE and KFE were found to be significantly reduced in both active and controlled patients compared with the controls. Two different theories have been proposed in the literature to explain the role of GH/IGF1 system in renal re-absorption regulation and water homeostasis. In rats and human liver, brain and kidney, exposure to
GH (22, 23) has been shown to increase the activity of Na-K-ATPase, which is mainly responsible for the transepithelial NaCl re-absorption. Recent studies (24, 25) have demonstrated in rats that the acute administration of rGH induces the phosphorylation-mediated activation of the kidney-specific Na, K, and Cl co-transporter. Owing to this phenomenon, a greater NaCl and K re-absorption into the interstitium was described (24, 25). In line with these studies, we found a significant decrease in NaFE and KFE in active patients compared with the controls. A role of the documented effect of GH and IGF1 in Na and K transporters cannot be ruled out. However, interestingly, controlled patients also showed a significant reduction in NaFE and KFE compared with the control subjects. The reasons are not clear, but we hypothesized that the persistently increased renal size and probably glomerular and tubular size may also explain the persistence of most electrolyte excretion, despite normalization of GH and IGF1 levels in patients with controlled disease. Alternatively, chronic exposure to GH and IGF1 excess and prolonged disease duration might have altered the response of kidney to GH stimulation and dissociated it from the physiological mechanisms. Finally, the possibility that a longer period of time is necessary to observe a complete recovery of the physiological Na and K excretions cannot be completely ruled out.

Hypercalciuria and hyperphosphaturia were also observed in active patients, and they partially persisted in controlled patients. It is well known that acromegaly is associated with the disturbances of Ca and Ph metabolism, and consequently with an increased risk of Ca stones (26, 27). In the general population, the risk of NL is related to hypercalciuria, hyperoxaluria, and hyperuricosuria but also to hypocitraturia (28). In acromegaly, both direct GH and indirect IGF1 effects and PTH and vitamin D actions on bone have been described to be involved in the stimulation of bone turnover, determining hypercalciuria and hyperphosphatemia (29). In our study, in active patients, increased urinary Ca and Ph levels were associated with hyperoxaluria and hypercitraturia. Previous studies have demonstrated that hyperoxaluria is associated with an increased predisposition to NL (30), whereas hypercitraturia seems to prevent it (31). The simultaneous presence of hyperoxaluria and hypercitraturia in our patients probably justified the low prevalence of overt NL and the significant increase in the prevalence of μNL that we observed in both active and controlled patients. Moreover, the results of the present study demonstrated that in all patients, mA was significantly correlated with disease duration and UHyd levels. Lepszy et al. (32) reported a significantly higher urinary output of hydroxyproline in active acromegalic patients compared with healthy subjects. We also found increased, although not significant, levels of UHyd in active patients, whereas controlled patients showed UHyd values that were similar to those of the controls. Anyhow, the results of the current study demonstrated that the changes in Ca and Ph excretions are significantly improved and almost recovered in patients with controlled disease, probably because they are mainly dependent on metabolic changes which revert with the normalization of GH and IGF1 after disease remission. Of course, a higher prevalence of mA persists also in patients with controlled disease.

A significant increase in mA was found in active patients. mA is defined as 30–300 mg/day albumin excretion in urine (33), and is known to be related to endothelial dysfunction (33) and associated with a higher risk of cardiovascular disease morbidity and mortality (34) in patients with metabolic syndrome. Previous literature reported a relationship between mA and renal injury in the presence of arterial hypertension (35) and/or insulin resistance (36, 37). However, several studies in the literature (38–42) have described mA as an independent cardiovascular risk factor not only in diabetic and hypertensive patients, but also in subjects without arterial hypertension, diabetes mellitus, ischemic heart disease, and renal injury, so that they are defined as ‘low-risk’ individuals. Furthermore, in USA and Europe, mA has been described as a common finding respectively in at least 5 and 7% of healthy general population (43). The precise pathophysiology associated with mA is still unclear, although it may reflect the renal manifestation of a global abnormality of endothelial function (43). In acromegaly, endothelial dysfunction has been reported as a common condition in patients with and without metabolic complications (44). The presence of mA has already been associated with acromegaly, especially if complicated with glucose intolerance or diabetes, and has also been described to normalize with disease remission (5) in line with the results of the current study. In our study, prevalence of mA was 13%. Moreover, the reason for the significant increase in mA in our study is not clear, considering that all
hypertensive and diabetic patients have been excluded from the statistical analysis. However, it could be interpreted as a further consequence of renal functional and/or morphological changes observed in acromegalic patients.

In conclusion, acromegaly is responsible for structural abnormalities and renal function impairment because it induces an increase in renal size together with an increase in CrC, decrease in Na and KFEs, hypercalciuria, hyperphosphaturia, increase in mA levels and high prevalence of μNL. These alterations seem to revert only partially after the correction of GH and IGF1 excess by treatment, independently on medical or surgical therapy. Further studies on the effects of acromegalic disease treatment and renal performance are mandatory.

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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References

24 Imbert-Teboul M, Doucet A, Chanson P & Lombès M. Epithelial sodium channel is a key mediator of growth hormone-induced sodium retention in acromegaly. Endocrinology 2008 149 3294–3305.

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