Impact of growth hormone hypersecretion on the adult human kidney

Impact rénal de l’hypersécrétion somatotrope chez l’homme

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Review

Abstract

Acromegaly is most often secondary to a GH-secreting pituitary adenoma with increased Insulin-like Growth Factor type 1 (IGF-1) level. The consequences of GH/IGF-1 hypersecretion reflect the diversity of action of these hormones. The genes of the GH receptor (GHR), IGF-1, IGF-1 receptor (IGF-1R) and IGF-binding proteins (IGF-BP) are physiologically expressed in the adult kidney, suggesting a potential role of the somatotropic axis on renal structure and functions. The expression of these proteins is highly organized and differs according to the anatomical and functional segments of the nephron suggesting different roles of GH and IGF-1 in these segments. In animals, chronic exposure to high doses of GH induces glomerulosclerosis and increases albuminuria. Studies in patients with GH hypersecretion have identified numerous targets of GH/IGF-1 axis on the kidney: 1) an impact on renal filtration with increased glomerular filtration rate (GFR), 2) a structural impact with an increase in kidney weight and glomerular hypertrophy, and 3) a tubular impact leading to hyperphosphatemia, hypercalciciuria and antinatriuretic effects. Despite the increased glomerular filtration rate observed in patients with GH hypersecretion, GH is an inefficient treatment for chronic renal failure. GH and IGF-1 seem to be involved in the physiopathology of diabetic nephropathy; this finding offers the possibility of targeting the GH/IGF-1 axis for the prevention and the treatment of diabetic nephropathy.

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Résumé

L’acromégalie est le plus souvent secondaire à un adénome hypophysaire sécrétant de l’hormone de croissance (GH) entraînant une synthèse d’Insulin-like Growth Factor type 1 (IGF-1). Les conséquences de l’hyperactivité de l’axe GH/IGF-1 reflètent la diversité des sites d’actions de ces hormones. Les gènes du récepteur de la GH (GHR), de l’IGF-1, du récepteur de l’IGF-1 (IGF-1R) et des protéines de transport de l’IGF-1 (IGF-BP) sont constitutivement exprimés dans le rein adulte, suggérant un rôle potentiel de l’axe somatotrope dans diverses fonctions rénales. L’expression de ces protéines est hautement organisée et diffère selon les segments anatomiques et fonctionnels du néphron évoquant des rôles différents de la GH et de l’IGF-1 dans ces différents segments. Chez l’animal, une exposition chronique à de fortes doses de GH induit une glomérulosclérose et une augmentation de l’albuminurie. L’observation de patients présentant une hypersécrétion somatotrope a permis de décrypter différentes actions de l’axe GH/IGF-1 dans le rein : 1) un impact sur la filtration rénale avec une augmentation du débit de filtration glomérulaire (DFG), 2) un impact structurel ou morphologique avec une augmentation de la masse rénale et une hypertrophie glomérulaire et 3) un impact tubulaire responsable notamment d’une hyperphosphorémie, d’une hypercalciciurie et d’un effet antinatriurétique. Malgré l’hyperfiltration glomérulaire observée en cas d’hypersécrétion somatotrope, la GH n’est pas un traitement efficace de l’insuffisance rénal chronique. La GH et l’IGF-1 paraissent impliqués dans la physiopathologie de la néphropathie diabétique, ce qui ouvre de nouvelles perspectives de prévention et de traitement de la néphropathie diabétique.

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1. Introduction

Growth hormone (GH) binds to its receptor (GHR), producing effects either directly or indirectly by inducing synthesis of Insulin-like Growth Factor 1 (IGF-1). GHR is a single-domain transmembrane receptor which, after binding with GH, requires homodimerisation for activation. There are several isoforms of GHR with different functional characteristics. The truncated form of GHR (GHRtr) has lost more than 97% of the intracellular portion of GHR [1]. Unlike GHR, GHRtr is bound to the cell membrane and is rarely internalized. It has a long half-life and an increased capacity to generate growth hormone binding protein (GHBP) [2]. GHRtr has been demonstrated in all organs but in lesser amount in the kidney, the liver and fibroblasts [1]. Moreover, acromegalics patients with GHR with a deleted exon 3 (GHRd3) [3] have less metabolic complications [4] and are more sensitive to treatment by pegvisomant, a GHR antagonist [5]. Synthesis of IGF-1, the major hormonal polypeptide targeted by GH, is ubiquitous, although liver synthesis predominates and controls plasma levels. In the blood, IGF-1 is bound to transport proteins: IGF binding proteins (IGF-BP). IGF-1 interacts with its receptor IGF-1R via an endocrine or paracrine mechanism. Over-function of the GH/IGF-1 axis generally results from a GH-secreting pituitary adenoma. It can exceptionally occur secondarily to GHRH hypersecretion related to hypophysal dysfunction or an extra-pituitary endocrine tumor (pancreatic endocrine tumor, pulmonary or gastrointestinal carcinoid tumor).

Acromegaly is a rare disease (prevalence 40 to 70/million inhabitants, incidence 2 to 3/million inhabitants/yr). The variable clinical presentations of acromegaly and its many complications reflect the diversity of GH and IGF-1 sites of action. Classically, GH/IGF-1 hypersecretion involves bone and joint, respiratory, cardiovascular, cutaneous, metabolic and neoplastic manifestations. GH/IGF-1 hypersecretion leads to pleiotropic effects, including changes in kidney structure and function. The mechanisms by which the somatotropic axis affects the kidney are not totally elucidated. The purpose of the present work is to review the effects of GH/IGF-1 hypersecretion on the kidney. The first part will be devoted to the sites of renal synthesis and action of the different elements of the somatotropic axis, as well as the currently recognized nephrological and pleiotropic effects, including changes in kidney structure and function. The mechanisms by which the somatotropic axis affects the kidney are not totally elucidated. The purpose of the present work is to review the effects of GH/IGF-1 hypersecretion on the kidney. The first part will be devoted to the sites of renal synthesis and action of the different elements of the somatotropic axis, as well as the currently recognized nephrological effects of GH/IGF-1 hypersecretion. The second part will concern the effects of changes in the somatotropic axis on renal failure. The role of the GH/IGF-1 somatotropic axis on renal development is beyond the scope of this review.

2. Expression of the growth hormone/insulin-like growth factor-1 system in the kidney

GHR, IGF-1, IGF-1R, and IGF-BPs are constitutionally expressed in the murine and human adult kidney, suggesting that the somatotropic axis plays a role in the organization and maintenance of diverse renal functions. The expression of these proteins is highly organized and differs within the different anatomic and functional segments of the nephron, suggesting diverse roles for GH and IGF-1 in the different segments (Fig. 1). Studies investigating the spatial distribution of the different elements of the GH/IGF-1 system have been conducted mainly in the rat using northern blots and hybridization in situ to recognize messenger RNA and western blots and immunohistochemistry to identify proteins. Data concerning expression of the GH/IGF-1 axis in the different segments of the human kidney are still incomplete and no study has described the distribution of the different isoforms of the GH receptor in the different segments of the nephron.

Besides its predominant expression in the liver, the IGF-1 gene has also been found to be synthesized in different organs, including the kidney [6]. This local synthesis of IGF-1 is GH-dependent. Nevertheless, the majority of the IGF-1 detected in the kidney appears to come from the general circulation rather than from local synthesis, as suggested by dissociations between mRNA and IGF-1 levels and their sub-localizations [7].

GH receptors have been demonstrated in human and murine glomeruli, and on the surface of mesangial cells [8] and podocytes [9], respectively supportive tissue and epithelial cells bordering the glomerular basement membrane. Activation of these receptors on the podocyte cell surface affects its cytoskeleton via activation of recognized GH mediators (JAK2, STAT5, SH2-Bβ, ERK1/2) this could have for consequence an increase in glomerular basement membrane pore size, eventually contributing to the development of microalbuminuria [9] (Fig. 2). These podocyte modifications would be induced by a GH-dependent increase in ZEB2 secretion secondary to increased activity of its promoter and induction of a natural antisense ZEB2 transcript [10]. Murine mesangial cells synthesize IGF-1 and express IGF-1 receptors on their surface. In vitro, in murine and human models, activation of the IGF-1 receptors present on the cell surface activates cell mitosis and increases synthesis of mesangial extracellular matrix proteins, including laminine. Finally, IGF-1 receptors are expressed on the surface of murine glomerular endothelial cells. Their activation triggers production of nitric oxide (NO) and probably increased membrane permeability.
In rats, the epithelial cells of the proximal tubules express GHR. In physiological conditions, these cells are probably unable to synthesize IGF-1 [11]; the action of GH at this level is most likely direct, i.e. independent of IGF-1. In the canine model, it has been demonstrated that GH stimulates neoglycogenesis in proximal tubule cells directly, without any increase in IGF-1 [12]. Conversely in the murine model, a large quantity of IGF-1 receptor is found on the proximal tubule cells, essentially on the basolateral membrane, most probably sensitive to the endocrine, as well as paracrine, action of this mediator, which would act at least as an epithelial growth factor [11,13]. No data are available in humans.

The rat model shows GHR, IGF-1, IGF-1R, and IGF-BP1 expression in the thick ascending arm of the loop of Henlé, suggesting that at this level GH induces IGF-1 expression. IGF-1 binds to IGF-BP1 and has an autocrine and paracrine effect by binding to the IGF-1 receptor [14,15].

Distal tubule expression of IGF-1R has been demonstrated in murine and human models [13]. GHR has been demonstrated in the rat, it activates a phospholipase C after binding to GH [16]. Human and murine medullary collecting duct cells express IGF-1R [13] and the presence of GHR has been demonstrated in vitro in the rat [17]. In vivo, the presence of GHR is strongly suggested by increased concentrations of GH-dependent IGF-1 mRNA [18] and more recently by the demonstration of GH-induced increased amiloride-sensitive epithelial sodium channel (ENaC) activity in cortical collecting ducts [19]. Epithelial cells express IGF-1 in the medullary portion of the collecting ducts, but not in the cortical portion [11,13].

3. Effects of growth hormone/insulin-like growth factor-1 hypersecretion on the kidney

Animal data and clinical observations in patients with acromegaly have enabled the description of different
consequences of chronic GH/IGF-1 hypersecretion on the kidney (Fig. 3). Effects include:

i) an early (5 days) impact on renal filtration with an increase in glomerular filtration rate (GFR),

ii) a later impact on renal structure or morphology with increased renal mass and glomerular hypertrophy,

iii) an impact on the renal tubules leading to hyperphosphatemia and hypercalciciuria.

3.1. Effects of the growth hormone/insulin-like growth factor-1 axis on renal filtration

The effects of altered GH/IGF-1 axis on renal function and structure were observed as early as 1938 in the animal model. Administration of exogenous GH leads to a two-fold increase in GFR. The effect of GH on GFR is perceptible within five days. This delay in the GH action, which occurs concomitantly with an increase in plasma levels of IGF-1 as confirmed in various animal models [20] and in humans [21], is an argument in favor of a role for IGF-1 in the renal hemodynamic effects of the somatotropic axis.

The effect of GH/IGF-1 hypersecretion on the human kidney is often assessed using estimations of renal function such as creatininemia. GH having a direct anabolic effect on muscles, variability in creatinine levels in patients must be interpreted with caution [22–24]. Nevertheless, the main studies have used diverse measures of GFR including insulin clearance [23,25–30] and isotopic methods [31,32].

The acute effect of GH has been studied in healthy volunteers. Administration of exogenous GH leads to a 10–50% increase in GFR [33] occurring in a delayed manner relative to the immediate increase in plasma levels of GH, but in parallel with the increased levels of IGF-1 observed towards the 24th hour [34]. This effect on GFR is not observed for short-duration infusion of GH (120 min) [32] and appears to be independent of the action on renal mass [30]. On the contrary, in GH-deficient patients, there is no increase in GFR after delivery of a therapeutic dose of GH [35] despite the significant increase in the size of the kidneys [36].

Changes in GFR observed in patients with acromegaly or hypopituitarism [37] suggest the existence of a chronic effect of the somatotropic axis on renal function in humans.

Five studies [26–29,37] have examined the functional consequences of GH/IGF-1 hypersecretion on renal filtration in acromegalic patients. These studies have noted an increase in renal plasma flow (approximately 20% increase) and an increase in GFR measured with insulin clearance (approximately 30% increase). These modifications are correlated with increased extracellular volume and remain globally proportional, explaining the absence of any change in the filtration fraction.

The modifications observed in glomerular filtration during the treatment of acromegalic patients differ according to the treatment modalities. After hypophysectomy in patients given cortico-thyreo-gonadotropic substitution therapy, there is an early and important decline in GFR (~40% in one month), while the decrease in renal mass occurs later and is less significant (~14% in 1 year) [29]. A few studies have examined the impact of dopaminergic agonists on renal function in acromegalic patients. Eskildsen et al. were unable to observe any change in GFR after seven months of bromocriptin treatment, but did not mention the efficacy of the dopaminergic agonist on GH secretion in these patients [22]. The effect of somatostatin analogs on the kidney is better known. Dullaart et al. observed a 10% decrease in GFR measured by an isotopic method three months after beginning octreotide treatment in acromegalic patients [24,31]. The estimated GFR in acromegalic patients was equivalent to that in the control population after 3 months of treatment. However, these results are partially contradicted by a recent study in twenty acromegalic patients controlled for 1 year either by surgery or by somatostatin analogs, where the GFR was slightly lower than in non-treated acromegalic patients, but still higher than in the control population [37]. It is noteworthy that in healthy volunteers somatostatin administered intravenously or somatostatin analogs delivered subcutaneously induce a rapid reduction of GFR (in 80 min) and a 30–50% decrease in diuresis, probably secondary to reduced renal perfusion [38]. This rapid effect of somatostatin suggests a direct effect on smooth muscles. Finally, in healthy volunteers, administration of somatostatin also affects the tubules. It increases phosphorus and sodium excretion and decreases potassium excretion [39]. The effect of GHR antagonist on renal function has not been studied other than in diabetic animals.

Few studies are available in patients with isolated GH deficiency. In the animals, anterior pituitary insufficiency causes decreased GFR and an absence of compensatory renal hypertrophy after unilateral nephrectomy; this phenomenon is reversible after administration of GH. In hypophysectomized patients, given substitutive therapy for all pituitary hormones except the somatotropic axis, GFR declines without parallel change in the extracellular volume.

These studies suggest that several mechanisms are involved in the effect of the somatotropic axis on renal function. In acromegaly, the increased GFR could be the consequence not only of increased extracellular volume but also a direct effect of GH on the kidney, independently of the increased extracellular volume [23,29]. Similarly, changes in GFR cannot be attributed only to changes in renal mass (detailed below) since this increased renal mass essentially concerns epithelial renal cells and is not proportional to the increased GFR. Thus, during treatment, acromegalic patients exhibit a dissociation: GFR declines before the involution of renal mass.

IGF-1 is most likely the mediator of the GH effect on GFR, as it is observed for most GH effects. Strong arguments can be put forward, including:

a) the absence of a temporal relationship between GH plasma levels and GFR after injections of GH while plasma levels of IGF-1 are tightly correlated with the observed increase in GFR [20,34];

b) the rapid increase in GFR after administration of recombinant IGF-1 (rIGF-1) in animals and in humans [21,24];
c) the normalization of GFR after rhIGF-1 treatment of Laron syndrome patients with a GHR gene inhibiting mutation [15];
d) the decrease in kidney size and absence of an increase in GFR in mice with bi-allelic knockout of the liver-specific IGF-1 gene despite increased GH levels [40].

Finally, this effect of IGF-1 on GFR is secondary to decreased arteriole resistance and increased coefficient of glomerular ultrafiltration [21,23] and would be mediated, at least partly, by synthesis and release of endothelial NO [41].

3.2. Effects of the growth hormone/insulin-like growth factor-1 axis on renal morphology

In the animals, chronic administration of exogenous GH or IGF-1 is followed by an increase in the size of the kidneys [42,43]. Kidney growth is not controlled only by the GH/IGF-1 axis: when a plasmid containing the GH gene is injected into the hypophysectomized mouse, GH and IGF-1 levels return to normal and trigger general growth with increased volume of the liver and nephrons, but with no change in the kidney size [44]. In the late 1980s, Doi et al. [45] observed modifications in the renal parenchyma in transgenic mice over-expressing genes coding for GH, IGF-1 or GHRH [46]. Kidneys of mice hypersecreting GH or GHRH exhibit early glomerular hypertrophy progressively associated with mesangial proliferation, then an accumulation of peri-cellular matrix, eventually leading to complete glomerulosclerosis suggesting the lesions observed in diabetic nephropathy (Fig. 4). In mice over-expressing the IGF-1 gene, the glomeruli are enlarged but morphologically unchanged, suggesting a dissociated action of GH and IGF-1. These early findings were confirmed several years later in the dog [43] and detailed in the mouse [47]. In the mouse over-expressing the GH gene, lesions are observed on the feet of the podocytes with hypertrophy then disappearance of the pedicles, finally denuding the glomerular basal membrane [47]. The experimental glomerulosclerosis induced by hypersomatotropism would result from a podocytopathy. This hypothesis is in agreement with GHR expression on the podocyte cell surface: activation of GHR leads to changes in the cytoskeleton and modifies the porosity of the glomerular basement membrane, as highlighted earlier [9,10]. In animals, administration of IGF-1 has similar but more modest effects than GH on glomerular hypertrophy and increased renal mass; but transgenic mice over-expressing IGF-1 do not develop glomerulosclerosis and do not exhibit any interstitial or tubular lesions [45,46]. Finally, mice over-expressing IGFBP-1 develop glomerulosclerosis without glomerular hypertrophy [48].

In humans, the size of the kidneys measured by ultrasound in healthy volunteers was unaffected seven days after GH injections [30] or three days after IGF-1 injections [23]. Hypersecretion of GH in humans leads to a 6 to 54% increase in kidney volume, assessed at necropsy [28,49] or with ultrasonography [37]. For some authors, this increase in kidney size is correlated with total body weight, with no increase in the kidney weight/body weight ratio [42,45]. Inversely, kidney size (assessed with computed tomography) decreases after hypophysectomy, 10 to 12% at one month and 20% at five months [50]. Whether the size of the kidneys increases after 6 months of GH treatment in patients with GH deficiency is controversial [35,36]. It can nevertheless be noted that, unlike what is observed in animal models, glomerulosclerosis or renal failure has never been reported in acromegalic patients despite the increased size of the kidneys and the glomerular hypertrophy [28,49]. The mechanisms of

Fig. 4. Histologic sections (PAS stain, original magnification × 1300) of glomeruli at 14 weeks. A: normal mouse; B: GH mouse: mesangial proliferation with sclerosis and a nodular pattern; C: IGF-1 mouse: enlarged but otherwise normal appearing; D: GHRF mouse: mesangial proliferation with sclerosis. (adapted from DOI [46]).
these inter-specific or inter-species differences have not been elucidated.

3.3. Effects of the growth hormone/insulin-like growth factor-1 axis on microalbuminuria

Several teams have studied urinary excretion of albumin (a marker of glomerular permeability) or β2-microglobulin (a marker or proximal tubular involvement) in acromegalic patients in order to investigate the impact of GH/IGF-1 hypersecretion on glomerular or tubular function. Findings are variable: no significant increase in urinary albuminuria and β2-microglobulin is observed in acromegalic patients [22], or with GH administration [30] or exogenous IGF-1 [23]. But significantly elevated microalbuminuria (not reaching pathological levels) has been observed in acromegalic patients [24,31,37], especially those presenting diabetes mellitus or hypertension [51]. After treatment of the acromegaly, albuminuria and β2-microglobulin levels are comparable to those observed in controls. One study of 25 acromegalic patients, with or without treatment, demonstrated a positive and independent correlation between albuminuria, GH, IGF-1 levels and creatinine clearance. The increased microalbuminuria is reversible after treatment of the GH/IGF-1 hypersecretion [24]. It can also be noted that the microalbuminuria induced by physical activity observed in acromegalic patients is inhibited by the administration of somatostatin analogs [52].

3.4. Effects of growth hormone/insulin-like growth factor-1 hypersecretion on the renal tubules

Classically, extracellular volume and blood pressure are elevated in acromegalic patients who also present fluid and electrolyte disorders, mainly hyperphosphatemia, hypophosphaturia, hypercalciuria, and acidification of the urine with reduced kaliuria [53–55].

Extracellular volume is increased in acromegalic patients (15.5 liters versus 10.4 liters in controls) [26]. Inversely, patients with GH deficiency exhibit a reduced extracellular volume [56], which can be restored with GH substitution therapy [50,57]. This increase in extracellular volume, and thus in the sodium stock, is one of the mechanisms underlying the volume-dependent hypertension observed in 40–50% of acromegalic patients. The GH-dependent increased extracellular volume results mainly from a tubular effect. GH has an anti-natriuretic effect [12,54] and an anti-aquaretic effect [58] related to the increased sodium and water re-absorption after the proximal tubule [37,59]. Activation of the renin-angiotensin system in acromegalic patients is controversial [14,54,59]. Unlike what is observed with GH, IGF-1 appears to have an anti-natriuretic effect alone, not associated with water re-absorption [54].

Dimke et al. recently demonstrated that acute administration of GH in the rats leads to sodium retention secondary to stimulation of a furosemide-sensitive NKCC2 (Na⁺K⁺2Cl⁻) co-transporter found in the thick ascending arm of the loop of Henlé (Fig. 5) [60]. Chronic administration of GH in the rats provokes sodium retention implicating the amiloride-sensitive epithelial sodium channel (ENaC) present in the distal tube (Fig. 6) [19].

Studies on phosphorus-calcium metabolism have provided the following information:

- the hyperphosphatemia, observed in 20 to 42% of acromegalic patients, is considered to be a marker of disease activity and results from increased absorption of phosphorus in the proximal tubule [33,37]. GH-dependent hypophosphaturia is secondary to the effect of IGF-1 on proximal tubule cells essential for phosphorus re-absorption [38]. The mechanism of action of IGF-1 on these cells is unknown. A recent study does not support the role of fibroblast growth factor-23 (FGF-23) on the development of hyperphosphatemia in acromegaly [61]. FGF-23 appears to increase secondarily to hyperphosphoremia and increased 1,25-(OH)₂...
vitamin D3 (1,25-(OH)2D3) observed in acromegalic patients [62].

- GH/IGF-1 hypersecretion has a hypercalciuric effect in 47 to 68% of acromegalic patients [37], probably contributing to the increased frequency of renal stones in acromegalic patients. The hypercalciuria observed in acromegaly is considerable (7.21 vs. 4.91 mmol/L/24 h in controls) [63] with a multiple gastrointestinal, renal and osseous origin. Increased gastrointestinal absorption of calcium [64,65] is secondary to increased circulating levels of 1,25-(OH)2D3 observed in acromegalic patients and after administration of exogenous GH [65]. Treatment of the acromegaly normalizes vitamin D levels [62]. The mechanism by which the somatotropic axis affects vitamin D metabolism remains unclear, but most likely involves a IGF-1-mediated regulation of renal hydroxylation of 25OHD3 [66], although a parathyroid hormone (PTH) effect cannot be excluded and remains controversial [65].

- Studies in acromegalic patients have revealed low [67], normal [62], and elevated [68] levels of PTH. Phosphorus-calcium disorders in acromegalic patients after parathyroidectomy [33] and measurements of cyclic-AMP in the urine of acromegalic patients [65] are not in favor of abnormal parathyroid function. Nevertheless, the administration of GH to healthy volunteers leads to a significant decrease in PTH levels, possibly secondary to increased bone turnover induced by GH.

- These alterations of phosphorus-calcium metabolism, as well as altered uric acid metabolism (hyperuricemia in 43% of acromegalic patients) lead to increased prevalence of renal stones in acromegalic patients (12.5%) [69]. Nevertheless, the prevalence of urinary lithiasis is low compared with the prevalence and the level of hypercalciuria. Increased urinary excretion of glycosaminoglycans (GAGs), powerful inhibitors of calcium oxalate crystals formation and aggregation, as well as the increased citraturia observed in acromegalic patients [37] probably have a protective effect against formation of renal stones [70].

- The acid-base balance is affected in animals and in children with an abnormal GH/IGF-1 axis: GH deficiency provokes moderate metabolic acidosis which can be corrected with administration of GH [71]. The tubular acidification induced by GH could be partially linked with modified NKCC2 activity in the Henlé loop described above [54].

- Finally, hypersecretion of GH/IGF-1 affects potassium balance. Acute administration of GH and IGF-1, like chronic GH/IGF-1 hypersecretion in acromegaly [37], triggers rapid decrease in urinary excretion of potassium as demonstrated in the rat [60] and observed in humans [53]. In the rat, chronic GH administration leads to prolonged decline in kaliuresis [72]. In humans, urinary excretion of potassium is normalized via an escape mechanism after a few days of GH [59] or IGF-1 [30] administration. The anti-kaliuretic action of GH is attributed to GH-induced activation of the furosemide-sensitive NKCC2 co-transporter [60]. In rats [72], healthy volunteers, or patients with GH deficiency [73], chronic administration of GH has no effect on serum potassium levels.
4. Somatotropic axis and renal failure

Use of GH for the treatment of renal failure is a complex question. Conceptually, the increase in GFR observed with hyperexpression of the GH/IGF-1 axis has to be balanced against the renal lesions described above (mesangial proliferation and glomerulosclerosis) observed in GH-hypersecreting mice [45].

In patients with chronic renal failure, GH levels are elevated while IGF-1 levels are normal up to end-stage renal failure where they decline [74,75], suggesting a resistance to GH during the phase of chronic renal failure via multiple mechanisms [76]: decreased expression of the GH receptor and altered activation of the intracellular transduction pathway JAK2/STAT, resulting in reduced expression of IGF-1 [77]. There is also a resistance to IGF-1, particularly via increased affinity for IGF-BPs [75,77]. This resistance to GH in chronic renal failure leads to growth retardation in children and adolescents and contributes to the state of malnutrition and perhaps the increased cardiovascular risk observed in adults. No functional benefit has been demonstrated in adults or children with renal failure treated with GH. The positive effect observed after 4 days of treatment with IGF-1 does not persist with prolonged treatment [78]. On the other hand, as suggested by animal studies, use of GH in children and adults with renal failure presenting growth retardation has a positive effect on height and weight gain; and all of the studies have been unable to demonstrate any deleterious effect on glomerular filtration [79–81]. This treatment has thus been used in routine practice for more than 15 years. In adult patients with chronic renal failure and malnutrition, administration of a GHRH agonist provides rapid improvement (28 days) in nutritional status [82]. Short-term administration of IGF-1 combined with GH provides an improvement in the biological parameters of anabolic metabolism [83]. Given for short term (seven days), GH also decreases the level of several markers of cardiovascular risk: LDL cholesterol, homocysteine, leptin [84]. To date, studies in uremic patients with malnutrition have been too limited to establish marketing authorization for GH in this indication.

Finally, GH and IGF-1 play likely a role in the pathophysiology of diabetic nephropathy [85]. Alterations in the plasma and renal levels of GH, IGFBP, and IGF-1 are observed in patients with type 1 diabetes mellitus [86]. Renal pathology of GH hypersecreting rats shows lesions similar to those observed in patients with diabetic nephropathy [46]. GH induces modification of the podocytes with increased podocyte permeability and thus may be responsible for the microalbuminuria associated with diabetic nephropathy [10]. These data suggest that the high GH level classically observed in type 1 diabetes mellitus contributes to glomerular hyperfiltration and the diabetic nephropathy observed in these patients [87].

GH-deficient dwarf rats with diabetes mellitus (induced by streptozotocin) exhibit less severe renal and glomerular lesions, and less elevated IGF-1 renal levels than diabetic control rats [88]. In the same way, transgenic diabetic mice expressing a GHR antagonist [89] or mice with a disrupted GHR gene [90] are protected against the development of diabetic nephropathy, without modification of the glycemic balance. Several studies have attempted to prevent diabetic nephropathy using treatments affecting the somatotropic axis. The results from studies using animal models of type 1 diabetes mellitus have been encouraging: administration of a GHR antagonist, pegvisomant, inhibits the usually observed increase in intra-renal IGF-1, kidney weight, glomerular volume, and albuminuria in diabetic mice [91,92]. Administration of somatostatin analogs to diabetic rats or mice early (before onset of diabetes mellitus) prevents the development of glomerular hyperfiltration, increased resistance of the afferent arterioles, accumulation of intra-renal IGF-1 and glomerular hypertrophy [93]. Nevertheless, the administration of exogenous IGF-1 to diabetic patients (to normalize GH level via pituitary feedback control) does not affect GFR nor microalbuminuria [94], this observation does not support the hypothesis of an IGF-1-related pathogenic process. Finally, the observation of lower GH and IGF-1 levels in animal models of type 2 diabetes mellitus, suggest that medications inhibiting the somatotropic axis would have little use for treatment of diabetic nephropathy [95].

5. Conclusion

Molecular studies on the renal expression of different elements of the GH/IGF-1 system and more recent functional studies in acromegalic patients before and after treatment have enabled a better understanding of the renal consequences of GH/IGF-1 hypersecretion. In the animals, chronic exposure to high-dose GH induces increased albuminuria then glomerulosclerosis. Observations in patients presenting GH/IGF-1 hypersecretion have enabled the identification of different renal effects of the GH/IGF-1 system:

i) an impact on renal function with increased glomerular filtration rate,
ii) an impact on renal structure and morphology with increased kidney size and glomerular hypertrophy,
iii) an impact on the renal tubules leading to hyperphosphatemia, hypercalciuria and sodium retention involving the epithelial sodium channel, ENAC, in the distal tubule.

Further studies will be needed to detail the full impact of GH/IGF-1 hypersecretion on the kidney observed in acromegalic patients and its reversibility after treatment. Treatment with GH or IGF-1 has no effect on the progress of chronic renal failure but can correct growth retardation and poor nutritional status often observed in these patients. Glomerular lesions similar to those observed in diabetic nephropathy (e.g. podocyte modifications associated with microalbuminuria) are observed in animal models of GH hypersecretion. Controlled somatostatin secretion has a nephroprotective effect in diabetic mice. The GH/IGF-1 axis thus appears to be implicated in diabetic nephropathy, opening up new perspectives for treatment.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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