Growth Hormone and Insulin-Like Growth Factor Dysregulation in Pediatric Chronic Kidney Disease

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Keywords

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Abstract

Poor growth is a common finding in children with chronic kidney disease (CKD) that has been associated with poor long-term outcomes. The etiology of poor growth in this population is multifactorial and includes dysregulation of the growth hormone (GH) and insulin-like growth factor (IGF) axis. In this review, we describe the data on GH resistance or insensitivity and inappropriate levels or reduced bioactivity of IGF proposed as contributing factors of growth impairment in children with CKD. Additionally, we describe the theorized negative effect of metabolic acidosis, another frequent finding in pediatric CKD, on the GH/IGF axis and growth. Last, we present the current and potential therapies for the treatment of short stature in pediatric CKD that target the GH/IGF hormonal axis.

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Introduction

Growth impairment or failure is a common comorbidity of pediatric chronic kidney disease (CKD). The current estimates hold that almost one-third of children with

CKD suffer from short stature [1, 2]. Growth impairment has been associated with increased mortality, poorer psychosocial functioning, and faster times to adverse post-transplant outcomes [3–5]. Growth failure is a consequence of multiple factors in CKD which include, but are not limited to, the duration of CKD, worsening kidney function, suboptimal nutrition, metabolic acidosis, mineral and bone disorder, and hormonal disturbances [6]. One key hormonal axis that is dysregulated in pediatric CKD is that of the growth hormone (GH) and insulin-like growth factor (IGF) axis. This review will focus on disturbances of the GH/IGF axis thought to contribute to poor growth in children with CKD.

Normal Action of GH/IGF on Bone

Long bone growth, and thus stature, is primarily determined by action at the growth plate through a process called endochondral ossification. The growth plate lies between the epiphyseal and diaphyseal portions of the long bone and is composed of several zones: (1) the resting zone, (2) the proliferative zone, (3) the hypertrophic zone, and (4) the degenerative zone [7]. Chondrocytes, the predominant cell type found within the growth plate (and various zones), align in a column-like fashion within these zones and parallel to the bone's long axis. Growth

Fig. 1. Normal GH and IGF-1 effects on longitudinal bone growth (black) and perturbations caused by impaired kidney function and uremia (red). Inhibitory effects represented by dashed arrows. GH, growth hormone; IGF, insulin-like growth factor; IGFBP, IGF-binding protein.

of long bones is a result of an increase in the chondrocyte number and size [7]. GH exerts its effects on several different tissue types such as the kidney, liver, and muscle but is generally regarded as the hormone primarily responsible for longitudinal bone growth [8]. It induces cellular differentiation which subsequently leads to the increase in the cellular size and number [9]. Much has been studied about the pathophysiology of the GH's effect on bone growth and mechanisms, including direct effects such as stimulation of prechondrocytes, and indirect effects via stimulation of IGF-1, a hormone known to have paracrine and endocrine effects [8, 10–12]. IGF-1, a hepatic growth factor, is thought to act on prechondrocytes once they have matured, causing proliferation and hypertrophy, which leads to elongation of the bone [13, 14]. GH stimulates IGF-1 production both at the liver and locally at the growth plate. IGF-1 also acts to regulate GH by inhibiting its release from the pituitary [12]. Altogether, GH and IGF-1 have been shown to be the key hormonal mediators of chondrocyte proliferation and maturation that lead to subsequent growth in long bones (shown in Fig. 1) and thus longitudinal skeletal growth.

GH/IGF Dysregulation in Pediatric CKD

GH Resistance (Table 1)

There are multiple disturbances in the GH/IGF axis noted in children with CKD that are theorized to contrib-

ute to the growth failure frequently observed in this population. Aberrations in GH sensitivity is one such cause [15, 16]. Numerous studies have demonstrated that in patients with impaired kidney function and poor growth, fasting serum GH levels are inappropriately normal or elevated, reflecting a degree of GH insensitivity or resistance [17, 18]. The normal or increased GH serum concentrations are thought, in part, to be caused by decreased metabolic clearance as a consequence of decreased kidney function as the GH elevation has been shown to be inversely correlated with glomerular filtration [19, 20]. This theory of GH resistance is further substantiated by studies of uremic rats that demonstrated decreased hepatic GH receptor (*GHR*) mRNA expression and required treatment of the rats with supraphysiologic doses of GH therapy before growth was observed [21–23]. Additional evidence of uremia-induced GH resistance is reflected in studies of children on dialysis who display poor growth, despite treatment with recombinant human GH (rhGH) [24–26]. Similarly, Fischbach et al. [27] found improved growth in children initiated on intensified daily dialysis regimens compared to when they were receiving standard, thrice weekly hemodialysis.

Other investigators posit that GH insensitivity could be related to uremia-induced impairment in hormone signal transduction, particularly the Janus kinase 2 (JAK2)-signal transducer and activator of transcription (STAT) pathway [28, 29]. In their study comparing rats with surgically induced CKD to controls, with subgroups

Table 1. Studies demonstrating GH resistance or insensitivity in CKD

Study	Population	Evaluated outcome(s)	Study finding(s)
Schaefer et al. [16]	43 boys with advanced CRF (conservative treatment, GFR <25 mL/min. 1.73 m ² or dialysis) 38 posttransplant boys 40 healthy boys (control)	Nighttime plasma GH concentration profile in peripubertal boys with advanced CRF	GH hyposecretion is associated with an increase in the plasma half-life of GH in peripubertal boys with CRF
Samaan and Freeman [17]	33 male, adult subjects Group 1: Patients receiving twice weekly HD (N = 10) Group 2: Patients with azotemia being evaluated for HD (N = 11) Group 3: Controls (N = 12)	Evaluate GH levels in patients on HD Evaluate whether there are changes in GH levels with changes in dialysate glucose concentration	High GH levels is a frequent finding in patients with CRF The mean fasting GH level of the controls (group 3) was lower than patients with azotemia not yet on dialysis (group 2) and the patients on HD (group 3) There was no suppression of GH with changes in dialysate glucose concentration
Haffner et al. [20]	Pediatric and adult patients with CRF (N = 6 children, N = 6 adults) Healthy adult volunteers (N = 24)	Investigate the pharmacokinetics of (rh)GH Determine (rh)GH MCR and elimination half-life Determine the effect of GFR on pharmacokinetics of (rh)GH	In comparison to healthy adults, MCR of rhGH was diminished by approximately half in CRF participants Plasma half-life of rhGH was increased by 25–50% in CRF participants compared to healthy controls There was an inverse relationship between elimination half-life of (rh)GH and GFR
Mehls et al. [21]	Subtotal nephrectomized rats Controls rats	Comparison of growth rate after administration of (rh)GH	In uremic rats, normal growth was not achieved after administration of (rh)GH
Tönshoff et al. [22]	Children with CRF (N = 126) Healthy children (N = 773)	Comparison of serum GHBP levels/ GHR expression	In comparison to age- and gender-matched controls, the majority of CRF patients (77%) had below average serum GHBP concentrations Low serum GHBP levels were associated with the degree of renal dysfunction → the lowest GHBP levels were observed in children with ESRD Serum GHBP levels were not affected by 3 months of GH therapy
Tönshoff et al. [23]	5/6th nephrectomized rats Pair-fed controls Ad libitum-fed controls	Evaluate the effect of uremia on GHR expression Evaluate the effect of uremia on circulating GHBP	Uremic rats demonstrated a 50% decrease in expression of hepatic GHR mRNA compared to pair-fed controls Plasma levels of GHBP in the uremic rats were significantly higher than levels observed in both control groups Treatment with large doses of (rh)GH caused similar increases in IGF-1 plasma levels in uremic rats and pair-fed controls indicating that GH insensitivity in uremia can be overcome by (rh)GH
Wühl et al. [24]	Prepubertal CRF (N = 38) and ESRD (N = 18) patients <10 years old at initiation of (rh)GH treatment	Evaluate response of CRF and dialysis patients to (rh)GH	In the first year of treatment, children on dialysis respond less to (rh)GH compared to CRF patients The change in height was greater in CRF patients in year 2 of treatment as well
Haffner et al. [25]	Children with CRF (N = 74) and ESRD (N = 29) treated with (rh)GH	Evaluate effects of short- and long-term use of (rh)GH in children with CRF/ESRD and growth impairment	In the CRF children, both standardized height and predicted adult height were higher than those in the children on dialysis GFR positively correlated with height SDS and height velocity
Fischbach et al. [27]	Children with ESRD (N = 5) on intensified daily dialysis (4/5 children started on (rh)GH before IDd initiation)	Evaluate linear growth rate in children before and after initiation of IDd	Height SDS improved for those children started on (rh)GH therapy prior to IDd, though change in SDS not significant Height SDS significantly increased after conversion to IDd

Table 1 (continued)

Study	Population	Evaluated outcome(s)	Study finding(s)
Schaefer et al. [29]	5/6th nephrectomized rats and pair-fed controls both treated with (rh)GH	Assess hepatic GH signal transduction in CRF	CRF rats had significantly decreased levels of GHR mRNA levels GH-induced JAK2, STAT5, and STAT3 tyrosine-phosphorylation was 75% lower in CRF rats SOCS3 expression was increased by 2-fold in CRF rats treated with GH, and mRNA levels were 60% higher than those in controls independent of GH treatment
Troib et al. [30]	Surgically induced CKD rats and pair-fed controls	Determine if changes in systemic and growth plate GH signaling affect linear growth	Similar serum GH levels in nephrectomized rats versus controls Serum IGF-1 levels were significantly lower in CKD rats versus controls Total growth plate JAK2 protein levels were significantly lower in CKD and CKD + GH rats compared to control groups Growth plate STAT5 phosphorylation (absolute and relative) was decreased in the CKD (basal) state SOCS2, a GH signaling inhibitor, mRNA levels were significantly higher in CKD and CKD +GH groups versus controls

CRF, chronic renal failure; CKD, chronic kidney disease; ESRD, end-stage renal disease; GH, growth hormone; GHBP, growth hormone binding protein; GFR, glomerular filtration rate; HD, hemodialysis; IDd, intensified daily dialysis; (rh)GH, recombinant growth hormone; SDS, standard deviation score; SOCS, suppressor of cytokine signaling; IGF, insulin-like growth factor; MCR, metabolic clearance rate; GHR, GH receptor; rhGH, recombinant human GH; JAK2, Janus kinase 2; STAT, signal transducer and activator of transcription.

administered GH or buffered solution, Troib et al. [30] found that total JAK2 protein levels in the growth plate were significantly lower in CKD and CKD +GH rats than control groups. Additional findings of that study included decreased growth plate STAT5 phosphorylation (absolute and relative) in basal CKD conditions and significantly increased SOCS2 mRNA levels in the CKD and CKD +GH groups. SOCS2 is a known inhibitor of GH signaling. The contribution of uremia-induced aberrations in JAK-STAT signaling to GH resistance was also studied by Schaefer and colleagues, with their investigation finding diminished phosphorylation of JAK2, STAT1, STAT3, and STAT5 and increased expression of SOCS2 and SOCS3 [29].

Corticosteroids, a common therapeutic agent used for treatment of numerous disorders that lead to CKD, have also been implicated as contributing to GH resistance and thus growth impairment in children with CKD [26, 31]. The adverse effects of corticosteroids on GH include stimulating hypothalamic somatostatin-releasing inhibiting factor which, in turn, suppresses pituitary release of GH, GH receptor downregulation, and reduction in IGF bioactivity by stimulation of IGF inhibitors [31].

Inappropriate IGF-1 Levels and Reduced Bioactivity (Table 2)

During periods of significant growth, the predominant IGF is IGF-1 [32]. While it is synthesized by other tissues, Daughaday et al. [12] proposed that GH stimulates hepatic synthesis and release of IGF-1 (previously named somatomedin), which then exerts linear growth-promoting effects on the growth plate. Based on this idea, also known as the somatomedin hypothesis, increased IGF-1 levels should be seen in children with CKD due to the elevated GH levels found in these patients. However, numerous investigations have demonstrated low IGF-1 levels, or disproportionately low, given increased GH levels, in states of uremia including, explicitly in children with kidney failure [33–36]. The etiology of this may be low production, as a consequence of GH insensitivity caused by uremia, or reduced expression of IGF-1 mRNA [36–39]. Inadequate nutrition, including protein restriction which is often an imposed dietary restriction as CKD worsens, has been implicated as one of the contributing causes of IGF-1 mRNA reduction [36, 38, 40].

In addition to the inappropriately normal or reduced total IGF-1, low free (bioactive) IGF-1 levels have been found in children with CKD with studies showing a cor-

Table 2. Studies demonstrating inappropriate IGF-1 levels and/or reduced bioactivity in CKD

Study	Population	Evaluated outcome(s)	Study finding(s)
Hokken-Koelega et al. [33]	22 prepubertal children with CRF (GFR <20 mL/min-1.73 m ²) and severe growth retardation Prepubertal, healthy, normal height children controls	24-h plasma GH profiles secretion Plasma IGF-I and IGF-II levels	A normal 24-h GH profile was noted in fourteen children, a low 24-h GH profile was noted in 4 children, and an elevated 24-h GH profile was noted in 4 children 24-h urinary GH excretion was 100–1,000× higher in all patients with renal insufficiency than in controls When grouped by 24-h GH profiles, the lowest IGF-I levels were found in patients with elevated profiles (for bone age), children with normal profiles had the highest IGF-I levels There was no correlation between IGF-II levels and GH secretion profiles
Blum et al. [34]	31 children with ESRD 11 children with CRF and residual kidney function	Assess IGF and IGFBP levels in uremia	IGFBP accumulates in states of uremia Excess IGFBP led to binding of free IGF, causing reduced bioactivity In uremic states, there is reduced IGF secretion (indicating a uremic induced GH resistance)
Tönshoff et al. [35]	54 children with ESRD	Assessing IGF-1 and -2 and IGFBP-1, -2, and -3 levels	IGF-1 levels were below mean age-related values IGF-2 levels were at the upper limit of normal to elevated IGFBP-1, -2, and -3 levels were all increased IGFBP-3 declined with transplantation and associated increase in kidney function
Tönshoff et al. [36]	5/6th nephrectomized rats Pair-fed controls Ad libitum-fed controls	Assess IGF-I and IGFBPs production rates in CRF	Compared to ad lib control, hepatic IGF-I gene expression was markedly reduced in uremic rats (37±5% of control) and pair-fed rats (65±10% of control) The concentration of IGFBPs in the plasma of uremic rats was increased
Blum et al. [37]	51 children with ESRD 11 children with CRF Healthy controls	Evaluate levels of IGF-1 and -2 and IGFBP 1, -2, and -3	Uremic children had significant elevation in all IGFBPs Despite normal GH secretion, IGF production is lower in uremic children by 2 orders of magnitude
Chan et al. [38]	5/6th nephrectomized rats Control rats (sham operated) Pair-fed controls rats	Evaluation of IGF-1 levels in response to (rh)GH administration	Steady-state hepatic IGF-1 mRNA levels were lower in uremic rats than controls After (rh)GH administration, there was a lack of significant increase in hepatic IGF-1 mRNA in uremic rats and pair-fed controls
Hanna et al. [39]	5/6th nephrectomized rats (N = 12) treated with (rh)GH (N = 6) versus saline (N = 6) Control rats (sham operated; N = 4)	Evaluate molecular mechanisms of longitudinal growth in uremia including (rh) GH effect on IGF-1 expression	Compared to controls, uremic rats had lower IGF-1 mRNA in the chondrocytes found in both the proliferative and hypertrophic zones of their tibial growth plates Treatment with (rh)GH increased chondrocyte IGF-1 mRNA in uremic rats, but its abundance was lower than that in controls
VandeHaar et al. [40]	Female rats fed a 15% protein-sufficient diet Female rats fed a 5% protein-deficient diet	Assess the effect of a low protein diet on serum IGF-1 levels and hepatic IGF-1 mRNA levels	Serum levels and hepatic mRNA levels were highly correlated Compared to controls, both serum and hepatic mRNA IGF-1 were lower in rats on the protein-restricted diet
Frystyk et al. [41]	Children with nondialysis-dependent CRF stage III-V (N = 25) Healthy controls (N = 13)	Evaluate alterations in free IGF-1 in children with CRF	Children with CRF had lower free IGF-1 levels There was a positive correlation between degree of kidney function (creatinine clearance) and free serum IGF-1 levels
Kiepe et al. [42]	Cultured rat growth plate chondrocytes	Investigate the effect of IGFBP-1, -2, -3, and -6 on IGF-1 binding cultured chondrocytes	DNA synthesis and cell production of IGF-dependent chondrocytes were decreased by IGFBP-1, -2, and -6 If preincubated with chondrocytes, IGFBP-3 increased IGF-1 activity (because it associates with the cell membrane under preincubation conditions) If co-incubated with chondrocytes, IGFBP-3 inhibited IGF-1 induction of chondrocytes

Table 2 (continued)

Study	Population	Evaluated outcome(s)	Study finding(s)
Ulinski et al. [43]	80 children with CRF 9 children with ESRD 32 healthy controls	Assess the effect of serum IGFBP-4, and -5 levels on IGF activity in children with CRF	Compared to healthy prepubertal controls, IGFBP-4 levels were fourfold higher in prepubertal children with CRF/ESRD There was an inverse correlation between serum IGFBP-4 levels (but not IGFBP-5 levels) and GFR There was an inverse correlation between standardized height and IGFBP-4 in prepubertal children with CRF IGFBP-5 levels did not differ significantly between CRF children and controls In CRF children, IGFBP-5 positively correlated with IGF-1 levels, height measurements, and its level increased with (rh)GH administration, suggesting it may be a growth stimulatory IGFBP in CRF
Tönshoff et al. [44]	94 children with CRF 68 prepubertal healthy controls (age matched to the 54 prepubertal children with CRF)	Quantifying serum levels of IGF-1 and -2 and IGFBP-1, -2, and -3 Results compared to age-normal values	Serum IGF-1 and -2 were largely normal throughout childhood There was a weaker correlation between IGF-1 levels and height in prepubertal children with CRF than that in controls CRF children had mild elevation in IGFBP-1 and markedly increased IGFBP-2 and -3 There was an inverse correlation between GFR and IGFBP-1, -2, and -3
Durham et al. [45]	Prepubertal children with CRF/ESRD with height <5%	Describe the serum bioactivity of IGFBP-3 in the ~35 KD fraction of serum	The 29-KD form of IGFBP-3 (IGFBP-3 ⁽²⁹⁾), a glycosylated fragment, predominates in ~35-KD serum fractions in growth-impaired children with CRF IGFBP-3 ⁽²⁹⁾ did not alter IGF-1 activity and mildly inhibited IGF-2
Powell et al. [46]	44 prepubertal children with CRF and short stature randomized to treatment with (rh)GH (<i>N</i> = 30) versus no treatment (<i>N</i> = 14) 10 healthy prepubertal controls	Assessment of serum IGF and IGFBPs during treatment with (rh)GH	Baseline levels of IGFBP-1 and -2 levels were higher in children with CRF than those in controls Baseline height SDS inversely correlated with IGFBP-2 At 12-month follow-up, compared to untreated children, (rh)GH treated children had higher height increases, higher serum IGF-1 and -2, free IGF-1, and IGFBP-3 levels but lower IGFBP-1 serum levels At 12-month follow-up, height SDS in treated children positively correlated with total IGF, IGF-1 and -2, free IGF-1, and IGFBP-3 levels
Blum et al. [47]	114 healthy children and adolescents	Evaluate the relationship between height and GH, IGF-1, and IGFBP-3	GH secretion positively correlated with IGF-1 and IGFBP-3 Height SDS correlated positively with IGF-1 SDS and IGFBP-3 SDS

CRF, chronic renal failure; ESRD, end-stage renal disease; GFR, glomerular filtration rate; GH, growth hormone; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; (rh)GH, recombinant growth hormone; SDS, standard deviation score; CKD, chronic kidney disease.

relation with renal function impairment [37, 41]. IGF-binding proteins (IGFBPs), found in circulation, have a high binding affinity for IGF-1 which prevents, or decreases, IGF-1 binding to its signal receptor [28, 37, 42]. Studies of patients with CKD have shown that with reduced kidney function, there may be decreased clearance of IGFBPs which, in turn, leads to decreased free IGF-1 [36, 43, 44]. There are 6 IGFBPs, but it is important to note that not all IGFBPs act similarly, particularly as it pertains to their effects on growth. Elevated levels of IGFBP-1, IGFBP-2, IGFBP-4, and IGFBP-6 have been reported in children with kidney impairment, as well as elevated fragmented

IGFBP-3 [18, 43–45]. There is no significant increase in IGFBP-5 with reduced kidney function [43]. Excess IGFBP-1, IGFBP-2, IGFBP-4, and IGFBP-6 have been proposed to have primarily growth inhibitory effects in children with CKD [42–44, 46]. The action of IGFBP-3 is more unclear with evidence of both negative and stimulatory effects on growth reported [42, 47, 48]. Overall, with excess IGFBPs in circulation caused by reduced kidney clearance, there is reduction of free IGF-1 levels and binding of free IGF-1 to receptors in bone cartilage. This then acts to diminish the normal negative feedback on the hypothalamic and pituitary stimulus of GH production [15, 32].

Potential Effect of Metabolic Acidosis

Metabolic acidosis is an early and frequent complication of pediatric CKD affecting approximately one-third of these children [49, 50]. It is a consequence of decreased ammonia excretion, which accompanies a decline in kidney function or impaired function of renal tubules commonly occurring in children with congenital anomalies of the kidney and urinary tract. There is a paucity of studies investigating the influence of metabolic acidosis on growth, even though nearly all children with renal tubular acidosis, the majority of whom have normal kidney function, exhibit growth restriction [51–54]. However, from the few studies that do exist, perturbations in the GH/IGF axis as a result of metabolic acidosis appears to be one of the primary mechanisms. Using a nonuremic rat model, Challa et al. [55] demonstrated that metabolic acidosis negatively alters GH secretory patterns. In follow-up studies, Challa and colleagues also posited that acidosis decreases both GHR mRNA and hepatic IGF-I mRNA (and thus IGF-1 production) [55]. Brüngger examined the effects of metabolic acidosis further in 6 “normal” human participants and found reduced IGF-1 serum levels theorized to be related to dampened response to GH stimulation in states of acidemia [56]. Given the prevalence of metabolic acidosis in pediatric CKD, especially as disease progresses, and widely available treatment for metabolic acidosis, more investigations of its potential adverse effects on growth are needed.

GH/IGF Axis-Targeted Therapies for Growth Impairment in Pediatric CKD

rhGH is widely used in the pediatric CKD population, including in posttransplant patients as it has been shown to be an effective and safe treatment of short stature in this group [18, 57–61]. It acts to increase serum GH, IGF-1, and IGFBP-5 levels and decrease IGFBP-1 serum concentrations [32, 62]. Haffner and colleagues investigated the long-term height outcomes in prepubertal children with kidney function impairment treated with rhGH and demonstrated that the majority of these children were able to reach near normal adult heights [63]. It should be noted however that children with CKD show better response to rhGH therapy than those children who have progressed to end-stage renal disease [24, 57]. Current consensus guidelines recommend consideration of rhGH therapy early in the course of CKD to increase the likelihood of attaining maximal height potential [57].

While (rh)GH is the only therapeutic agent targeting the GH/IGF axis approved for the treatment of short stature in pediatric patients with kidney impairment, recombinant IGF-1 (rhIGF-1) has been proposed as a potentially beneficial option for these patients, given observed low levels of IGF-1 [64]. Added benefits of rhIGF-1 may be its positive effects on glomerular filtration. In a randomized, double-blinded, placebo-controlled study using a small cohort of adult patients with end-stage renal disease and healthy participants, rhIGF-1 administered in intermittent doses increased inulin clearance, a surrogate of glomerular filtration [65].

Since both disturbances of GH and IGF-1 are described as potential contributors to linear growth restriction in pediatric CKD, combination therapy with rhGH and rhIGF-1 has also been suggested as a future therapeutic consideration. In female rats that underwent subtotal nephrectomy, Kovács et al. [66] observed additive effects on length when these uremic rats were treated simultaneously with rhGH and rhIGF-1. However, thus far, this concomitant therapy has only been studied in animal models.

Hyperparathyroidism and Mineral and Bone Disorder

Parathyroid hormone (PTH) overactivation is a key factor in growth failure caused by CKD mineral and bone disorder (MBD). Aberrations in calcium, phosphorus, and vitamin D balance, as a consequence of chronic and progressive kidney function impairment, drive PTH hyperactivity; this even occurs during early stages of CKD. This secondary hyperparathyroidism subsequently results in increased bone turnover and defects in bone mineralization, causing abnormal architecture of the growth plate which can impair appropriate growth [67, 68]. While a complete discussion of MBD due to hyperparathyroidism is beyond the scope of this review, it is important to mention a few key pieces of evidence supporting the important role that PTH plays in impairing growth in these children. The relationship between hyperparathyroidism and poor growth in children with CKD has been exemplified in studies where poor PTH control was associated with an increased risk for slipped capital femoral epiphysis in children with chronically impaired kidney function as well as a decreased height standard deviation score (SDS) in children receiving peritoneal dialysis whose PTH average was >500 pg/mL [69]. Additional evidence is provided by data demonstrating an association

between PTH control and an improved height SDS (0.09 SD per year) [70, 71]. Current CKD management guidelines recommend that in children with severe hyperparathyroidism (PTH > 500 pg/mL), rhGH treatment should be held until appropriate PTH control is achieved [72, 73]. As such, in considering the effects of hormonal dysregulation on growth in children with CKD, and treatment with rhGH in this population, providers should also be mindful of the influence of MBD.

Conclusion

Perturbations in the GH/IGF axis that contribute to poor growth commonly observed in children with impaired kidney function include GH resistance or insensitivity caused by uremia and low (bioactive) IGF-1, largely as a consequence of decreased renal clearance of IGFBPs (shown in Fig. 1). An understudied area is the contribution of metabolic acidosis to GH/IGF axis dysfunction, but reported effects include adverse alterations in GH secretion, diminished response to GH stimulation, and decreased GHR and IGF-1 mRNA. rhGH is safe and effective in treating short stature in children with im-

paired kidney function and should be considered early in the course of CKD in order to maximize final height outcomes. Future therapeutic regimens that may prove beneficial to children with CKD and growth restriction may include treatment with rhIGF-1 as monotherapy or concomitantly with rhGH, but more investigations of these regimens are needed.

Conflict of Interest Statement

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