The Kidney in Acromegaly: renal structure and function in patients with acromegaly during active disease and one year after disease remission.

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Short Title
Renal Structure and Function in Acromegaly

Key Words
Acromegaly, GH, IGF-I, kidney, renal structure, renal function, creatinine clearance, calcium, phosphorus, nephrolithiasis

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ABBREVIATIONS: BMI= body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure; CrC= creatinine clearance; UFE= urea fractional excretion; NaFE= sodium fractional excretion; KFE= potassium fractional excretion; CaFE= calcium fractional excretion; PhFE= phosphorus fractional excretion; UAFe= uric acid fractional excretion; UCa= urinary calcium; UPh= urinary phosphorus; UOx= urinary oxalates; UHyd= urinary hydroxyproline; UBc= urinary bicarbonate; UCit= urinary citrate; mA= microalbuminuria; NL= overt nephrolithiasis; µNL= micronephrolithiasis.
ABSTRACT

Background: The GH/IGF-I axis is physiologically involved in regulation of electrolytes and water homeostasis by kidneys and influences glomerular filtration and tubular reabsorption 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, 15 females), aged 32-70 years, entered the study. Ten *de novo* patients had active disease whereas twenty patients showed disease remission 1 year after medical treatment with SA (10 patients) or surgery (10 patients). Thirty healthy subjects, matched for age, gender and body surface area (BSA) were enrolled as controls.

Results: Both in active (A) and controlled (C) patients, creatinine clearance ($p<0.001$), citrate ($p<0.05$) and oxalate levels ($p<0.001$) were higher and whereas filtered sodium ($p<0.001$) and potassium ($p<0.001$) fractional excretions were lower than in controls. Urinary calcium ($p<0.001$) and phosphorus ($p<0.05$) levels were significantly increased compared to controls, and in patients with disease control, urinary calcium ($p<0.001$) levels were significantly reduced compared to active patients. Microalbuminuria was significantly increased in active patients ($p<0.05$) compared to controlled patients and healthy control subjects. The longitudinal ($p<0.05$) and transverse ($p<0.05$) diameters of kidneys were significantly higher than in controls. In all patients the prevalence of micronephrolithiasis was higher than in 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.
INTRODUCTION

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

Distinctly from the cardio-respiratory and the gastrointestinal systems, kidney has been only superficially investigated in acromegalic patients, so that little data are today available on renal structure and function in acromegaly. In acromegalic patients, the exposure to chronic GH and IGF-I levels have been found to induce an increase in renal plasma flow (RPF), glomerular filtration rate (GFR) and renal size, with the effects on RPF and GFR being mediated by IGF-I (5). Recently, Baldelli et al. reported a high prevalence of microalbuminuria in patients with acromegaly, particularly those with diabetes mellitus or impaired glucose tolerance, finding 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 IGF-I excess on kidney.

This cross-sectional study aimed at investigating renal structure and function in acromegalic patients during active disease and one 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 yrs) 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: 1) mean integrated 24-h GH was > 2.5 µg/L; 2) GH nadir was > 1.0 µg/L after an oral glucose tolerance test (oGTT); 3) IGF-I was above the normal range adjusted for gender and age (7). Similarly, the achievement of biochemical control of acromegaly was considered when: 1) mean integrated 24-h GH was < 2.5 µg/L; 2) GH nadir was < 1.0 µg/L after oGTT; 3) IGF-I 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 an exclusion criteria, because it might interfere with renal filtration and reabsorption processes, so that all hypertensive and diabetics patients (28 pts, 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 in the study. The patient’s profile at the study entry is reported in Table 1. Ten patients (33.3%) had active disease whereas twenty 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 pts were evaluated 12 months after transsphenoidal selective adenomectomy and 10 pts 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 patients in each subgroup are reported in Table 2. None of the patients showed secondary hormonal deficiencies or abnormal parathormone (PTH) or calcitonin (CT) 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 controls group. In all patients the spontaneous GH secretion (as 6 blood samples at 30 minutes intervals) and IGF-I levels were measured. All subjects were enrolled in the study after their written informed consent had been obtained. The study was conducted in line with the Helsinki Declaration 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 meet the inclusion criteria were enrolled in the study. All parameters were recorded at diagnosis in 10 de novo patients, 12 months after the achievement of disease control by surgery in 10 patients and 12 months after the achievement of disease control by medical treatment with SA in 10 patients. At study entry, in both active and controlled patients clinical parameters, including age, disease duration, height, weight and BMI, and hemodynamic parameters, such as heart rate, SBP and DBP, were recorded. The standard urine analysis, as well as the measurement of serum and urinary creatinine (Cr), urea (Ur), uric acid (UA), sodium (Na), potassium (K), calcium (Ca) and phosphorus (Ph) levels were performed. Urinary hydroxyproline (UHyd), citrate (UCit), bicarbonate (UBic) and oxalate (UOx), and microalbuminuria (mA) were also evaluated. To investigate the glomerular filtration and tubular reabsorption function, creatinine (CrC) clearance and renal fractional excretion (FE) of electrolytes, urea and uric acid 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 DuBois formula :\[ BSA = 0.007184 \times (\text{Height (cm)}^{0.725} \times \text{Weight (kg)}^{0.425}. \] Both serum GH and IGF-I levels
were measured by chemiluminescent immunometric assay using commercially available kits (Immulate, DPC, Llamberis, UK). For GH assay, the sensitivity was 0.05 µg/L; the intra-assay and inter-assay coefficient of variation (CV) were 5.3-6.5 % and 5.5-6.2% respectively. For IGF-I assay, the sensitivity was 20 µg/L; the intra-assay and inter-assay CV were 3.1-6.1 % and 3.2-6.0 % respectively.

The urine analysis, serum and urinary creatinine, electrolytes, uric acid and urea, as well as UCit and Uox, and mA were measured by standard available procedures.

In order to guarantee an unique and repeatable method of urine collection and to minimize any possible interference of water and dietary protein intake, both patients and controls have been accurately trained. According to literature (12, 13) and taking into account that in acromegalic patients body composition and lean/fat mass ratio are different from healthy subjects (14), creatinine clearance was calculated by the following formula: [urinary creatinine (mg/dl) x 24 h urinary volume (ml/min) / serum creatinine (mg/dl)]. In line with previous studies (15), electrolytes fractional excretions were calculated by the following formula: [UV (mmol/L) x serum creatinine (mg/dl)/ SV (mmol/L) x urinary creatinine (mg/dl)] x 100, where UV indicates the urinary values and SV the serum values. Similarly, urea and uric acid excretion fraction was calculated by the following formula: [UV (mg/dl) x serum creatinine (mg/dl)/ SV (mg/dl) x urinary creatinine (mg/dl)] x 100.

**Ultrasonographic study**

Renal US was performed by a commercially available real-time machine. Scans were obtained by 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 exams were performed by the a single operator, blinded in respect to patient or control study. According to Middleton et al
(16), overt NL and mNL was 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 package). Data are reported as Mean±SD. The comparison between the numerical data was made by Kruskal-Wallis H test followed by Dunn’s test for the adjustment of multiple comparison. The comparison between prevalence was performed by \( \chi^2 \) test corrected by Fisher exact test when necessary. The correlation study was done by calculating the Spearman’s correlation coefficients. Significance was set at 5%.

RESULTS

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

Patients with active disease. CrC (\( p<0.001 \)) was significantly increased, whereas sodium (NaFE, \( p<0.001 \)) and potassium (KFE, \( p<0.01 \)) fractional excretions were significantly decreased compared to controls (Fig. 1). UCa (\( p<0.001 \)) and UPh (\( p<0.05 \)) were significantly increased compared to control subjects. UOx (\( p<0.001 \)), UCit (\( p<0.05 \)) and mA (\( p<0.05 \)) levels were significantly increased compared to controls. No significant difference was found in the remaining parameters between active patients and controls. The US exams 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 to controls.

Patients with controlled disease. Compared to 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 to 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 whereas 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 parameters between those treated by surgery and those treated by medical therapy with somatostatin analogues. The US exams 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 to controls., and not significant difference with the patients with active disease.

**Correlations:** In both active and controlled patients, the prevalence of 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.

As for the cardio-respiratory and gastrointestinal systems, the kidney is a target organ in acromegaly. Kidneys have been reported to be heavier in acromegalic patients than in healthy control subjects (2). Moreover, the administration of recombinant human (rh) IGF-I to rats has been reported to induce selective hypertrophy of kidney, whereas elevated levels of circulating GH also cause renal growth, inducing a gain in renal mass mediated by IGF-I (2). Many evidences in literature have clearly demonstrated in human and rodents models that the exposure to endogenous
or exogenous GH and IGF-I 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 persisted increased 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 one 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 to a more significant reversibility of these changes in renal structure and function.

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

In particular, it is noteworthy that NaFE and KFE were found to be significantly reduced in both active and controlled patients compared to controls. Two different theories have been proposed in
the literature to explain the role of GH/IGF-I system in renal re-absorption regulation and water homeostasis. Exposure to GH (22, 23) has shown in rats and human liver, brain and kidney to increase the activity of Na-K-ATPase, which is the main responsible for the transepithelial NaCl reabsorption. 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. Due 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 to controls. A role of the documented effect of GH and IGF-I on Na and K transporters cannot be ruled out. However, interestingly, also controlled patients showed a significant reduction in NaFE and KFE compared to control subjects. The reasons are not clear, but we hypothesized that the persistently increased renal size and probably of glomerular and tubular size may also explain the persistence of most electrolyte excretion, despite normalization of GH and IGF-I levels in patients wit controlled disease. Alternatively, chronic exposure to GH and IGF-I excess and prolonged disease duration might have altered the response of kidney to GH stimulation and dissociate 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 excretion cannot be completely ruled out.

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

A significant increase in microalbuminuria was found in active patients. Microalbuminuria 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 higher risk of cardiovascular disease morbidity and mortality (34) in patients with metabolic syndrome. Previous literature reported a relationship between microalbuminuria 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 microalbuminuria 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 to be defined “low risk” individuals. Furthermore, in USA and Europe microalbuminuria has been described as a common finding respectively in at least 5% and 7% of healthy general population (43). The precise pathophysiology associated with microalbuminuria 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 microalbuminuria has been already associated with acromegaly, especially if complicated with glucose intolerance or diabetes, and has been also described to normalize with disease remission (5) in line with the results of the current study. In our series, prevalence of microalbuminuria was 13%. Moreover, the reason of the significant increase microalbuminuria in our series is not clear, considering that all hypertensive and diabetics patients have been excluded from 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 structure abnormalities and renal function impairment because it induces increase in renal size together with increase in creatinine clearance, decrease in sodium and potassium fractional excretion, hypercalciuria, hyperphosphaturia, increase in microalbuminuria levels and high prevalence of micronephrolithiasis. These alterations seem to revert only partially after the correction GH and IGF-I excess by treatment, independently on medical or surgical therapy. Further studies on the effects of acromegalic disease treatment and renal performance are mandatory.

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


LEGEND TO FIGURES

**Fig. 1:** CrC (up) in active ($p<0.001$) and controlled ($p<0.01$) patients compared to controls. NaFE (bottom, left) in active ($p<0.001$) and controlled ($p<0.05$) patients compared to controls. KFE (bottom, right) in active ($p<0.01$) and controlled ($p<0.001$) patients compared to controls.

**Fig. 2:** Longitudinal (up, left, $p<0.05$) and transverse (bottom, right, $p<0.05$) renal diameters in active and controlled patients compared to controls.

**Fig. 3:** Prevalence of $\mu$NL (up, left, $p<0.001$) and correlation with disease duration (up, right, $r=0.871$, $p<0.001$) and urinary hydroxyproline (bottom, $r=0.639$, $p<0.001$) in active (left) and controlled (right) patients compared to controls.
Figure 2

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Figure 3

Prevalence of μNL

Disease duration (months)

IXP

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Table 1: Patients and controls profile 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,B)</th>
<th>P-VALUE (A,C)</th>
<th>P-VALUE (B,C)</th>
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<td>30</td>
<td>---</td>
<td>---</td>
<td>---</td>
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<td>AGE (years)</td>
<td>44.35±9.93</td>
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<td>NS</td>
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<tr>
<td>WEIGHT (kg)</td>
<td>82.59±15.59</td>
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<td>82.30±18.72</td>
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<tr>
<td>BSA (m²)</td>
<td>2.01±0.30</td>
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<td>1.96±0.10</td>
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<td>NS</td>
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<td>DISEASE DURATION (months)</td>
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<td>152.88±42.89</td>
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<td>SBP (mmHg)</td>
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<td>121.33±22.23</td>
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<td>NS</td>
<td>NS</td>
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<td>DBP (mmHg)</td>
<td>68.80±10.99</td>
<td>68.14±9.63</td>
<td>67.33±7.98</td>
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<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>
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<td>FASTING GLUCOSE (mg/dl)</td>
<td>91.07±19.14</td>
<td>89.95±26.81</td>
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<td>NS</td>
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<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>
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</table>

BMI= body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure.
### Table 2: Profile of patients in each subgroup at the study entry

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>DE NOVO PTS (A)</th>
<th>OPERATED PTS (B)</th>
<th>SA-RESPONDER PTS (C)</th>
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<th>P-VALUE (A,C)</th>
<th>P-VALUE (B,C)</th>
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<tr>
<td>AGE (years)</td>
<td>42.26±8.44</td>
<td>42.85±8.82</td>
<td>52.45±9.39</td>
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<td>NS</td>
<td>NS</td>
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<tr>
<td>WEIGHT (kg)</td>
<td>85.01±16.18</td>
<td>85.50±17.34</td>
<td>78±10.89</td>
<td>NS</td>
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<tr>
<td>BSA (m²)</td>
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<td>1.97±0.21</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>DISEASE DURATION (months)</td>
<td>101.76±35.88</td>
<td>126.84±56.16</td>
<td>178.92±29.64</td>
<td><strong>&lt;0.05</strong></td>
<td><strong>&lt;0.05</strong></td>
<td><strong>&lt;0.05</strong></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>129.26±15.13</td>
<td>124.0±15.16</td>
<td>126.0±11.73</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.17±11.97</td>
<td>78.8±7.56</td>
<td>80.0±7.45</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>HEART RATE (bpm)</td>
<td>71.3±9.28</td>
<td>75.2±9.54</td>
<td>67.5±6.02</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>FASTING GLUCOSE (mg/dl)</td>
<td>98.56±16.45</td>
<td>84.80±9.98</td>
<td>98.8±13.83</td>
<td><strong>0.01</strong></td>
<td>NS</td>
<td><strong>0.01</strong></td>
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<tr>
<td>SERUM CREATININE (mg/dl)</td>
<td>0.76±0.18</td>
<td>0.81±0.17</td>
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BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
Table 3: Effects of GH and IGF-I levels on kidney function and structure in active and controlled patients compared to control subjects

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>ACTIVE PATIENTS (A)</th>
<th>CONTROLLED PATIENTS (B)</th>
<th>CONTROLS (C)</th>
<th>P-VALUE (A, B)</th>
<th>P-VALUE (A, C)</th>
<th>P-VALUE (B, C)</th>
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</thead>
<tbody>
<tr>
<td>GH (µg/L)</td>
<td>13.93±16.14</td>
<td>2.13±1.64</td>
<td>0.70±0.31</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>IGF-I(µg/L)</td>
<td>767.70±196.65</td>
<td>248.77±124.48</td>
<td>199.13±23.48</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Urine pH (units)</td>
<td>6.19±1.07</td>
<td>5.97±0.49</td>
<td>6.04±0.31</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CcC (ml/min)</td>
<td>162.15±45.01</td>
<td>154.94±51.21</td>
<td>83.59±18.70</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UFE (%)</td>
<td>0.60±0.30</td>
<td>0.95±0.78</td>
<td>0.68±0.63</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>NaFE (%)</td>
<td>0.49±0.17</td>
<td>0.66±0.14</td>
<td>0.82±0.32</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>KFE (%)</td>
<td>5.16±1.83</td>
<td>6.49±5.48</td>
<td>11.01±3.95</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CaFE (%)</td>
<td>2.24±1.97</td>
<td>1.31±0.64</td>
<td>1.34±0.55</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PhFE (%)</td>
<td>7.72±3.64</td>
<td>10.13±2.23</td>
<td>9.79±3.66</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>UAFE (%)</td>
<td>6.52±2.18</td>
<td>8.47±2.94</td>
<td>10.66±11.89</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>UCa (mg/24hs)</td>
<td>275.30±136.35</td>
<td>194.30±58.16</td>
<td>120.10±29.33</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>UPh (mg/24 hs)</td>
<td>974.50±319.13</td>
<td>755.70±322.81</td>
<td>578.13±130.72</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UOx (mg/24hs)</td>
<td>36.00±14.26</td>
<td>34.50±13.08</td>
<td>18.30±5.68</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UHyd (mg/24 hs)</td>
<td>55.90±26.74</td>
<td>39.75±20.30</td>
<td>63.76±52.47</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>UBc (mg/24hs)</td>
<td>0.30±0.56</td>
<td>0.12±0.08</td>
<td>0.24±0.29</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>UCit (mg/24hs)</td>
<td>433.90±204.16</td>
<td>283.65±265.14</td>
<td>272.03±198.55</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>mA (mg/L)</td>
<td>16.30±8.50</td>
<td>11.59±1.34</td>
<td>12.32±5.43</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Longitudinal Diameter (mm)</td>
<td>148.3±12.7</td>
<td>117.50±3.8</td>
<td>89.6±7.1</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Transverse Diameter (mm)</td>
<td>112.6±8.9</td>
<td>108.1±7.1</td>
<td>74.2±8.1</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>----------</td>
<td>----</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Prevalence of NL (% , nr)</td>
<td>10 (1/10)</td>
<td>10 (2/20)</td>
<td>16.6(5/30)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Prevalence of mNL (% , nr)</td>
<td>50 (5/10)</td>
<td>50 (10/20)</td>
<td>10 (3/30)</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CrC= creatinine clearance; UFE=urea fractional excretion; NaFE= sodium fractional excretion; KFE=potassium fractional excretion; CaFE= calcium fractional excretion; PhFE=phosphorus fractional excretion; UAFE= uric acid fractional excretion; UCa= urinary calcium; UPh= urinary phosphorus; UOx= urinary oxalates; UHyd= urinary hydroxyproline; UBc= urinary bicarbonate; UCit= urinary citrate; mA= microalbuminurA; NL= overt nephrolithiasis; µNL= micronephrolithiasis.

IGF-I NORMAL RANGE