Growth Hormone and IGF1 Actions in Kidney Development and Function

Evgenia Gurevich 1, Yael Segev 2 and Daniel Landau 1,3,*

1 Department of Nephrology, Schneider Children’s Medical Center of Israel, 14 Kaplan Street, Petach Tikva 4920235, Israel; gurevichjeny@gmail.com
2 Shraga Segal Department of Microbiology and Immunology, Ben Gurion University, Beer Sheva 8410501, Israel; yaelse@bgu.ac.il
3 Sackler School of Medicine, Tel Aviv University, P.O. Box 39040, Tel Aviv 6997801, Israel
* Correspondence: danny_L@clalit.org.il; Tel.: +972-3925-3651

Abstract: Growth hormone (GH) exerts multiple effects on different organs including the kidneys, either directly or via its main mediator, insulin-like-growth factor-1 (IGF-1). The GH/IGF1 system plays a key role in normal kidney development, glomerular hemodynamic regulation, as well as tubular water, sodium, phosphate, and calcium handling. Transgenic animal models demonstrated that GH excess (and not IGF1) may lead to hyperfiltration, albuminuria, and glomerulosclerosis. GH and IGF-1 play a significant role in the early development of diabetic nephropathy, as well as in compensatory kidney hypertrophy after unilateral nephrectomy. Chronic kidney disease (CKD) and its complications in children are associated with alterations in the GH/IGF1 axis, including growth retardation, related to a GH-resistant state, attributed to impaired kidney postreceptor GH-signaling and chronic inflammation. This may explain the safety of prolonged rhGH-treatment of short stature in CKD.

Keywords: growth hormone; insulin-like growth factor 1; growth hormone receptor; receptor signaling; diabetic nephropathy; chronic kidney disease; kidney hypertrophy

1. Introduction

Most animals must undergo a transition from maternal environment to independent life through processes of growth and maturation. Important hormonal regulators of childhood growth are growth hormone (GH), insulin-like growth factor 1 (IGF1), sex steroids, and thyroid hormone. GH and IGF1 are part of an axis, which is essential for bone and organs growth. The kidneys express both GH as well as IGF1 receptors, and are one of the key target organs for these hormones’ actions. This review concentrated on the roles of these hormones in physiological and pathological kidney conditions.

2. Normal GH-IGF1 Axis and Physiology

GH is produced by somatotroph cells of the anterior pituitary and secreted in a pulsatory way under the positive control of hypothalamic GH-releasing hormone (GHRH) and the negative control of somatostatin [1]. The response to GHRH is mediated via GH-releasing hormone receptor (GHRHR), a G protein–coupled receptor (GPCR) expressed specifically in somatotrophs [2]. Other factors such as insulin-like growth factor (IGF1), neuropeptide Y, and hyperglycemia inhibit GH secretion, and hypoglycemia, thyroxine, ghrelin, klotho, and glucocorticoids stimulate GH secretion [3].

GH acts by binding to GH receptor (GHR) to stimulate, among other genes, the synthesis of insulin-growth factor-1 (IGF1). The bioavailability of GH is regulated by GH-binding protein (GHBP), which is the extracellular part of GHR. Intracellular signal transduction after GH binding to its receptor requires the activation of Janus-associated kinase 2 (JAK2) [4], which stimulates phosphorylation of signal transducer and activator...
of transcription (STAT) proteins MAPK and PI3K. STAT proteins migrate to the nucleus, activating, among others, gene transcription of IGF1, the main mediator of GH action. In addition, suppressors of cytokine signaling (SOCS) are activated, which dephosphorylate STAT, leading to a negative feedback action on GH [5]. Circulating IGF1 suppresses pituitary GH secretion in a negative feedback loop. IGF1 is synthesized mostly in the liver, but also in peripheral tissues under GH regulation, although nutrition, insulin, thyroid, and sex hormones also affect its expression [6]. The effects of IGF1 are mediated by the type 1 IGF receptor (IGF1R) in a signaling pathway similar to insulin/insulin receptor (IR). IGF1R and IR share amino acid identity, and can be activated both by insulin, IGF1, and IGF2. [7]. IGF1R is a membrane-bound tyrosine kinase heterotetramer, and its activation leads to autophosphorylation of tyrosine residues, leading to signal transduction [8]. The bioactivity of circulating IGF1 is modulated by IGF-binding proteins (IGFBPs 1-6), which facilitate its stability in serum and extracellular matrices. Most IGFs in serum are bound to IGFBP and the acid-labile subunit (ALS), a protein that stabilizes IGF [9,10], and this complex serves as reservoir of IGFs, keeping serum concentration of free IGFs constant. Plasma concentration of IGFBP3 and ALS are also increased by GH, similar to IGF1.

3. GH-IGF1: Axis or Independent Functions?

Whereas GH is only synthesized in pituitary, GHR and IGF1 are expressed in many tissues including the kidneys. Originally GH action was thought to be mediated only through IGF1, called somatomedin, without any direct effects (“somatomedin theory”) [11]. Later, “dual effector hypothesis” suggested that GH also acts directly to promote cell differentiation, independent of IGF1 [12–14]. Concentrating on kidneys as one of the target organs for both GH and IGF-1, GH treatment increased kidney IGF1 mRNA levels in hypophysectomized rats, confirming local renal IGF1 production [15]. IGF1 levels are higher in renal venous blood than in renal arterial blood, suggesting significant renal IGF1 biosynthesis [16]. Evidence for a direct IGF1 action in the kidney also comes from studies showing that prolonged treatment with recombinant human (rh) IGF1 increased kidney size in hypophysectomized rats [17] and enhanced the glomerular filtration rate (GFR) in healthy men [18].

4. Observations from Knockout and Transgenic Animals

Animal models of gene inactivation, as well as pathophysiological models, provide important data on mechanisms and role of GH/IGF1 in renal organogenesis. Evidence of both dependent and independent functions of GH and IGF1 on the kidney come from genetically engineered animal models (see Tables 1 and 2). Examples of the knockout models, where mutations were introduced in every step of the axis (GHRH → GH → GHR/GHPB → JAK2 → STAT5 → IGF1 → IGF1R), followed by the transgenic models, overexpressing genes along this axis, are discussed here.

Biallelic mutation in GHRH causes isolated growth hormone deficiency due to impaired GH secretion in anterior hypophysis [2].

GH knockout mice (GH −/−), which show no circulating GH, also show disproportionately reduced kidney weight compared with wild-type mice, even after correction for reduced body weight [19].

GHR/GHPB knockout mice lack functional GH receptors and exhibit GH resistance manifested by decrease in circulating IGF1 levels and growth retardation, starting later after birth. These mice also have disproportionally small kidneys [20].

Germline deletion of Jak2 (downstream of GHR, but also of other hormones and cytokines) in mice resulted in embryonic lethality due to a lack of hematopoiesis [21]. Homozygous mutation in the gene for STAT5 resulted in IGF-1 deficiency and growth hormone insensitivity, indicating impaired postreceptor signaling for GH. It leads to abnormal postnatal growth, facial dysmorphism, and markedly reduced serum concentrations of IGF-1, IGFBP-3, and acid-labile subunit, and immunodeficiency [22]. The latter seems to be due to the importance of both JAK2 and STAT5 not just in mediati
also other cytokines involved in immune as well as hematopoetic regulation, such as the erythropoietin receptor [23]. STAT5 knockout mice died perinatally, and 1–2% of survivors were dwarf, with anemia and immunodeficiency [24].

IGF1 knockout mice have severe growth retardation, deficiencies in bone and muscle development, infertility, and lethal respiratory failure due to lung hypoplasia, highlighting the importance of GH/IGF1 axis in different tissues development. Their kidneys are proportionally small with decreased glomerular size and nephron number [25,26].

Prenatal IGF1R knockout embryos exhibit growth retardation and generalized developmental abnormalities, comprising hypoplasia, altered central nervous systems, abnormal skin formation, delayed bone development, reduced pancreatic beta-cells, failure of testicular determination, lung immaturity, and cochlear defects [27]. As IGF1R is closely related to the IR, partly sharing amino acid identity, increased IGF2-mediated IR signaling can rescue mouse embryonic development to prevent dwarfism in IGF1R knockout mice [28].

Mice with homozygous null mutations in \( \text{Igf1r} \) had normal embryonic development but had low weight and died soon after birth, whereas heterozygous mice had normal growth up to the weaning period, followed by a significant reduction in weight gain and development of insulin resistance [29]. Therefore, the phenotype of the knockout animal is more severe as the location of the affected gene is more distal along the signaling pathway, as described for example for other pathways where the kidneys are a target organ [30].

Excessive GH levels are associated with renal hypertrophy in humans and rodents [31]. Transgenic mice overexpressing the GH gene exhibit excessive GH and IGF1 concentrations, resulting in a giant phenotype and organomegaly, including increased kidney weight even when related to increased body weight [32]. These animals also develop glomerulosclerosis and kidney failure, in association with glomerular hypertrophy and progressive albuminuria [33]. Transgenic mice overexpressing IGF1 are larger than wild-type mice, have proportionately enlarged kidneys [34], and also show glomerular hyperthrophy, but do not develop glomerulosclerosis [35,36]. These findings indicate that GH excess causes glomerular and podocyte hypertrophy sufficient to induce glomerulosclerosis independently of IGF1.

A study on GH-transgenic IGF1-deficient mice allowed for the demonstration of the dissociated effects of IGF-dependent and independent actions of GH on tubular and glomerular growth in vivo. These mice developed glomerular hypertrophy, hyperplasia, and glomerulosclerosis, similar to GH-transgenic mice with normal IGF1 expression but, in contrast to them, which did not develop proximal tubular cells hyperplasia. These data indicate that IGF1 is not necessary for mediation of the effects of GH-overabundance causing progressive glomerulosclerosis in GH-transgenic mice, but showed that IGF1 is an important mediator of excess GH-induced proximal tubular hyperplasia [37].

Consistent with the role of IGFBPs as inhibitors of IGF action, their generalized overexpression predominantly results in growth retardation. Mice engineered to overexpress IGFBP-1 have prenatal and postnatal growth retardation, disproportionally small brains, splenomegaly, and glucose intolerance. Their kidneys are proportionally small with a decreased nephron number; they also develop glomerulosclerosis without glomerular hypertrophy [38–41]. Transgenic mice that overexpress IGFBP-2 have only mild growth retardation, with proportionally small kidneys [42]. Mice overexpressing IGFBP-3 have selective organomegaly (spleen, liver, heart) [43], and disproportionally small kidneys [44], whereas those overexpressing a mutant of IGFBP-3 with impaired IGF binding have normal postnatal growth and kidney size [45], suggesting that the effects on the kidney seen in the former are due to inhibition of IGF actions. IGFBP-4 overexpression in various tissues in mice resulted in hypoplasia of the affected tissue, suggesting a common action in different cell types [37]. Interestingly, only few or no phenotypic changes were observed when separately knocking out each specific IGFBP [46–50].

In the 5/6 nephrectomy mouse model of chronic kidney disease, silencing of SOCS2, a negative regulator of GH action, was shown to overcome CKD-related growth retardation without worsening kidney function. This was explained by elevation of inflammatory cy-
tokines in uremic mice and upregulation of SOCS3, another regulator of cytokine signaling, leading to the prevention of renal GHR overstimulation [51].

Additional experiments have shown that most growth-stimulating effects of IGF1 are mediated by its locally produced form, acting in an autocrine or paracrine fashion [14,52]. Inactivation of the liver-specific IGF-1 gene in mice had no effect on somatic growth, demonstrating that local IGF-1 plays an auto/paracrine role in tissues [53].

5. GH and IGF1 in Normal Renal Development

The GH/IGF1 system plays a key role in normal kidney development, although it does not impair basic kidney formation mediated by the branching morphogenesis process [54]. During embryogenesis, GHR mRNA was detected in rat kidneys from embryonic day 20 and was mainly expressed in the proximal tubules [55]. In the human fetal kidney, GHR-specific immunostaining was shown as early as 8.5 to 9 weeks and most renal tubular epithelial cells became positive by week 13. The staining was stronger in the outer medulla than in the cortex and remained similar at midgestation and after birth. Weak staining was also found in immature glomeruli in early gestation, but disappeared at later developmental stages, suggesting specific GH involvement in glomerular morphogenesis [56].

IGF1 and -2 are required for normal metanephric development [57]. Studies of IGF1 expression during mouse kidney development revealed IGF1 mRNA expression in all renal cells at embryonic day 15, with a drastic decrease after birth [58].

During early embryogenesis, the IGF1R mRNA is expressed in the rat mesonephros [59] and is detected in all nephron segments through adulthood. In the human kidney, the IGF1R is strongly expressed in glomeruli and the tubular epithelium [60].

IGF-2 plays an important role during embryonic and fetal development, but its function after birth has not been fully elucidated [61]. Transgenic mice overexpressing IGF-2 have disproportionately enlarged kidneys relative to body weight [62].

6. GH/IGF1 Effects on Normal Tubular and Glomerular Functions

Normal kidney function includes glomerular filtration and tubular secretion and reabsorption, leading to fluid and electrolyte balance. In addition, kidneys control blood pressure, as well as hormonal synthesis (such as EPO and active Vitamin D).

GH and IGF1 deficient patients have reduced glomerular filtration rate (GFR) and renal perfusion flow (RPF) [63,64]. Hypophysectomy in humans leads to a rapid decrease in GFR [65], and rhGH treatment leads to GFR and RPF improvement in a dose and time-dependent manner [63,64]. In a cohort of GH-deficient children (isolated or multiple pituitary), GFR was in normal physiological levels but lower than in controls and significantly increased after 3 years of rhGH in parallel to kidney and body growth [66]. In contrast, acromegalic patients have increased GFR and RPF [65,67] and albuminuria [68–70] compared with healthy subjects.

Evidence on direct actions of IGF1 on glomerular function comes from patients with GH-insensitivity due to GHR mutations, where treatment with rhIGF1 improves GFR [71]. Injection of IGF1 in rodents and humans increases RPF and GFR [72], influencing single-nephron GFR and blood flow by increasing the ultrafiltration coefficient and decreasing efferent arteriolar resistance [73]. This effect depends on the synthesis of endogenous vasodilators including NO and prostaglandins, and can be blocked by inhibition of NO-synthase and COX [74].

Recent studies elucidated the action of IGFs on the glomerular podocyte. IGF-2 action, mediated by the IGF1R, is important for podocyte cell survival and integrity of the glomerular filtrating barrier. Mice with reduced IGF-2 production have abnormal glomeruli, indicating the role of IGF-2 throughout the glomerulus [75].

GH and IGF1 are involved in tubular handling of sodium, water, calcium, and phosphate, and are also known to regulate tubular gluconeogenesis [76]. GH deficiency is associated with reduced sodium and total body water content [77], and rhGH-replacement therapy improves these parameters [78]. Treatment with high rhGH doses may even lead
to acute fluid retention [79]. In contrast to that, acromegalic patients show an increase in total body water and sodium and may present with edema. Treatment of GH-producing tumors reverses these changes [80,81].

The direct, IGF-1-independent effect of GH on sodium and fluid retention is controversial: infused recombinant IGF1 did not change body weight and sodium excretion in healthy subjects [18,82], but treatment with rhIGF1 improved hydration status in children with GH insensitivity due to GHR inactivating mutations, indicating that sodium and water retaining properties of GH are at least partly mediated by IGF1 [83].

Liver-specific deletion of the IGF1 gene increased urinary sodium and potassium excretion [84], confirming the role of IGF1 in water and sodium handling. Evidence for both direct GH/IGF1 action on kidney tubule and indirect mechanisms involving the renin-angiotensin-aldosterone system (RAAS) or natriuretic peptides exists. Rapid increase in plasma renin activity and aldosterone level after rhGH administration in healthy men was reported [85], and treatment with angiotensin converting enzyme (ACE)-inhibitor captopril and mineralocorticoid receptor antagonist spironolactone abolished the GH-induced increase in extracellular volume [86]. Decrease of atrial natriuretic peptide concentration after rhGH treatment was also shown [87]. Recent data show evidence for direct action of GH and IGF1 on epithelial sodium channels (controlled by aldosterone) in cortical collecting ducts [88]. Reversal of GH/IGF1 excess in acromegalic patients decreases ENaC activity [89]. In rats with GH-secreting tumors, the direct stimulatory effect of excess GH on ENaC-dependent sodium transport in distal nephron was demonstrated. Enhanced natriuretic response after ENaC blocking by amiloride and enhanced Na/K-ATPase activity selectively in the cortical collecting ducts were demonstrated, providing additional evidence for increased sodium reabsorption in the late distal nephron during a chronic GH excess. Changes in ENaC subunit proteins, known to be associated with increased ENaC activities [90], were shown in these rats and were not accompanied by elevated aldosterone levels [88]. In humans, active acromegaly was also associated with an increased response to amiloride, providing evidence of increased renal ENaC activity in excess of GH/IGF1 [89]. Another possible molecular target of GH/IGF1 in the kidney tubule is the sodium-potassium pump Na/K-ATPase. GH has been shown to enhance the hydrolytic activity of Na/K-ATPase in rat kidney [91].

Being the major hormones mediating somatic growth, GH and IGF1 promote positive calcium and phosphate balance, influencing, for example, 1.25 (OH)2 vitamin D synthesis, which is crucial for intestinal calcium absorption. GH stimulation of renal calcitriol synthesis is mediated by IGF1 via induction of 1α-hydroxylase in the proximal tubule [92]. GH-replacement therapy, as well as treatment with rhIGF1, increased serum calcitriol levels in GH-deficient patients [93]. Several studies in GH-deficient adults have shown transient elevation in blood calcium level and urinary calcium excretion during rhGH-treatment [94,95]. In contrast, studies in children showed unchanged or even decreased blood calcium levels during long-term rhGH replacement, probably related to modifications of mineral metabolism and a significant increase in bone density [96].

In adults and children with GHR insensitivity (Laron dwarfism), treatment with rhIGF1 resulted in increases in urinary calcium excretion without changes in serum calcium levels [83,97].

Patients with an excess of GH often have serum calcium concentrations toward the upper-normal range in association with hypercalciuria, which can be consistent with increased calcitriol synthesis [98]. Treatment of healthy subjects, patients with CKD, and GH-deficient patients with rhGH has been shown to increase the circulating levels of sKlotho. Klotho is a co-receptor for the phosphaturic hormone FGF23, which also enhances calcium reabsorption in distal nephron [99–101].

Long-term rhGH treatment leads to a persistent increase in plasma phosphate concentrations in GH-deficient children [93] and adults [91,92,102], which is mediated by a direct antiphosphaturic action of IGF1 in the proximal tubule [103]. IGF1 directly increases phosphate reabsorption via increase of Na-Pi2a expression in proximal tubule,
which could be completely blocked by an anti-IGF1R antibody [104,105]. Patients with acromegaly may have mild hyperphosphatemia that normalizes after treatment of their GH-secreting tumor [106].

The physiologic roles of GH and IGF1 in different nephron segments are depicted in Figure 1.

Figure 1. Physiological (main figure) and pathophysiological actions of GH (upper left insert) and IGF-1 on the kidneys. The original figure has been published by Hafner et al. [107] and published here with permission. The figure is licensed under a Creative Commons Attribution 4.0 International License. See link to the Creative Commons license (http://creativecommons.org/licenses/by/4.0/, accessed on 29 November 2021). No changes to the original figure were made.

7. GH/IGF1 Involvement in Kidney Diseases

Compensatory Renal Hypertrophy

Following unilateral nephrectomy, the remaining kidney undergoes compensatory growth with an increase in single-nephron GFR and hypertrophy of all nephron segments, especially proximal tubuli. This process is activated by glomerular hemodynamic changes and regulated by positive and negative growth factors [108], including GH and IGF1 in early stages [109,110]. The GH-IGF1 axis is involved in remnant kidney hypertrophy only in early stages, and other mechanisms are involved in the kidney compensatory hypertrophy afterwards [111]. IGF1 was proposed to mediate protein-induced kidney growth. Healthy infants, fed with high-protein formula during the first year of life, showed correlations between IGF1 levels and kidney volume [112].

In adult rats, changes in the pulsatile release of growth hormone (GH), which facilitates compensatory renal growth after unilateral nephrectomy, was observed [113]. Developmental and sex differences in the initial phase of compensatory renal growth following unilateral nephrectomy was shown in animal models. In adult rats, compensatory
renal growth was GH-dependent, and GH-independent in immature rats, associated with an increase in local renal IGF-1 and IGF1R mRNA, an effect not seen in adult rats. These age-dependent differences were observed in male rats, but in females compensatory renal growth was associated with increased expression of IGF1 both in juvenile and adult rats, indicating potential gender differences [114].

Table 1. Chain of GH-IGF signals: general and kidney phenotypes with loss of function. KO: knockout mice model; NA: not available; m: mouse; h: human.

| KO/Human Mutation General Phenotype | KO/Kidney Phenotype                                                                 | Ref.         |
|-----------------------------------|------------------------------------------------------------------------------------|--------------|
| GH                                | Growth retardation                                                                  | [17]         |
| GHR/GHBP                          | Growth retardation after birth, low IGF1, greater longevity                         | [18]         |
| JAK2                              | Embryonic lethality due to a lack of hematopoiesis                                   | [19]         |
| STAT5                             | Abnormal postnatal growth, facial dysmorphism, immunodeficiency (h) perinatal death, dwarfish, anemia, immunodeficiency (m) | [20,22]     |
| IGF1                              | Severe growth retardation, infertility, deficiencies in bone and muscle development, lethal respiratory failure | [23,24,114] |
| IGF1R                             | Respiratory failure, low birth weight, developmental abnormalities, perinatal death | [25]         |
| SOCS2                             | Gigantism, improved somatic growth in CKD model                                      | [47]         |
| IGFBP1                            | indistinguishable from wild-type, no embryonic lethality                             | [44]         |
| IGFBP2                            | minor gender specific changes in bone structure, minor changes in the weights of spleen and liver in adult males | [43,45]     |
| IGFBP3                            | Normal                                                                              | [42]         |
| IGFBP4                            | mild 10%-15% reduction in prenatal growth                                            | [42]         |
| IGFBP5                            | Normal                                                                              | [42]         |
| IGFBP6                            | Normal                                                                              | [42]         |

GH regulation of angiotensin II receptor 1 (AT1R) expression in the kidney is important for GH-dependent compensatory renal growth in the adult male, but not female, rats. GH suppression abolishes the increase in AT1R expression in remnant kidney in male rats after unilateral nephrectomy [115].

In a knockout mouse model in which the major GH signaling mediator JAK2 was specifically inactivated in the liver, hepatic IGF1 production was demonstrated to be crucial for GH-mediated kidney mass stimulation, suggesting that locally produced renal IGF1 had little or no effect on kidney growth. However, skeletal length was dependent upon or compensated for by locally produced IGF1 [116]. On the other hand, in liver specific IGF1 knockout mice, which showed a major decrease in circulating IGF-1 levels (>90% reduction)
and impaired body growth, unilateral nephrectomy induced a significant and proportional increase in renal mass despite markedly decreased kidney IGF-1 levels and no significant change in IGF1R phosphorylation. This suggests that factors other than circulating and locally produced IGF-1 are responsible for compensatory renal enlargement [117].

Table 2. Effects on general and kidney phenotypes by gain of function in GH-IGF pathway. There are no data about transgenic models for GHR/GHBP, IGF1R, SOCS, and IGFBP5 and -6.

| General Phenotype | Kidney Phenotype | Ref. |
|------------------|------------------|-----|
| GH | Giant phenotype, organomegaly | Kidney hypertrophy, glomerular hypertrophy, progressive albuminuria, glomerulosclerosis | [27–29] |
| IGF1 | Enhanced growth | Proportionately enlarged kidneys, glomerular hypertrophy, no glomerulosclerosis | [30–32] |
| IGFBP1 | Low birth weight, postnatal growth retardation, disproportionally small brain, splenomegaly, hyperglycemia | Small kidneys, decreased nephron number; glomerulosclerosis without glomerular hypertrophy | [34–37] |
| IGFBP2 | Mild growth retardation, mildly reduced organs weight NA | [38] |
| IGFBP3 | Increased spleen, liver, heart weight | Disproportionally small kidneys | [38–40] |
| IGFBP4 | Different tissues hypoplasia | [37] |
| IGF2 | | Disproportionately enlarged kidneys | [58] |

8. Diabetic Nephropathy

Diabetic nephropathy is characterized by glomerular hyperfiltration, glomerular/tubular hypertrophy, thickening of the glomerular basement membrane, and mesangial matrix expansion/proliferation, resulting in increased glomerular permeability, albuminuria, tubulointerstitial fibrosis, and progressive CKD [118]. GH and IGFs play a significant role in the early development of diabetic renal disease [119]. Increased GH secretion with decreased expression of GHR in the liver and decreased serum IGF1, consistent with the GH resistance, was shown in diabetic mice as well as in patients with uncontrolled diabetes mellitus [120,121]. As previously mentioned, excessive levels of GH induce glomerular hypertrophy and glomerulosclerosis [32,33].

In diabetic rats, GH treatment exacerbated the course of diabetic renal disease [122]. In contrast, GH-deficient rats are relatively protected from diabetic related renal hypertrophy [123]. GH antagonist administration to non-obese diabetic mice inhibited early diabetic glomerular hypertrophy, hypertrophy, and albuminuria [124]. Treatment with GH antagonist in T1DM patients resulted in significant reduction in kidney volume and hyperfiltration [125]. The effects of somatostatin analogs on nephropathy in type 1 diabetes are comparable to the effect of angiotensin-converting enzyme inhibitor treatment [126]. Reduced circulating IGF1 was reported in T1DM patients, while renal IGF1 concentration was increased in an animal diabetic model, suggesting increased local synthesis [127]. Increased IGF1R and IGFBP in renal tissue was found in the early course of diabetic nephropathy in experimental models as well [128,129].

The early increase in IGF1 leads to the rise in GFR by reducing renal arteriolar resistance and increases the glomerular ultrafiltration coefficient, as previously mentioned [72]. GHR and IGF1R are highly abundant in glomerular cells, including podocytes and mesangial cells. Podocyte hypertrophy, apoptosis, dedifferentiation due to epithelial-to-mesenchymal transition, and detachment from the glomerular basement membrane were shown to be early events in the development of diabetic nephropathy in humans and various animal models of diabetic nephropathy [130]. GH increases levels of reactive oxygen species and induces actin cytoskeleton reorganization in podocytes, causing abnormal
functioning of the slit diaphragm, increased permeability of the filtration barrier, and albuminuria [131]. Mesangial cells isolated from experimental models of diabetic nephropathy exhibit altered IGF1 synthesis, IGF1 pathway activation, and higher IGF1R expression and activation compared with controls [132]. Hyperglycemia reduces IGFBP-2 expression in mesangial cells, exacerbating IGF1 effects on mesangial cells, and increases the expression of IGFBP-3, which mediates mesangial cell apoptosis [133,134].

Several mechanisms have been proposed to explain the role of GH and IGF1 in diabetic nephropathy. GH stimulates the expression of transforming growth factor-beta-induced protein (TGFBlp) in cultured podocytes, increasing podocyte migration and permeability of podocyte layer to albumin [135]. TGFBlp was found to be upregulated in renal tissue from patients with diabetic nephropathy, suggesting GH induction of TGFBlp, which may contribute to podocyte depletion in diabetes mellitus.

Using cultured immortalized podocytes and mouse models, it was demonstrated that GH excess activates Notch1 signaling in podocytes, resulting in podocyte loss. GH-induced glomerular fibrosis, glomerular basement membrane thickening, and albuminuria in vivo were prevented by pharmacological inhibition of Notch1 [136]. Upregulated Notch signaling was also noted in kidney biopsies from patients with diabetic nephropathy.

IGF1 effects in the kidney are modulated by nitric oxide, and nitric oxide synthase inhibition reduced renal hypertrophy and hyperfiltration in STZ-induced diabetes mellitus rats [137]. Prevention of advanced glycation end products accumulation in the STZ-induced model of diabetes has been reported to inhibit overexpression of IGF1, IGFBP-1, and IGFBP-4 mRNAs, suggesting the role of glycation end products in activation of IGF1 renal expression in diabetes mellitus [138]. In the diabetic rat model, insulin inhibits IGF1’s action on glomeruli by upregulation of the STAT5/SOCS2 pathway. STAT proteins activate gene transcription of IGF1, and SOCS proteins inhibit it. Thus, downregulation of this pathway in mesangial cells in insulin deficiency leads to increased actions of IGF1 on matrix production, glomerular enlargement, and progression of diabetic nephropathy [139].

9. Chronic Kidney Disease (CKD)

CKD is defined as permanent kidney damage, structural or functional, with or without a decrease in glomerular filtration rate (GFR). CKD is divided into five stages according to the decrease in estimated GFR. The nature of CKD is progressive in most patients, in association with many complications. CKD progression is related to many signaling pathways, mostly the renin-angiotensin-aldosterone system. CKD and its complications in children are associated with alterations in the GH/IGF1 axis, including growth retardation. GH levels in CKD are slightly elevated due to its impaired renal clearance, prolonged half-life, and the state of GH resistance. Renal GH resistance results from reduced GH receptor numbers in target tissues, post-receptor defects in GH signaling, and reduced levels of free IGF1 [140].

Reduced expression of the GH receptor has been shown in the epiphyseal growth plate of uremic rats [141]. GHBP is reduced in CKD proportionally to the degree of renal dysfunction [142]. Impaired postreceptor GH-activation of the JAK2 signaling pathway and downstream phosphorylation of STAT proteins and overexpression of SOCS, an inhibitor of JAK2/STAT5 signal transduction and GHR, also results in CKD-associated GH resistance [143]. Elevated expressions of SOCS proteins mRNA in skeletal muscle, liver, and epiphyseal growth plate have been found in uremic rats [144–146]. Impaired equilibrium between GHR-JAK2-STAT signaling and SOCS expression has also been described in chronic inflammation [140]. Proinflammatory cytokine IL-6, its signaling protein STAT3, and its gene product SOCS-3 were found to be significantly increased in uremia. SOCS-3 is a potent negative feedback inhibitor of GH signaling and may contribute to the GH-resistant state in CKD [147].

There is also evidence for IGF1 insensitivity in CKD [148]. Serum total IGF1 concentration is normal in patients with CKD, but reduced bioavailability is related to inhibitory effects of IGFBPs, which levels are increased in CKD. Both decreased renal clearance and
increased hepatic production contribute to accumulation of IGFBPs in uremia [149]. In addition, impaired cellular IGF signaling was demonstrated in experimental uremia [150]. GH treatment in CKD increases serum IGF1 levels and alters the balance of IGFBPs, resulting in a marked increase in IGF1 bioactivity [151].

CKD complications also contribute to GH/IGF1 axis alteration. Metabolic acidosis inhibits pituitary GH secretion and down-regulates hepatic IGF1 and GH receptor mRNA expression [152]. Long-term steroid therapy affects pulsatile GH secretion and inhibits hepatic production of IGF1 [153].

As discussed previously, GH increases GFR and RPF, and leads to glomerulosclerosis in transgenic mice overexpressing GH, raising concern about adverse effects of rhGH treatment on CKD progression. Indeed, in subtotally nephrectomized rats, treatment with high doses of rhGH resulted in a high glomerular sclerosing index, but low rhGH-dose did not result in significant changes in GFR or glomerular sclerosis index compared to controls [154]. Other animal studies did not show significant changes in GFR and RPF after treatment with bovine GH and rhIGF1 in 5/6 nephrectomized rats. In contrast, healthy rats showed an increase in GFR and RPF after treatment with bovine GH and rhIGF1 [155]. Clinical studies of rhGH therapy for short stature in CKD do not support preclinical findings on kidney function deterioration obtained in animals. Treatment with pharmacologic doses of rhGH did not increase GFR in patients with CKD 3–4 [156,157]. Recent experimental studies suggest that the safety of prolonged rhGH-treatment in CKD may be explained by a GH-resistant state in CKD [51].

10. Summary

The GH/IGF-1 axis plays a significant role in kidney growth, physiology, and pathophysiology. Its main actions become apparent in pathophysiologic situations of GH excess or deficiency, and the pathophysiological pathways behind these clinical observations were clarified with the development of transgenic and knockout animal models. GH and IGF-1 are involved in regulation of glomerular hemodynamics and tubular handling of water, sodium, calcium, and phosphorus. They participate in pathophysiology of diabetic nephropathy, as well as in compensatory kidney hypertrophy after unilateral nephrectomy. Alterations in GH/IGF-1 system are involved in pathogenesis of growth retardation in children with CKD. Studies on GH-IGF1 axis in CKD and diabetic nephropathy showed that systemic levels of GH and IGF1 do not always reflect their local levels and actions in the kidney. Treatment with rhGH for short stature in CKD was shown to be safe regarding the lack of impairment in renal function deterioration, which can probably be explained by a significant kidney GH resistance state in CKD.

Author Contributions: D.L. conceptualized the manuscript scope. E.G. wrote the manuscript’s first draft. D.L. and Y.S. critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Hartman, M.L.; Veldhuis, J.D.; Thorner, M.O. Normal control of growth hormone secretion. Horm. Res. 1993, 40, 37–47. [CrossRef] [PubMed]
2. Pang, A.L.-Y.; Chan, W.Y. Chapter 22—Molecular Basis of Diseases of the Endocrine System. In Molecular Pathology, 2nd ed.; Elsevier: Amsterdam, The Netherlands, 2018.
3. Rubinek, T.; Modan-Moses, D. Klotho and the growth hormone/insulin-like growth factor 1 axis: Novel insights into complex interactions. Vitam. Horm. 2016, 101, 85–118. [CrossRef] [PubMed]
4. Parganas, E.; Wang, D.; Stravopodis, D.; Topham, D.J.; Marine, J.C.; Teglund, S.; Vanin, E.F.; Bodner, S.; Colamonomi, O.R.; van Deursen, J.M.; et al. Jak2 is essential for signaling through a variety of cytokine receptors. *Cell* **1998**, *93*, 385–395. [CrossRef]

5. Hansen, J.A.; Lindberg, K.; Hilton, D.J.; Nielsen, J.H.; Billestrup, N. Mechanism of inhibition of growth hormone receptor signaling by suppressor of cytokine signaling proteins. *Mol. Endocrinol.* **1999**, *13*, 1832–1843. [CrossRef]

6. Frystyk, J.; Skjaerbaek, C.; Dinesen, B.; Orskov, H. Free insulin-like growth factors (IGF-I and IGF-II) in human serum. *FEBS Lett.* **1994**, *348*, 185–191. [CrossRef]

7. Taniguchi, C.M.; Emanuelli, B.; Kahn, C.R. Critical nodes in signalling pathways: Insights into insulin action. *Nat. Rev. Mol. Cell Biol.* **2006**, *7*, 85–96. [CrossRef]

8. Werner, H.; Bruchim, I. The insulin-like growth factor-I receptor as an oncogene. *Arch. Physiol. Biochem.* **2009**, *115*, 58–71. [CrossRef]

9. Baxter, R.C. Insulin-like growth factor (IGF)-binding proteins: Interactions with IGFs and intrinsic bioactivities. *Am. J. Physiol. Metab.* **2002**, *19*, 17–31. [CrossRef]

10. Mohan, S.; Baylink, D.J. IGF-binding proteins are multifunctional and act via IGF-dependent and -independent mechanisms. *J. Endocrinol.* **2002**, *175*, 19–31. [CrossRef]

11. Salmon, W.D., Jr.; Daughaday, W.H. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in vitro. *J. Lab. Clin. Med.* **1957**, *49*, 825–836.

12. Green, H.; Morikawa, M.; Nixon, T. A dual effector theory of growth-hormone action. *Differentiation* **1985**, *29*, 195–198. [CrossRef]

13. Yakar, S.; Liu, J.L.; Le Roith, D. The growth hormone/insulin-like growth factor-I system: Implications for organ growth and development. *Pediatr. Nephrol.* **2000**, *14*, 544–549. [CrossRef]

14. Le Roith, D.; Bondy, C.; Yakar, S.; Liu, J.L.; Butler, A. The somatomedin hypothesis: 2001.* Endocr. Rev.* **2001**, *22*, 53–74. [CrossRef]

15. Roberts, C.T., Jr.; Lassy, S.R.; Lowe, W.L., Jr.; Seaman, W.T.; LeRoith, D. Molecular cloning of rat insulin-like growth factor I complementary deoxyribonucleic acids: Differential messenger ribonucleic acid processing and regulation by growth hormone in extrahepatic tissues. *Mol. Endocrinol.* **1987**, *1*, 243–248. [CrossRef]

16. Schimpf, R.M.; Donnadieu, M.; Duval, M. Serum somatomedin activity measured as sulphation factor in peripheral, hepatic and renal veins in normal mongrel dogs: Early effects of intravenous injection of growth hormone. *Acta Endocrinol.* **1980**, *93*, 155–161. [CrossRef]

17. Guler, H.P.; Zapf, J.; Scheiwiller, E.; Froesch, E.R. Recombinant human insulin-like growth factor I stimulates growth and has distinct effects on organ size in hypophysectomized rats. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 4889–4893. [CrossRef]

18. Guler, H.P.; Schmid, C.; Zapf, J.; Froesch, E.R. Effects of recombinant insulin-like growth factor I on insulin secretion and renal function in normal human subjects. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 2868–2872. [CrossRef]

19. Lupu, F.; Terwilliger, J.D.; Lee, K.; Segre, G.V.; Efstratiadis, A. Roles of growth hormone and insulin-like growth factor 1 in complementary deoxyribonucleic acids: Differential messenger ribonucleic acid processing and regulation by growth hormone in extrahepatic tissues. *Mol. Endocrinol.* **1988**, *2*, 195–198. [CrossRef]

20. List, E.O.; Sackmann-Sala, L.; Berryman, D.E.; Funk, K.; Kelder, B.; Gosney, E.S.; Okada, S.; Ding, J.; Cruz-Topete, D.; Kopchick, J.J. Endocrine parameters and phenotypes of the growth hormone receptor gene disrupted (GHR−/−) mouse. *Endocrinol. Rev.* **2011**, *32*, 356–386. [CrossRef]

21. Neubauer, H.; Cumano, A.; Müller, M.; Wu, H.; Hußfisch, U.; Pfeffer, K. Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis. *Cell* **1998**, *93*, 397–409. [CrossRef]

22. Kofoid, E.M.; Hwa, V.; Little, B.; Woods, K.A.; Buckway, C.K.; Tsukabi, J.; Pratt, K.L.; Bezrodni, L.; Jasper, H.; Tepper, A.; et al. Growth hormone insensitivity associated with a STAT5b mutation. *N. Engl. J. Med.* **2003**, *349*, 1139–1147. [CrossRef]

23. Landau, D.; London, L.; Bandach, I.; Segev, Y. The hypoxia inducible factor/erythropoietin (EPO)/EPO receptor pathway is disturbed in a rat model of chronic kidney disease related anemia. *PloS One* **2018**, *13*, e0196684. [CrossRef]

24. Cui, Y.; Riedlinger, G.; Miyoshi, K.; Tang, W.; Li, C.; Deng, C.X.; Robinson, G.W.; Hennighausen, L. Inactivation of Stat5 in mouse mammary epithelium during pregnancy reveals distinct functions in cell proliferation, survival, and differentiation. *Mol. Cell Biol.* **2004**, *24*, 8037–8047. [CrossRef]

25. Liu, J.L.; Yakar, S.; LeRoith, D. Conditional knockout of mouse insulin-like growth factor-1 gene using the Cre/loxP system. *Proc. Soc. Exp. Biol. Med.* **2000**, *223*, 344–351. [CrossRef]

26. Rogers, S.A.; Powell-Braxton, L.; Hammerman, M.R. Insulin-like growth factor I regulates renal development in rodents. *Dev. Genet.* **1999**, *24*, 293–298. [CrossRef]

27. Liu, J.P.; Baker, J.; Perkins, A.S.; Robertson, E.J.; Efstratiadis, A. Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type I IGF receptor (Igf1r). *Cell* **1993**, *75*, 59–72. [CrossRef]

28. Louvi, A.; Accili, D.; Efstratiadis, A. Growth-promoting interaction of IGF-II with the insulin receptor during mouse embryonic development. *Dev. Biol.* **1997**, *189*, 33–48. [CrossRef]

29. Holzenberger, M.; Dupont, J.; Ducos, B.; Leneuve, P.; Geloen, A.; Even, P.C.; Cervera, P.; Le Bouc, Y. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature* **2003**, *421*, 182–187. [CrossRef]

30. Rotem-Grunbaum, B.; Landau, D. Genetic renal disease classification by hormonal axes. *Pediatr. Nephrol.* **2020**, *35*, 2211–2219. [CrossRef]

31. Kamenický, P.; Mazzotti, G.; Lombès, M.; Giustina, A.; Chanson, P. Growth hormone, insulin-like growth factor-1, and the kidney: Pathophysiological and clinical implications. *Endocr. Rev.* **2014**, *35*, 234–281. [CrossRef]

32. Striker, L.J.; Doi, T.; Striker, G.E. Transgenic mice in renal research. *Adv. Nephrol. Necker Hosp.* **1991**, *20*, 91–108. [PubMed]
33. Pesce, C.M.; Striker, L.J.; Peten, E.; Elliot, S.J.; Striker, G.E. Glomerulosclerosis at both early and late stages is associated with increased cell turnover in mice transgenic for growth hormone. Lab. Invest. 1991, 65, 601–605. [PubMed]
34. Mathews, L.S.; Hammer, R.E.; Behringer, R.R.; D’Ercole, A.J.; Bell, G.I.; Brinster, R.L.; Palmiter, R.D. Growth enhancement of transgenic mice expressing human insulin-like growth factor I. Endocrinology 1988, 123, 2827–2833. [CrossRef] [PubMed]
35. Doi, T.; Striker, L.J.; Quaiife, C.; Conti, F.G.; Palmiter, R.; Behringer, R.; Brinster, R.; Striker, G.E. Progressive glomerulosclerosis develops in transgenic mice chronically expressing growth hormone and growth hormone releasing factor but not in those expressing insulin like growth factor-I. Am. J. Pathol. 1988, 131, 398–403.
36. Doi, T.; Striker, L.J.; Gibson, C.C.; Agodoa, L.Y.; Brinster, R.L.; Striker, G.E. Glomerular lesions in mice transgenic for growth hormone and insulin-like growth factor-I. Relationship between increased glomerular size and mesangial sclerosis. Am. J. Pathol. 1990, 137, 541–552.
37. Blüttke, A.; Schneider, M.R.; Wolf, E.; Wanke, R. Growth hormone (GH)-transgenic insulin-like growth factor 1 (IGF1)-deficient mice allow dissociation of excess GH and IGF1 effects on glomerular and tubular growth. Physiol. Rep. 2016, 4, e12709. [CrossRef]
38. Rajkumar, K.; Barron, D.; Lewitt, M.S.; Murphy, L.J. Growth retardation and hyperglycemia in insulin-like growth factor binding protein-1 transgenic mice. Endocrinology 1995, 136, 4029–4034. [CrossRef]
39. Doublier, S.; Sourin, D.; Fouqueray, B.; Verpont, M.C.; Callard, P.; Striker, L.J.; Striker, G.E.; Binoux, M.; Baud, L. Glomerulosclerosis in mice transgenic for human insulin-like growth factor-binding protein-1. Kidney Int. 2000, 57, 2299–2307. [CrossRef]
40. Doublier, S.; Amri, K.; Sourin, D.; Moreau, E.; Merlet-Benichou, C.; Striker, G.E.; Gilbert, T. Overexpression of human insulin-like growth factor binding protein-1 in the mouse leads to nephron deficit. Pediatr. Res. 2001, 49, 660–666. [CrossRef]
41. Schneider, M.R.; Lahm, H.; Wu, M.; Hoeflich, A.; Wolf, E. Transgenic mouse models for studying the functions of insulin-like growth factor-binding proteins. FASEB J. 2000, 14, 629–640. [CrossRef]
42. Hoeflich, A.; Wu, M.; Mohan, S.; Föll, J.; Wanke, R.; Froehlich, T.; Arnold, G.J.; Lahm, H.; Kolb, H.J.; Wolf, E. Overexpression of insulin-like growth-factor-binding protein-2 in transgenic mice reduces postnatal body weight gain. Endocrinology 1999, 140, 5488–5496. [CrossRef]
43. Murphy, L.J.; Molnar, P.; Lu, X.; Huang, H. Expression of human insulin-like growth factor-binding protein-3 in transgenic mice. J. Mol. Endocrinol. 1995, 15, 293–303. [CrossRef]
44. Modric, T.; Silha, J.V.; Shi, Z.; Gui, Y.; Suwanichkul, A.; Durham, S.K.; Powell, D.R.; Murphy, L.J. Phenotypic manifestations of insulin-like growth factor-binding protein-3 overexpression in transgenic mice. Endocrinology 2001, 142, 1958–1967. [CrossRef]
45. Silha, J.V.; Gui, Y.; Mishra, S.; Leckstrom, A.; Cohen, P.; Murphy, L.J. Overexpression of gly56/gly80/gly81-mutant insulin-like growth factor-binding protein-3 in transgenic mice. Endocrinology 2005, 146, 1523–1531. [CrossRef]
46. Ning, Y.; Scholler, A.G.; Bradshaw, S.; Rotwein, P.; Ludwig, T.; Frystyk, J.; Pintar, J.E. Diminished growth and enhanced glucose metabolism in triple knockout mice containing mutations of insulin-like growth factor binding protein-3, -4, and -5. Mol. Endocrinol. 2006, 20, 2173–2186. [CrossRef]
47. Wood, T.L.; Rogler, L.E.; Czick, M.E.; Scholler, A.G.; Pintar, J.E. Selective alterations in organ sizes in mice with a targeted disruption of the insulin-like growth factor binding protein-2 gene. Mol. Endocrinol. 2000, 14, 1472–1482. [CrossRef]
48. Leu, J.I.; Crissey, M.A.; Craig, I.E.; Taub, R. Impaired hepatocyte DNA synthetic response posthepatectomy in insulin-like growth factor binding protein 1-deficient mice with defects in C/EBP beta and mitogen-activated protein kinase/extracellular signal-regulated kinase regulation. Mol. Cell. Biol. 2003, 23, 1251–1259. [CrossRef]
49. DeMambro, V.E.; Clemons, D.R.; Horton, L.G.; Boussein, M.L.; Wood, T.L.; Beamer, W.G.; Canalis, E.; Rosen, C.J. Gender-specific changes in bone turnover and skeletal architecture in igfbp-2-null mice. Endocrinology 2000, 149, 2051–2061. [CrossRef]
50. Gray, A.; Aronson, W.J.; Barnard, R.J.; Mehta, H.; Wan, J.; Said, J.; Cohen, P.; Galet, C. Global Igfbp1 deletion does not affect prostate cancer development in a c-Myc transgenic mouse model. J. Endocrinol. 2011, 211, 297–304. [CrossRef]
51. Landau, D.; Assadi, M.H.; Abu Hilal, R.; Chen, Y.; Rabin, R.; Segev, Y. SOCS2 Silencing Improves Somatic Growth without Worsening Kidney Function in CKD. J. Am. J. Nephrol. 2020, 51, 520–526. [CrossRef]
52. Stratikopoulos, E.; Szabolcs, M.; Dragatis, I.; Klinakis, A.; Efstratiadis, A. The hormonal action of IGF1 in postnatal mouse growth. Proc. Natl. Acad. Sci. USA 2008, 105, 19378–19383. [CrossRef] [PubMed]
53. Sjögren, K.; Liu, J.L.; Blad, K.; Skrtic, S.; Vidal, O.; Wallenius, V.; LeRoith, D.; Törnell, J.; Isaksson, O.G.; Jansson, J.O.; et al. Liver-derived insulin-like growth factor I (IGF-I) is the principal source of IGF-I in blood but is not required for postnatal body growth in mice. Proc. Natl. Acad. Sci. USA 1999, 96, 7088–7092. [CrossRef] [PubMed]
54. Lindström, N.O.; McMahon, J.A.; Guo, J.; Tran, T.; Guo, Q.; Rutledge, E.; Parvez, R.K.; Saribeykoy, G.; Schuler, R.E.; Liao, C.; et al. Conserved and divergent features of human and mouse kidney organogenesis. J. Am. Soc. Nephrol. 2018, 29, 785–805. [CrossRef] [PubMed]
55. Chin, E.; Zhou, J.; Bondy, C.A. Renal growth hormone receptor gene expression: Relationship to renal insulin-like growth factor system. Endocrinology 1992, 131, 3061–3066. [CrossRef]
56. Simard, M.; Manthos, H.; Giaid, A.; Lefèbvre, Y.; Goodyer, C.G. Ontogeny of growth hormone receptors in human tissues: An immunohistochemical study. J. Clin. Endocrinol. Metab. 1996, 81, 3097–3102. [CrossRef]
57. Rogers, S.A.; Ryan, G.; Hammerman, M.R. Insulin-like growth factors I and II are produced in the metanephros and are required for growth and development in vitro. J. Cell Biol. 1991, 113, 1447–1453. [CrossRef]
58. Lindenbergh-Kortleve, D.J.; Rosato, R.R.; van Neck, J.W.; Nauta, J.; van Kleffens, M.; Groffen, C.; Zwarthoff, E.C.; Drop, S.L. Gene expression of the insulin-like growth factor system during mouse kidney development. Mol. Cell. Endocrinol. 1997, 132, 81–91. [CrossRef]
59. Bondy, C.A.; Werner, H.; Roberts, C.T., Jr.; LeRoith, D. Cellular pattern of insulin-like growth factor-I (IGF-I) and type I IGF receptor gene expression in early organogenesis: Comparison with IGF-II gene expression. Mol. Endocrinol. 1990, 4, 1386–1398. [CrossRef]
60. Chin, E.; Bondy, C. Insulin-like growth factor system gene expression in the human kidney. J. Clin. Endocrinol. Metab. 1992, 75, 962–968. [CrossRef]
61. Daughaday, W.H.; Rotwein, P. Insulin-like growth factors I and II. Peptide, messenger ribonucleic acid and gene structures, serum, and tissue concentrations. Endocr. Rev. 1989, 10, 68–91. [CrossRef]
62. Wolf, E.; Kramer, R.; Blum, W.F.; Föll, J.; Brem, G. Consequences of postnatally elevated insulin-like growth factor-II in transgenic mice: Endocrine changes and effects on body and organ growth. Endocrinology 1994, 135, 1877–1886. [CrossRef]
63. Caidahl, K.; Edén, S.; Bengtsson, B.A. Cardiovascular and renal effects of growth hormone. Clin. Endocrinol. 1994, 40, 393–400. [CrossRef]
64. Jørgensen, J.O.; Pedersen, S.A.; Thuesen, L.; Jørgensen, J.; Ingemann-Hansen, T.; Skakkebaek, N.E.; Christiansen, J.S. Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet 1989, 333, 1221–1225. [CrossRef]
65. Falkheden, T.; Sjoegren, B. Extracellular fluid volume and renal function in pituitary insufficiency and acromegaly. Acta Endocrinol. 1964, 64, 80–88. [CrossRef]
66. Ece, A.; Çetinkaya, S.; Eksişoglu, S.; Şenel, S.; Özkasap, S.; Giniş, T.; Sen, V.; Şahin, C. Kidney growth and renal functions under the growth hormone replacement therapy in children. Ren. Fail. 2014, 36, 508–513. [CrossRef]
67. Ikkos, D.; Ljunggren, H.; Luft, R. Glomerular filtration rate and renal plasma flow in acromegaly. Acta Endocrinol. 1956, 21, 226–236. [CrossRef]
68. Grunenwald, S.; Tack, I.; Chauveau, D.; Bennet, A.; Caron, P. Impact of growth hormone hypersecretion on the adult human kidney. Ann. Endocrinol. 2011, 72, 485–495. [CrossRef]
69. Hoogenberg, K.; Sluiter, W.J.; Dullaart, R.P. Effect of growth hormone and insulin-like growth factor I on urinary albumin excretion: Studies in acromegaly and growth hormone deficiency. Acta Endocrinol. 1993, 129, 151–157. [CrossRef]
70. Manelli, F.; Bossoni, S.; Burattin, A.; Doga, M.; Solerte, S.B.; Romanelli, G.; Giustina, A. Exercise-induced microalbuminuria in patients with active acromegaly: Acute effects of slow-release lanreotide, a long-acting somatostatin analog. Metabolism 2000, 49, 634–639. [CrossRef]
71. Klinger, B.; Laron, Z. Renal function in Laron syndrome patients treated by insulin-like growth factor-I. Pediatr. Nephrol. 1994, 8, 684–688. [CrossRef]
72. Hirschberg, R.; Kopple, J.D. Evidence that insulin-like growth factor I increases renal plasma flow and glomerular filtration rate in fasted rats. J. Clin. Invest. 1989, 83, 326–330. [CrossRef] [PubMed]
73. Hirschberg, R.; Kopple, J.D.; Blantz, R.C.; Tucker, B.J. Effects of recombinant human insulin-like growth factor I on glomerular dynamics in the rat. J. Clin. Invest. 1991, 87, 1200–1206. [CrossRef] [PubMed]
74. Tönshoff, B.; Nowack, R.; Kurilenko, S.; Blum, W.F.; Seyberth, H.W.; Mehls, O.; Ritz, E. Growth hormone-induced glomerular hyperfiltration is dependent on vasodilating prostanooids. Am. J. Kidney Dis. 1993, 21, 145–151. [CrossRef]
75. Hale, L.J.; Welsh, G.I.; Perks, C.M.; Romer, T.E.; Pucilowska, J.B.; Underwood, L.E. Insulin-like growth factor-II is produced by, signals to and is an important survival factor for the mature podocyte in man and mouse. J. Pathol. 2013, 230, 95–106. [CrossRef]
76. Feld, S.; Hirschberg, R. Growth hormone, the insulin-like growth factor system, and the kidney. Endocr. Rev. 1996, 17, 423–480. [CrossRef]
77. De Boer, H.; Blok, G.J.; Van der Veen, E.A. Clinical aspects of growth hormone deficiency in adults. Endocr. Rev. 1995, 16, 63–86. [CrossRef]
78. Jørgensen, J.O. Human growth hormone replacement therapy: Pharmacological and clinical aspects. Endocr. Rev. 1991, 12, 189–207. [CrossRef]
79. Boguszewski, M.C.S. Growth hormone deficiency and replacement in children. Rev. Endocr. Metab. Disord. 2021, 22, 101–108. [CrossRef]
80. Ikkos, D.; Luft, R.; Sjögren, B. Body water and sodium in patients with acromegaly. J. Clin. Invest. 1954, 33, 989–994. [CrossRef]
81. Kamenický, P.; Maione, L.; Chanson, P. Cardiovascular complications of acromegaly. Ann. Endocrinol. 2020, 82, 206–209. [CrossRef]
82. Hirschi, R.; Brunori, G.; Kopple, J.D.; Guler, H.P. Effects of insulin-like growth factor I on renal function in normal men. Kidney Int. 1993, 43, 387–397. [CrossRef]
83. Walker, J.L.; Ginalska-Malinowska, M.; Romer, T.E.; Pucilowska, J.B.; Underwood, L.E. Effects of the infusion of insulin-like growth factor I in a child with growth hormone insensitivity syndrome (Laron dwarfism). N. Engl. J. Med. 1991, 324, 1483–1488. [CrossRef]
84. Svensson, J.; Tivesten, A.; Sjögren, K.; Isaksson, O.; Bergström, G.; Mohan, S.; Mölne, J.; Isgaard, J.; Ohlsson, C. Liver-derived IGF-I regulates kidney size, sodium reabsorption, and renal IGF-II expression. J. Endocrinol. 2007, 193, 359–366. [CrossRef]
85. Ho, K.Y.; Weissberger, A.J. The antinatriuretic action of biosynthetic human growth hormone in man involves activation of the renin-angiotensin system. *Metabolism* **1990**, *39*, 133–137. [CrossRef]

86. Möller, J.; Möller, N.; Frandsen, E.; Wolters, T.; Jørgensen, J.O.; Christiansen, J.S. Blockade of the renin-angiotensin-aldosterone system prevents growth hormone-induced fluid retention in humans. *Am. J. Physiol. Content* **1997**, *272*, E803–E808. [CrossRef]

87. Möller, J.; Jørgensen, J.O.; Möller, N.; Hansen, K.W.; Pedersen, E.B.; Christiansen, J.S. Expansion of extracellular volume and suppression of atrial natriuretic peptide after growth hormone administration in normal man. *J. Clin. Endocrinol. Metab.* **1991**, *72*, 768–772. [CrossRef]

88. Kamenicky, P.; Viengchareun, S.; Blanchard, A.; Meduri, G.; Zizzari, P.; 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. [CrossRef]

89. Kamenicky, P.; Blanchard, A.; Frank, M.; Salenave, S.; Letierce, A.; Azizi, M.; Lombès, M.; Chanson, P. Body fluid expansion in acromegaly is related to enhanced epithelial sodium channel (ENaC) activity. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 2127–2135. [CrossRef]

90. Hughey, R.P.; Bruns, J.B.; Kinlough, C.L.; Harkleroad, K.L.; Tong, Q.; Carattino, M.D.; Johnson, J.P.; Stockand, J.D.; Kleyman, T.R. Epithelial sodium channels are activated by furin-dependent proteolysis. *J. Biol. Chem.* **2004**, *279*, 18111–18114. [CrossRef]

91. Shimomura, Y.; Lee, M.; Oku, J.; Bray, G.A.; Glick, Z. Sodium potassium dependent ATPase in hypophysectomized rats: Response to growth hormone, triiodothyronine, and cortisol. *Metabolism* **1982**, *31*, 213–216. [CrossRef]

92. Nesbitt, T.; Drezner, M.K. Insulin-like growth factor-I regulation of renal 25-hydroxyvitamin D-1-hydroxylase activity. *Endocrinology* **1993**, *132*, 133–138. [CrossRef] [PubMed]

93. Bianda, T.; Glatz, Y.; Bouillon, R.; Frosch, E.R.; Schmid, C. Effects of short-term insulin-like growth factor-I (IGF-I) or growth hormone (GH) treatment on bone metabolism and on production of 1,25-dihydroxycholecalciferol in GH-deficient adults. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 81–87. [CrossRef] [PubMed]

94. Bengtsson, B.A.; Edres, M.; Lund, B.; et al. FGF23 promotes renal calcium reabsorption through the TRPV5 channel. *EMBO J.* **2014**, *33*, 229–246. [CrossRef] [PubMed]

95. Hansen, T.B.; Brixen, K.; Vahl, N.; Jørgensen, J.O.; Christiansen, J.S.; Mosekilde, L.; Hagen, C. Effects of 12 months of growth hormone (GH) treatment on calciotropic hormones, calcium homeostasis, and bone metabolism in adults with acquired GH deficiency: A double blind, randomized, placebo-controlled study. *J. Clin. Endocrinol. Metab.* **1996**, *81*, 3352–3359. [CrossRef]

96. Saggese, G.; Baronacci, G.L.; Bertelloni, S.; Cinquanta, L.; Di Nero, G. Effects of long-term treatment with growth hormone on bone and mineral metabolism in children with growth hormone receptor deficiency/Laron syndrome. *J. Clin. Endocrinol. Metab.* **1993**, *76*, 309–317. [CrossRef] [PubMed]

97. Manroa, P.; Kannan, S.; Hatipoglu, B.; Licata, A. Hypercalcemia and acromegaly—clarifying the connections. A case report and review of the literature. *Endocr. Pract.* **2014**, *20*, e86–e90. [CrossRef]

98. Adema, A.Y.; de Roij van Zuijldewijn, C.L.M.; Hoenderop, J.G.; de Borst, M.H.; Ter Wee, P.M.; Heijboer, A.C.; Vervloet, M.G.; NIGRAM Consortium. Influence of exogenous growth hormone administration on circulating concentrations of α-klotho in healthy and chronic kidney disease subjects: A prospective, single-center open case-control pilot study. *BMC Nephrol.* **2018**, *19*, 327. [CrossRef]

99. Hansen, T.B.; Brixen, K.; Vahl, N.; Jørgensen, J.O.; Christiansen, J.S.; Mosekilde, L.; Hagen, C. Effects of 12 months of growth hormone (GH) treatment on calciotropic hormones, calcium homeostasis, and bone metabolism in adults with acquired GH deficiency: A double blind, randomized, placebo-controlled study. *J. Clin. Endocrinol. Metab.* **1996**, *81*, 3352–3359. [CrossRef]

100. Saggese, G.; Baronacci, G.L.; Berteltoni, S.; Cinquanta, L.; Di Nero, G. Effects of long-term treatment with growth hormone on bone and mineral metabolism in children with growth hormone deficiency. *J. Pediatr.* **1993**, *122*, 37–45. [CrossRef]

101. Vaccarello, M.A.; Diamond, F.B., Jr.; Guevara-Aguirre, J.; Rosenbloom, A.L.; Fielder, P.J.; Gargosky, S.; Cohen, P.; Wilson, K.; Rosenfeld, R.G. Hormonal and metabolic effects and pharmacokinetics of recombinant insulin-like growth factor-I in growth hormone receptor deficiency/Laron syndrome. *J. Clin. Endocrinol. Metab.* **1993**, *77*, 273–280. [CrossRef]

102. Ahmad, A.M.; Thomas, J.; Clewes, A.; Hopkins, M.T.; Guzder, R.; Ibrahim, H.; Durham, B.H.; Vora, J.P.; Fraser, W.D. Effects of growth hormone replacement on parathyroid hormone sensitivity and bone mineral metabolism. *J. Clin. Endocrinol. Metab.* **2003**, *88*, 2860–2868. [CrossRef]

103. Moskowitz, D.W.; Liu, W. Gene expression after uninephrectomy in the rat: Simultaneous expression of positive and negative growth control elements. *J. Urol.* **1995**, *154*, 1560–1565. [CrossRef]
109. Flyvbjerg, A.; Bennett, W.F.; Rasch, R.; van Neck, J.W.; Groffen, C.A.; Kopchick, J.J.; Scarlett, J.A. Compensatory renal growth in uninephrectomized adult mice is growth hormone dependent. *Kidney Int.* **1999**, *56*, 2048–2054. [CrossRef]

110. Mulroney, S.E.; Haramati, A.; Werner, H.; Bondy, C.; Roberts, C.T., Jr.; LeRoith, D. Altered expression of insulin-like growth factor-I (IGF-I) and IGF receptor genes after unilateral nephrectomy in immature rats. *Endocrinology* **1992**, *130*, 249–256. [CrossRef]

111. McArule, Z.; Schreuder, M.F.; Moritz, K.M.; Denton, K.M.; Singh, R.R. Physiology and pathophysiology of compensatory adaptations of a solitary functioning kidney. *Front. Physiol.* **2020**, *11*, 725. [CrossRef]

112. Luque, V.; Escribano, J.; Grote, V.; Ferre, N.; Koletzko, B.; Grusfeld, D.; Socha, P.; Langhendries, J.P.; Goyens, P.; Closa-Monasterol, R. European childhood obesity project. Does insulin-like growth factor-I mediate protein-induced kidney growth in infants? A secondary analysis from a randomized controlled trial. *Pediatr. Res.* **2013**, *74*, 223–229. [CrossRef] [PubMed]

113. Haramati, A.; Lumpkin, M.D.; Mulroney, S.E. Early increase in pulsatile growth hormone release after unilateral nephrectomy in adult rats. *Am. J. Physiol. Physiol.** 1994**, *266*, F628–F632. [CrossRef] [PubMed]

114. Mulroney, S.E.; Woda, C.; Johnson, M.; Pesce, C. Gender differences in renal growth and function after uninephrectomy in adult rats. *Kidney Int.* **1999**, *56*, 944–953. [CrossRef]

115. Mok, K.-Y.; Sweeny, J.M.; Zheng, W.; Sandberg, K.; Mulroney, S.E. Gender differences in renal Ang II AT1 receptor regulation after uninephrectomy: GH dependence in the male rat. *FASEB J.* **1998**, *12*, A1154.

116. Nordstrom, S.M.; Tran, J.L.; SoS, B.C.; Wagner, K.U.; Weiss, E.J. Liver-derived IGF-I contributes to GH-dependent increases in lean mass and bone mineral density in mice with comparable levels of circulating GH. *Mol. Endocrinol.* **2011**, *25*, 1223–1230. [CrossRef] [PubMed]

117. Landau, D.; Biada, J.; Chen, Y.; Sood, S.; Yakar, S.; Leroith, D.; Segev, Y.; Rabkin, R. A marked deficiency in circulating and renal IGF-I peptide does not inhibit compensatory renal enlargement in uninephrectomized mice. *Growth Horm. IGF Res.* **2011**, *21*, 279–284. [CrossRef] [PubMed]

118. Young, B.A.; Johnson, R.J.; Alpers, C.E.; Eng, E.; Gordon, K.; Fleoge, J.; Couser, W.G.; Seidel, K. Cellular events in the evolution of experimental diabetic nephropathy. *Kidney Int.* **1995**, *47*, 935–944. [CrossRef] [PubMed]

119. Flyvbjerg, A. Putative pathophysiological role of growth factors and cytokines in experimental diabetic kidney disease. *Diabetologia* **2000**, *43*, 1205–1223. [CrossRef]

120. Landau, D.; Segev, Y.; Eshet, R.; Flyvbjerg, A.; Phillip, M. Changes in the growth hormone-IGF-I axis in non-obese diabetic mice. *Int. J. Exp. Diabetes Res.* **2000**, *1*, 9–18. [CrossRef]

121. Mercado, M.; Molitch, M.E.; Baumann, G. Low plasma growth hormone binding protein in IDDM. *Diabetes* **1992**, *41*, 605–609. [CrossRef]

122. Landau, D.; Israel, E.; Rivkis, I.; Kachko, L.; Schrijvers, B.F.; Flyvbjerg, A.; Phillip, M.; Segev, Y. The effect of growth hormone on the development of diabetic kidney disease in rats. *Nephrol. Dial. Transplant.* **2003**, *18*, 694–702. [CrossRef]

123. Muchaneta-Kubara, E.C.; Sayed-Ahmed, N.; Besbas, N.; Zhang, G.; Cope, G.H.; el Nahas, A.M. Experimental diabetic renal growth: Role of growth hormone and insulin-like growth factor-I. *Nephrol. Dial. Transplant.* **1994**, *9*, 1395–1401. [CrossRef]

124. Segev, Y.; Landau, D.; Rasch, R.; Flyvbjerg, A.; Phillip, M. Growth hormone receptor antagonism prevents early renal changes in nonobese diabetic mice. *J. Am. Soc. Nephrol.* **1999**, *10*, 2374–2381. [CrossRef] [PubMed]

125. Serri, O.; Beauregard, H.; Brazeau, P.; Abriot, T.; Lambert, J.; Harris, A.; Vachon, L. Somatostatin analogue, octreotide, reduces increased glomerular filtration rate and kidney size in insulin-dependent diabetes. *JAMA* **1991**, *265*, 888–892. [CrossRef]

126. Segev, Y.; Eshet, R.; Rivkis, I.; Hayat, C.; Kachko, L.; Phillip, M.; Landau, D. Comparison between somatostatin analogues and ACE inhibitor in the NOD mouse model of diabetic kidney disease. *Nephrol. Dial. Transplant.* **2004**, *19*, 3021–3028. [CrossRef]

127. Segev, Y.; Landau, D.; Marbach, M.; Shahadeh, N.; Flyvbjerg, A.; Phillip, M. Renal hypertrophy in hyperglycemic non-obese diabetic mice is associated with persistent renal accumulation of insulin-like growth factor I. *J. Am. Soc. Nephrol.* **1997**, *8*, 436–444. [CrossRef]

128. Park, I.S.; Kiyomoto, H.; Alvarez, F.; Xu, Y.C.; Abboud, H.E.; Abboud, S.L. Preferential expression of insulin-like growth factor binding proteins-1, -3, and -5 during early diabetic renal hypertrophy in rats. *Am. J. Kidney Dis.* **1998**, *32*, 1000–1010. [CrossRef]

129. Flyvbjerg, A.; Kessler, U.; Kiess, W. Increased kidney and liver insulin-like growth factor II/mannose-6-phosphate receptor concentration in experimental diabetes in rats. *Growth Regul.* **1994**, *4*, 188–193.

130. Verzola, V.; Gandolfo, M.T.; Ferrario, F.; Rastaldi, M.P.; Villaggio, B.; Gianiorio, F.; Giannoni, M.; Rimpli, L.; Lauria, F.; Miji, M.; et al. Apoptosis in the kidneys of patients with type II diabetic nephropathy. *Kidney Int.* **2007**, *72*, 1262–1272. [CrossRef]

131. Vasylyeva, T.L.; Chen, X.; Ferry, R.J.; Jr. Insulin-like growth factor binding protein-3 mediates cytokine-induced mesangial cell apoptosis. *Growth Horm. IGF Res.* **2005**, *15*, 207–214. [CrossRef]
135. Chitra, P.S.; Swathi, T.; Sahay, R.; Reddy, G.B.; Menon, R.K.; Kumar, P.A. Growth Hormone Induces Transforming Growth Factor-Beta-Induced Protein in Podocytes: Implications for Podocyte Depletion and Proteinuria. J. Cell. Biochem. 2015, 116, 1947–1956. [PubMed]

136. Nishad, R.; Mukhi, D.; Talaseen, S.V.; Mungamuri, S.K.; Pasupulati, A.K. Growth hormone induces Notch1 signaling in podocytes and contributes to proteinuria in diabetic nephropathy. J. Biol. Chem. 2019, 294, 16109–16122. [PubMed]

137. Levin-Iaina, N.; Iaina, A.; Raz, I. The emerging role of NO and IGF-1 in early renal hypertrophy in STZ-induced diabetic rats. Diabetes Metab. Res. Rev. 2011, 27, 235–243. [PubMed]

138. Bach, L.A.; Dean, R.; Youssef, S.; Cooper, M.E. Aminoguanidine ameliorates changes in the IGF system in experimental diabetic nephropathy. Nephrol. Dial. Transplant. 2000, 15, 347–354. [CrossRef]

139. Isshiki, K.; He, Z.; Maeno, Y.; Ma, R.C.; Yasuda, Y.; Kuroki, T.; White, G.S.; Patti, M.E.; Weir, G.C.; King, G.L. Insulin regulates SOCS2 expression and the mitogenic effect of IGF-1 in mesangial cells. Kidney Int. 2008, 74, 1434–1443. [PubMed]

140. Mahesh, S.; Kaskel, F. Growth hormone axis in chronic kidney disease. Pediatr. Nephrol. 2008, 23, 41–48. [CrossRef]

141. Edmondson, S.R.; Baker, N.L.; Oh, J.; Kovacs, G.; Werther, G.A.; Mehls, O. Growth hormone receptor abundance in tibial growth plates of uremic rats: GH/IGF-I treatment. Kidney Int. 2000, 58, 62–70. [CrossRef]

142. Tönshoff, B.; Cronin, M.J.; Reichert, M.; Haffner, D.; Wingen, A.M.; Blum, W.F.; Mehls, O. How safe is the treatment of uraemic children with recombinant human growth hormone? Pediatr. Nephrol. 2000, 15, 1007–1013. [CrossRef]

143. Rabkin, R.; Sun, D.F.; Chen, Y.; Tan, J.; Schaefer, F. Growth hormone resistance in uremia, a role for impaired JAK/STAT signaling. Pediatr. Nephrol. 2005, 20, 313–318. [CrossRef]

144. Schaefer, F.; Chen, Y.; Tsao, T.; Nouri, P.; Rabkin, R. Impaired JAK-STAT signal transduction contributes to growth hormone resistance in chronic uremia. J. Clin. Investig. 2001, 108, 467–475. [CrossRef]

145. Troib, A.; Landau, D.; Kachko, L.; Rabkin, R.; Segev, Y. Epiphyseal growth plate growth hormone receptor signaling is decreased in chronic kidney disease-related growth retardation. Kidney Int. 2013, 84, 940–949. [CrossRef]

146. Sun, D.F.; Zheng, Z.; Tummala, P.; Oh, J.; Schaefer, F.; Rabkin, R. Chronic uremia attenuates growth hormone-induced signal transduction in skeletal muscle. J. Am. Soc. Nephrol. 2004, 15, 2630–2636. [CrossRef]

147. Wiezel, A.; Assadi, M.H.; Landau, D.; Troib, A.; Kachko, L.; Rabkin, R.; Segev, Y. Impaired renal growth hormone (GH)-binding protein in children with chronic renal failure: Correlation with GH insensitivity. The European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. The German Study Group for Growth Hormone Treatment in Chronic Renal Failure. J. Clin. Endocrinol. Metab. 1997, 82, 107–108. [CrossRef]

148. Bach, L.A.; Hale, L.J. Insulin-like growth factors and kidney disease. Am. J. Kidney Dis. 2015, 65, 327–336. [CrossRef]

149. Powell, D.R.; Durham, S.K.; Liu, F.; Baker, B.K.; Lee, P.D.; Watkins, S.L.; Campbell, P.G.; Brewer, E.D.; Hintz, R.L.; Hogg, R.J. The insulin-like growth factor axis and growth in children with chronic renal failure: A report of the Southwest Pediatric Nephrology Study Group. J. Clin. Endocrinol. Metab. 1998, 83, 1654–1661. [CrossRef]

150. Ding, H.; Gao, X.L.; Hirschberg, R.; Vadgama, J.V.; Kopple, J.D. Impaired actions of insulin-like growth factor 1 on protein synthesis and degradation in skeletal muscle of rats with chronic renal failure. Evidence for a postreceptor defect. J. Clin. Investig. 1996, 97, 1064–1075. [CrossRef]

151. Tönshoff, B.; Kiepe, D.; Ciaramatori, S. Growth hormone/insulin-like growth factor system in children with chronic renal failure. Pediatr. Nephrol. 2005, 20, 279–289. [CrossRef]

152. Challa, A.; Chan, W.; Krieg, R.J., Jr.; Thabet, M.A.; Liu, F.; Hintz, R.L.; Chan, J.C. Effect of metabolic acidosis on the expression of insulin-like growth factor and growth hormone receptor. Kidney Int. 1993, 44, 1224–1227. [CrossRef]

153. Hochberg, Z. Mechanisms of steroid impairment of growth. Horm. Res. 2002, 58, 33–38. [CrossRef]

154. Kawaguchi, H.; Hattori, M.; Ito, K. Somatic and renal effects of growth hormone in rats with chronic renal failure. Pediatr. Nephrol. 1997, 11, 280–284. [CrossRef]

155. Miller, S.B.; Hansen, V.A.; Hammerman, M.R. Effects of growth hormone and IGF-I on renal function in rats with normal and reduced renal mass. Am. J. Physiol. 1990, 259, F747–F751. [CrossRef]

156. Tönshoff, B.; Heinrich, U.; Mehls, O. How safe is the treatment of uraemic children with recombinant human growth hormone? Pediatr. Nephrol. 1991, 5, 454–460. [CrossRef]

157. Maxwell, H.; Nair, D.R.; Dalton, R.N.; Rigden, S.P.; Rees, L. Differential effects of recombinant human growth hormone on glomerular filtration rate and renal plasma flow in chronic renal failure. Pediatr. Nephrol. 1995, 9, 458–463. [CrossRef]