Growth Hormone and the Kidney: A Case Presentation and Review of the Literature

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ABSTRACT

Hypersomatotropism is accompanied by a significant increase in GFR and RPF. A case of a patient with acromegaly and supranormal renal function as measured by inulin and p-aminohippurate clearances is reported. The literature regarding the effects of growth hormone on renal function is reviewed, and the potential mechanisms of action and therapeutic implications of these effects are discussed.

Key Words: GFR, RPF, insulin-like growth factor 1, acromegaly

A 31-yr-old white man with a history of acromegaly and a consequent transphenoidal resection of a pituitary adenoma at age 23 was admitted in October 1991 with a wk history of fatigue, a frontal headache, visual symptoms, polyuria, polydipsia, and polyphagia. Three years previously, he had been treated for diabetic ketoacidosis at which time computed tomographic scan of the head revealed a recurrence of the pituitary tumor. He was placed on insulin
and bromocriptine but stopped taking the latter medication after 2 months. Over the next 3 yr, he was seen sporadically in a medicine clinic, where his insulin therapy was monitored. Several months before presentation, he switched from insulin to an oral hypoglycemic agent. His only medication at the time of admission was glipizide.

A physical examination revealed a well-developed young man of average height and weight. It was otherwise remarkable for a prominent forehead, prognathism, large hands and feet, and thick, leathery skin. Visual field testing revealed bitemporal defects.

Laboratory studies at this time revealed a plasma bicarbonate of 12 mmol/L, a plasma glucose of 21.5 mmol/L, and a serum creatinine of 53 μmol/L. The anion gap was 18 mmol/L. Serum ketones were positive at 1:8 titers. Serum growth hormone (GH) was 77.8 μg/L (normal range, less than 8.0 μg/L), and the serum insulin-like growth factor 1 (IGF-1) level was 1,083 μg/L (normal range, 90 to 318 μg/L). A magnetic resonance imaging scan of the head revealed a 5-cm lobulated pituitary mass compressing the optic chiasm and nerves. A 24-h urine collection obtained at the time of admission revealed a creatinine clearance of 4.07 mL/s/1.73 m² and a 24-h urine protein of <372 mg.

The patient responded quickly to treatment of the diabetic ketoacidosis and was subsequently placed back on a stable insulin regimen. Bromocriptine therapy was restarted and resulted in a rapid resolution of the patient’s headache and visual symptoms. The patient is to be reevaluated for surgery in the near future.

During the course of the above evaluation, the patient underwent inulin and p-aminohippurate (PAH) clearance studies and a renal ultrasound. Serum glucosecs at the time were consistently less than 8.9 mmol/L. The glucose clearance was 224 mL/min/1.73 m², and the PAH clearance was 1,020 mL/min. The filtration fraction (GFR/CPAH) was 0.22. On ultrasound, the left kidney measured 13.7 cm in length and the right kidney measured 13.9 cm in length. The estimated volume of the left kidney by the prolate ellipsoid formula was 269 mL and that of the right was 253 mL; both of these volumes are more than 2 SD above published means.

This patient provides a striking example of the increased renal function observed in individuals with acromegaly. Over the past 40 yr, our understanding of the effects of GH on GFR and RPF has steadily progressed, but with the recent explosion of interest in growth factors, we will likely see larger strides being made in this area. This review traces and summarizes our current understanding of the effects of GH on GFR and RPF and briefly discusses its therapeutic potential.

HISTORICAL PERSPECTIVES: ACROMEGALY

It has long been known that kidney size is increased in patients with acromegaly. Only in the late 1930s and early 1940s, however, did the renal functional changes of acromegaly come to be appreciated. This discovery was presaged by the landmark studies of White and coworkers, wherein they described the renal functional changes accompanying hypophysectomy in the dog (1,2). Inulin, diodrast, creatinine, and urea clearances were all shown to be reduced in this experimental setting, indicating a reduction in RPF and GFR by as much as 50 to 75%. They also reported the absence of compensatory hypertrophy of the remaining kidney after unilateral nephrectomy in dogs subsequently undergoing hypophysectomy, indicating not only a functional but also a structural influence of the pituitary gland on the kidney. The observation that pituitary hypofunction in humans is similarly accompanied by a decreased GFR and RPF was made subsequently by Talbott and coworkers (3).

Barnett et al. followed these studies with the observation that the urea clearances of three patients with acromegaly were 30 to 100% increased above the normal standard (4). They further hypothesized that an unknown substance secreted by the eosinophil cells of the glandular hypophysis mediated these effects on the kidney.

In the 1950s, attention was turned more resolutely to the renal functional changes accompanying acromegaly. Luft and Sjogren compared the inulin and diodrast clearances of 8 patients with acromegaly with those of 10 control subjects (5). The mean GFR of the acromegalic patients was 26% higher than that of the control subjects. At the same time, RPF was found to be slightly diminished and the filtration fraction was found to be 40% increased in the acromegals when compared with controls. Using inulin clearance (C_in) and PAH clearance (C_PAH), Heller et al. found GFR and filtration fraction to be similarly increased in five patients with acromegaly but found that RPF also increased, contrary to findings from the previous study (6). Ikkos et al. in 1956 again looked at C_in and C_PAH in 13 patients with acromegaly and in 22 normal controls. They also measured total body water and extracellular water (ECW) using the volumes of distribution of deuterium oxide and insulin, respectively (7). In that study, both GFR and RPF in the acromegals were found to be significantly increased (27 and 29%, respectively) over those of controls but filtration fractions were essentially the same in both groups. Furthermore, those investigators noted an increase in the ECW that appeared to parallel the increases noted in the GFR and RPF. They hypothesized that the renal functional changes noted in acromegaly might be due to primary increases in extracellular fluid volume. The parallel
changes in renal function and ECW observed in that study were later confirmed by Falkheden and Sjögren, who also found normal filtration fractions in their study of 12 patients with acromegaly (8). Those authors cautioned, however, that although a relationship between renal functional changes and ECW did appear to exist, it was not necessarily a causal one. This latter point was a particularly compelling one because they also observed that in 12 patients without acromegaly who had undergone a hypophysectomy, GFR and RPF were significantly decreased without a parallel change in ECW. To round out the picture, Gershberg and coworkers compared the results of renal functional studies (C\textsubscript{\text{in}} and C\textsubscript{\text{PAH}}) with the autopsy findings of a patient with acromegaly (9). They found a striking elevation of the GFR (237 mL/min/1.73 m\textsuperscript{2}) and, at autopsy, kidney weights of 600 and 550 g. A histologic examination of the kidneys revealed markedly enlarged glomeruli with tubules enlarged to a lesser extent: no evidence of glomerulosclerosis was noted. Of interest, it was also noted that the increase in GFR was not proportional to the increase in kidney weight, indicating that growth hormone may have an effect on renal function independent of its effect on kidney mass. Certainly, then, the bulk of evidence from these early studies indicated that hyperosmotropism is associated with increased GFR and RPF without a change in filtration fraction and that these alterations cannot be explained simply on the basis of an increase in kidney mass or ECW.

In the 1960s and 1970s, attention turned to the effects of the treatment of acromegaly on renal function. Falkheden and Wickbom measured C\textsubscript{\text{in}} and C\textsubscript{\text{PAH}} and estimated the kidney sizes and weights, using roentgenographic techniques, of five acromegalic patients who had undergone hypophysectomy (10). They found that estimated kidney sizes, weights, GFR, and RPF all decreased significantly after hypophysectomy in these patients. However, there was also a lack of correlation between the renal structural and functional changes, not only in terms of the absolute magnitude of the change but also when the time course of the change was considered. These authors concluded that because the changes in kidney size over time do not correlate well with the decreases in GFR and RPF, the reduction in renal function observed after hypophysectomy again cannot be explained by changes in kidney mass alone. Eskildsen et al. examined the effect of bromocriptine treatment on the creatinine clearances of seven patients with acromegaly and found that the creatinine clearances did not change over a 7-month period of observation (11). Likewise, they found no significant change in urinary albumin, beta-2 microglobulin, or growth hormone excretion after bromocriptine treatment. They do not report, however, whether the patients manifested any clinical response to the bromocriptine treatment.

**HISTORICAL PERSPECTIVES: EXOGENOUS GH**

In seeking to further define the nature of the effect of hypophysectomy on renal function, White and coworkers first administered growth hormone to both normal and hypophysectomized dogs in the late 1940s (12). Both groups of dogs showed marked increases in C\textsubscript{\text{in}} and C\textsubscript{\text{PAH}}, whereby it was concluded that it was the loss of GH that is responsible for the depression of renal function after hypophysectomy. Enlarging upon this experience, Gershberg administered extractive human GH to two patients with chronic glomerulonephritis and uremia in the late 1950s (13). Each patient demonstrated a modest increase in creatinine clearance. Three other patients, two with postpartum hypopituitarism and one with cirrhosis and ascites, displayed more marked increases in creatinine clearance after treatment with GH. These renal effects became manifest 3 to 4 days after the initiation of treatment and dissipated about 2 days after treatment was stopped. Corvilain et al. subsequently showed that GFR and RPF increased in nine hospitalized patients after 4 days of extractive human GH treatment (14). Parving and coworkers measured GFR and RPF in a group of nine healthy males during a 2-h infusion of GH and found no change in these functional parameters (15). They concluded that GH requires hours to days for its renal effects to become evident. Finally, Christiansen et al. showed that 1 wk of GH administration to seven normal volunteers increased both GFR and RPF by about 10% without significantly affecting kidney size (16). A similar study of the effects of GH in seven well-controlled type 1 diabetic males showed not only that GFR and RPF increased but also that kidney size increased modestly after 1 wk (17).

**ETIOLOGY OF RENAL FUNCTIONAL CHANGES: IGF-1**

Although it has become quite clear that GH has pronounced effects on GFR and RPF, the exact mechanism whereby these effects are mediated is not known. Early hypotheses that the effects could be attributed to increases in extracellular fluid volume or absolute kidney mass alone are not supported by the available experimental or clinical evidence, as noted above. It has been known since the mid-1950s that many of the growth-promoting effects of GH are mediated by the peptide now designated IGF-1 (18,19). Several lines of evidence suggest that a similar mechanism obtains in the actions of GH on renal function (Table 1). First, as already discussed, the short-term infusion of GH has no effect on renal function;
TABLE 1. Evidence that the renal effects of GH are mediated by IGF-1

| Renal Functional Effects of GH Infusion are Delayed (Hours to Days) |
| Lack of a Temporal Relationship Between GH Levels and Changes in Renal Function |
| Increased Renal IGF-1 mRNA and Immunostainable IGF-1 in Experimental States of GH Excess |
| Recombinant IGF-1 Produces a Rapid (Minutes to Hours) Increase in GFR and RPF in Both Experimental Animals and Humans |

function, whereas renal effects are clearly observed after a more prolonged period of infusion and observation (14–17). Second, there does not appear to be a temporal relationship between plasma GH levels and the renal functional effects. Indeed, GFR and RPF were observed to increase in human subjects after a single injection of recombinant human GH only after plasma levels of GH had declined to close to baseline. On the other hand, plasma IGF-1 levels correlated very well with the observed increases in GFR and RPF (20). Third, it has been convincingly shown that in rats with GH-producing tumors and in normal rats administered exogenous GH, both renal IGF-1 mRNA and immunostainable IGF-1 are significantly increased over those in controls (21). Fourth, and most compelling, the administration of recombinant IGF-1 to both experimental animals and humans results in a rapid (minutes to hours) increase in GFR and RPF (22,23). Hirschberg and coworkers examined further the mechanism whereby IGF-1 increases GFR and RPF (24). Using micropuncture techniques in rats given an infusion of IGF-1, they found that the increase in single-nephron GFR is due primarily to an increase in the glomerular ultrafiltration coefficient with a lesser contribution of a decrease in efferent arteriolar resistance. Importantly, the IGF-1 treatment had no significant effect on either the absolute glomerular capillary pressure or the transglomerular capillary pressure difference.

Clearly then, there is persuasive evidence that the effects of GH on renal function, like its effects on somatic growth, are mediated in an endocrine fashion by IGF-1. This, of course, does not exclude the possibility that IGF-1 of renal origin also functions in an autocrine or paracrine fashion (21). Further, it would appear that the mechanism whereby IGF-1 increases GFR primarily involves an increase in the glomerular ultrafiltration coefficient. THERAPEUTIC IMPLICATIONS: A DOUBLE-EDGED SWORD?

Given the apparent salutary effect on renal function, the potential use of either IGF-1 or GH in the treatment of renal insufficiency is of obvious clinical interest. The issue is, however, a complicated one. First, the available evidence suggests that GH and IGF-1 may have no effect on renal function in the setting of renal insufficiency or reduced renal mass. Miller et al. found that GH and IGF-1 had no effect on renal function in rats that had undergone 1% nephrectomy (25). Haffner et al. also found that 3 days of intermittent sc GH had no effect on the renal function of seven patients with chronic renal insufficiency (Cr range, 15 to 30 mL/min/1.73 m²) (26). In addition, GH administration to children with chronic renal insufficiency and growth failure has no significant effect on renal function despite its beneficial effect on somatic growth (27). It has been suggested that the uremic state is one of relative resistance to the effects of GH and IGF-1 (28). It is possible that this resistance is mediated by a down-regulation of growth hormone receptors or by an increase in IGF-1-binding proteins, which would in turn decrease levels of circulating free IGF-1 (29). Second, although it is a controversial issue, renal hypertrophy and chronic hyperfiltration as induced by GH and IGF-1 may actually speed the progression of renal injury. Indeed, a role for GH and IGF-1 in diabetic nephropathy has been postulated (30,31). Whether this represents anything more than a theoretical concern cannot be answered at this time. However, in a very interesting series of experiments with transgenic mice chronically expressing either GH or IGF-1, Doi and coworkers found that those mice expressing GH went on to develop mesangial proliferation and glomerulosclerosis, whereas in those mice expressing IGF-1, the glomeruli remained normal (31). In addition, although there is not an extensive literature specifically addressing this issue, it would appear that acromegals do not develop glomerulosclerosis and renal insufficiency (9).

CONCLUSION

Acromegaly might be viewed as an experiment of nature that has increased our understanding of renal physiology. From early observations of the renal function of acromegalic patients has come an understanding of the profound effects of GH and IGF-1 on GFR and RPF. Obvious issues that still need to be resolved, however, include the exact mechanism whereby these growth factors exert their effects on renal function, an understanding of their role in mediating glomerulosclerosis and compensatory renal hypertrophy, and their potential role as therapeutic agents in acute or chronic renal insufficiency.

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REFERENCES


