Growth and Pubertal Development in Dialyzed Children and Adolescents

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Dialyzed children • Pediatric dialysis • Adolescents • Pubertal development

Body growth is an exceedingly complex and temporally regulated biological process which depends on adequate nutrition as well as metabolic and endocrine homeostasis. Infancy, mid-childhood, and puberty are characterized by distinct growth patterns (Fig. 24.1), with nutrition being critical during infancy, the somatotropic hormone axis during mid-childhood, and the gonadotropic hormones during puberty [1].

Chronic kidney disease (CKD) interferes with this complex network at various levels and pediatric patients are at high risk of growth failure and disproportionate growth patterns [2, 3]. In this chapter, we will discuss the current knowledge on the phenotype and underlying pathophysiology of growth failure in children suffering from end-stage renal disease (ESRD) and line out the currently available therapeutic options.

Growth impairment and disproportionality is most obvious in early childhood when the growth of legs and arms is most affected, whereas trunk length is somewhat better preserved.

The introduction of dialysis therapies in the 1970s and 1980s raised initial hopes that this would improve growth. However, most reports on growth after initiation of dialysis are disappointing. The younger the patient at onset of CKD the higher is the risk of severe growth retardation and stunting, putting additional strain on patients and families and making psychosocial integration even more difficult. Beyond this, the degree of growth retardation and mortality are closely associated, suggesting that the growth rate is a sensitive marker of overall patient well-being [4, 5]. Thus, beyond careful monitoring of growth, adequate measures to prevent and treat growth failure are of crucial importance for pediatric CKD patients at all ages and any degree of renal failure. In fact, while this chapter focuses on growth in children on maintenance dialysis, it should be emphasized that early intervention is critical since measures such as the correction of malnutrition and renal osteodystrophy, and treatment with recombinant human growth hormone (rhGH) are considerably more effective when started before initiation of dialysis.

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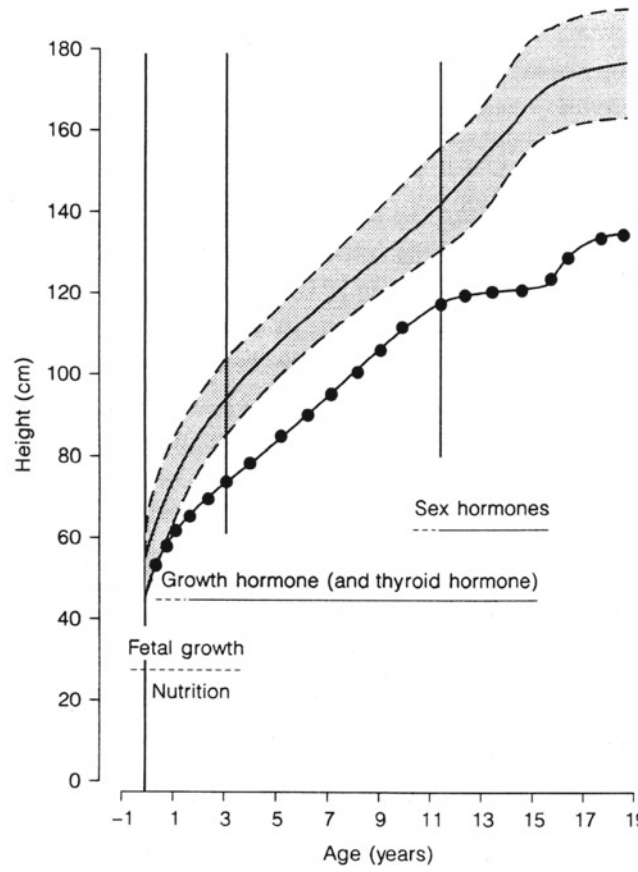


Fig. 24.1 Typical growth pattern in congenital chronic renal failure. Relative loss in the nutrient-dependent infantile and gonadal hormone–dependent puberty phases, and percentile-parallel growth in the mainly GH-dependent growth period in mid-childhood are shown. The *shaded area* represents the normal range, 3rd to 97th percentiles (Reproduced with permission of Schaefer and Mehls [22])

Final Height and Height Prediction

Reduced adult height has been reported in about 30% to 50% of pediatric CKD patients, although a trend toward improved final height was noted during the past decade [6–15]. Mean final height in CKD patients stage 3–5 ranged between −0.6 and −3.5 SDS. In general, patients receiving renal transplants or additional treatment with rhGH showed improved mean levels of final height compared to patients on long-term dialysis and those without concomitant rhGH therapy [16]. Young age at onset of ESRD, long duration of renal failure, male gender, and the presence of congenital nephropathies are the most relevant risk factors of attaining a poor final height. Among the different renal disease entities, patients suffering from nephropathic cystinosis or primary hyperoxaluria show most markedly compromised final heights [17, 18].

The applicability of adult height prediction methods in children suffering from CKD is questionable. Final height was overpredicted by 3–10 cm in several validation studies testing final height prediction in children with CKD [12, 14, 16]. Most likely, this reflects the complexity and thus unpredictability of growth and development under the condition of chronic uremia with highly variable and dynamic impact of disease progression, medications, renal replacement treatment modalities, skeletal maturation, and pubertal timing.

Clinical Presentation

Children with congenital CKD are prone to marked growth retardation already during the first 2 years of life. Growth during mid-childhood tends to be percentile parallel but height velocity

decreases disproportionately during the last 2–3 prepubertal years. Eventually, growth potential is irreversibly lost in the peripubertal period due to a delayed pubertal growth spurt of insufficient magnitude (Fig. 24.1).

Growth During Infancy

Approximately one third of total postnatal growth occurs during the first 2 years of life. Therefore, any growth-suppressing conditions during this early period of life result in severe growth retardation and probably irreversible loss of growth potential [19, 20]. A recent retrospective study in infants with severe CKD clearly demonstrated that the most critical period for loss of height potential is the first 6 months of life, a time that is particularly dependent on nutrition, which may be very hard to maintain because of prematurity, poor feeding, vomiting, and episodes of fasting as a result of surgery or sepsis [21]. In addition, infants with comorbidities presented with much more severe growth failure than infants without comorbidities (Fig. 24.2). In infants with ESRD, i.e., those with severe congenital CKD, the decrease in mean standardized height can be as much as 0.6 SD per month [22]. At 3 years of age these children may have lost already 3 SD scores (SDS). According to the Infancy-Childhood-Puberty model approximately 1 SDS each is lost during fetal life, during the first postnatal months and between 9 and 18 months of age, the latter being due to either delayed onset of the "childhood" growth phase or regression to the infancy phase pattern. It has been suggested that the growth failure during fetal life and the first postnatal months reflects metabolic and/or nutritional influences, and the impaired growth around the first birthday may be related to a partial insensitivity to GH. The increasing incidence of renal replacement therapy offered even to multimorbid infants makes the achievement of normal growth during infancy particularly challenging [21, 23].

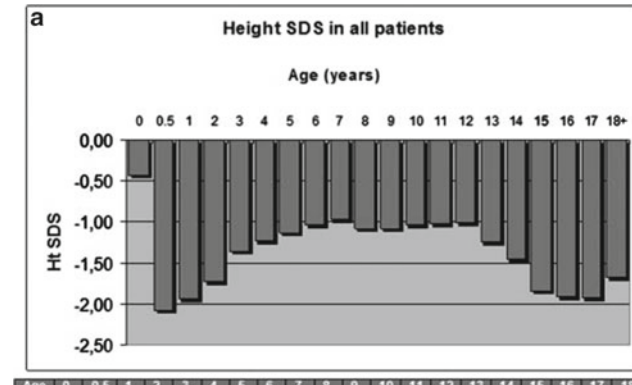
Growth During Mid-childhood

Patients with congenital CKD usually show percentile-parallel growth during the mid-childhood years. In this period growth is closely correlated with the degree of renal dysfunction. Although there is no critical threshold of GFR growth patterns are typically stable if GFR remains above 25 mL/min/1.73 m² and tends to diverge from the percentiles below this level [24, 25]. A mean cumulative loss of 6 cm from predicted final height was observed in children with mean GFR below 25 mL/min/1.73 m² between early childhood and the age of 10 years [24]. Sequelae of CKD such as anemia, metabolic acidosis, and malnutrition seem to be less-important determinants of statural growth in mid-childhood.

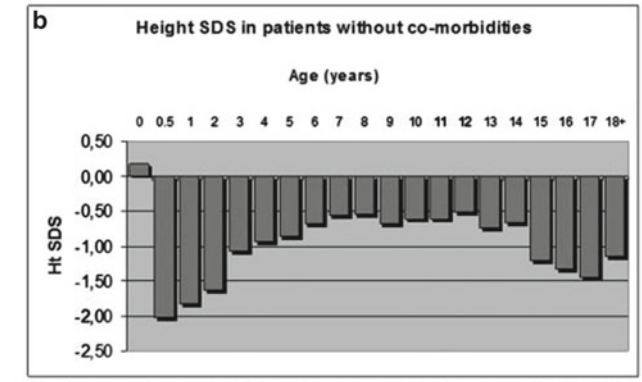
Pubertal Development

Clinical signs of puberty as well as the start of the pubertal growth spurt in children with CKD stage V appear with a delay of approximately 2 years. At least 50% of adolescents with ESRD achieve the pubertal milestones later than 95% of their healthy peers [26]. The "Cooperative Study for Pubertal Development in Chronic Renal Failure" showed that start of genital growth (Tanner stage G2) was delayed by 1.8 years in boys on dialysis and by 2.5 years in transplanted boys. Full genital maturation was achieved with a delay of 2.2 and 3.2 years, respectively. Likewise, the maturation of reproductive function is altered by the uremic state. Germ cell depletion in the testicular tubules of uremic boys was found in postmortem studies [27]. In patients exposed to chronic uremia before or during adolescence, i.e., during the period crucial for spermatogenesis, semen quality is severely and irreversibly affected [28, 29]. Several studies revealed reduced sperm cell count, erectile dysfunction, decreased libido, and decreased fertility in uremic patients on dialysis [30].

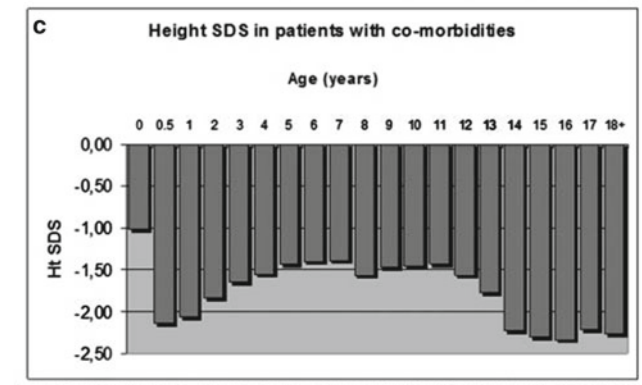
Menarche occurs in almost beyond the upper limit of the normal age range (i.e., 15 years) in



Age	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+
N	40	57	72	76	73	71	67	65	66	62	59	62	53	52	44	46	40	40	31	32
BMI	13	13	13	14	14	15	16	16	17	19	20	20	21	22	23	22	23	23	23	25



Age	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+
N	20	33	38	39	38	37	35	33	33	30	29	31	27	28	23	23	17	17	12	17
BMI	14	12	12	14	14	15	16	16	17	18	20	21	20	22	23	23	23	23	22	25



Age	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18+
N	20	24	34	37	35	34	32	32	33	32	30	31	26	24	21	23	23	23	19	15
BMI	12	13	13	14	14	15	15	16	17	19	19	20	21	22	23	22	22	22	23	25

Fig. 24.2 Course of mean standardized height and body mass index (BMI) of children presenting within the first 6 months of life with a glomerular filtration rate less than 20 mL/min/1.73 m^2 receiving tube feeding in order to provide at least 100% of the recommended daily allowance (RDA) of healthy children. (**a**) Height SDS and BMI values for all patients. (**b**) Height SDS and BMI values for patients without comorbidites. (**c**) Height SDS and BMI values for patients with comorbidities. (Reproduced with permission of Mekahli et al. [21])

50% of girls with ESRD [31], and conception rates in adolescent girls and women with ESRD are diminished. In those who manage to get pregnant, intrauterine growth retardation and low birth weight are frequently noted [32].

Pubertal Growth

Total pubertal height gain is subnormal in ESRD patients [6, 12, 19, 33, 34], with an average 1 SD loss of standardized height. In the seminal study of Schaefer et al. pubertal growth in 29 CKD patients attaining ESRD before the age of 15 years was assessed [34]. In these patients the pubertal growth spurt started with a mean delay of 2.5 years and this delay was related to the duration of uremia. While an acceleration of height velocity comparable to that seen in healthy adolescents was observed, the mean height velocity at start of the pubertal growth spurt was reduced and its duration was shortened by approximately 1.5 years.

Etiology of Growth Failure in Chronic Kidney Disease

There is no single cause of growth failure in CKD (Table 24.1). Children may suffer from various acquired or congenital renal abnormalities, manifesting in early or late childhood and differing widely with respect to severity and rate of progression. Likewise, a broad spectrum of concomitant complications (e.g., metabolic acidosis, electrolyte disturbances, and malnutrition) has to be considered. Furthermore, children with CKD may undergo various therapeutic interventions and different modes of renal replacement therapy of variable timing and duration during their growth period. Hence, growth in children with CKD is not only influenced by renal dysfunction but also by specific disease-related comorbidities and treatment modalities.

Table 24.1 Etiology of growth failure in children suffering from CKD

Genetic factors
Parent height
Gender
Syndromal disorders (with kidney involvement as a part)
Age at onset of CKD
Residual renal function
Treatment modalities for CKD
Energy malnutrition
Water and electrolyte disturbances
Metabolic acidosis
Renal anemia
Hormonal disturbances affecting the
Somatotropic hormone axis
Gonadotropic hormone axis
PTH-, FGF-23-, and vitamin D metabolism/action (renal osteodystrophy)
Other hormones

Underlying Renal Disease

Congenital anomalies of the kidneys and urinary tract (CAKUT), characterized by renal hypoplasia or dysplasia with and without refluxive or obstructive uropathy, are the most common cause of ESRD during infancy and childhood. Renal dysplasia is often associated with electrolyte and/or water losses, and both are likely to contribute to growth failure. Thus, it is important to compensate for these losses and to provide appropriate treatment of concomitant urinary tract infections.

In children suffering from *glomerulopathies* growth rates might decline even with rather mild renal insufficiency [35]. The nephrotic state per se and glucocorticoid treatment are known risk factors for growth delay [36, 37]. The *congenital nephrotic syndrome* is usually associated with severe early infantile growth failure, which may occur even with preserved global renal function and seems to be secondary to persistent edema, recurrent infections, losses of peptide and

protein-bound hormones, and/or protein-calorie malnutrition [38]. In Finnish-type nephrotic syndrome, aggressive nutritional support is vital and bilateral nephrectomy and initiation of peritoneal dialysis may be necessary to stabilize growth. In other types of congenital nephrotic syndrome unilateral nephrectomy and treatment with prostaglandin synthesis inhibitors and renin-angiotensin system (RAS) antagonists can reduce proteinuria and thereby stabilize growth and overall clinical condition [39, 40].

Nephropathic cystinosis results in complex tubular dysfunction and consecutive severe growth failure already during infancy when glomerular function is not yet compromised [41, 42]. Progressive growth failure is further sustained by generalized deposition of cystine crystals altering the function of growth plates, bone marrow, hypothalamus, pituitary gland, and thyroid gland. Early initiation of treatment with the cystine depleting agent cysteamine improves growth rates and has the potential to delay the development of chronic renal failure [43]. In patients with *primary hyperoxaluria* supplementary treatment with citrate and pyridoxine can protract progression of renal failure, and possibly improve longitudinal growth [42]. In patients with *systemic oxalosis* combined liver and kidney transplantation is a curative option; however, real catch-up growth after combined transplantation is rarely observed even in prepubertal oxalosis patients [44].

In summary, every measure directed to preserve kidney function except glucocorticoid therapy has a beneficial impact on growth.

Consequences of Renal Disease

Protein-Calorie Malnutrition

Nutritional imbalances, particularly protein-energy malnutrition, are frequently seen in children suffering from CKD [45]. Particularly infants and young children are vulnerable to malnutrition because of low nutritional stores and high energy demands which are in turn necessary to allow high growth rates in this age group. Malnutrition is a crucial clinical issue since it is significantly associated with increased mortality in children suffering from CKD [4, 5]. Recently, the term "malnutrition-inflammation complex syndrome" (MICS) has been coined to describe the association between chronic inflammation and malnutrition in dialyzed children and adults [46]. Possible causes of MICS include comorbid illnesses, oxidative and carbonyl stress, nutrient loss through dialysis, anorexia and low nutrient intake, uremic toxins, cytokine induction by exposure to bio-incompatible dialysis materials, decreased clearance of inflammatory cytokines, volume overload, and other dialysis-related factors. MICS is considered the main cause of erythropoietin hyporesponsiveness, early cardiovascular atherosclerotic disease, decreased quality of life, and increased mortality and hospitalization in dialysis patients, and may also be causative of growth hormone resistance and growth failure in children on dialysis [47–49]. Indeed, a recent in vitro study could demonstrate that uremia attenuates GH-stimulated IGF-I expression in the liver, which was further aggravated by inflammation [50].

There is no consensus about how to determine the degree of severity of MICS or how to manage it. Anorexia manifests early in the course of renal failure, and usually progresses with declining renal function [25]. In addition, protein synthesis is decreased in uremia and catabolism increased [51]. In CKD patients, spontaneous energy intake is correlated with growth rates if it is less than 80% of recommended dietary allowance [52]. However, a further augmentation of energy above this level translates in increasing obesity rather than additional length gain [52–54]. Other approaches to prevent MICS include the preferential use of biocompatible dialysis materials to minimize inflammatory responses and intensified dialysis protocols to increase cytokine clearance and improve the volume status. Preliminary results support the efficacy of these measures in improving growth hormone sensitivity and inducing catch-up growth (see below).

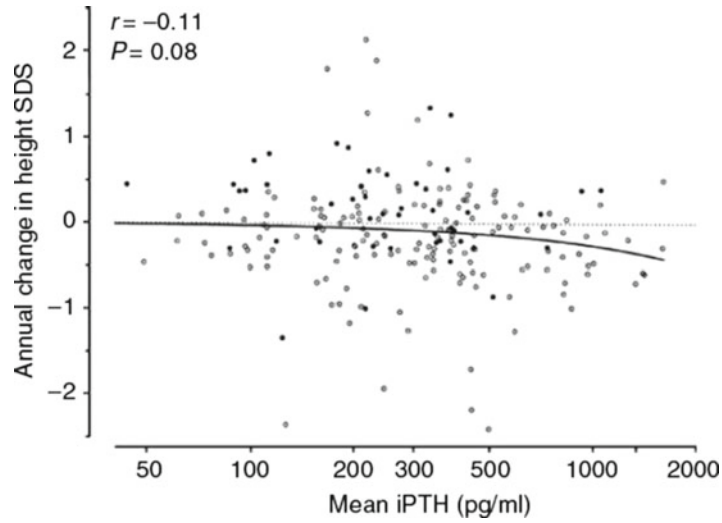


Fig. 24.3 Time-averaged mean plasma intact parathyroid hormone (iPTH) concentrations and change in standardized height in 214 pre- and early pubertal children on peritoneal dialysis followed prospectively for at least 12 months. *Full circles* indicate patients receiving recombinant growth hormone (Reproduced with permission of Borzych et al. [71])

Metabolic Acidosis

Metabolic acidosis usually occurs when GFR is below 50% of normal, although nutritional intake (protein and acid load), catabolism, and alterations in electrolyte balance contribute markedly. Subsequent metabolic and endocrine aberrations are triggered by metabolic acidosis and aggravate uremic growth failure. In fact, metabolic acidosis is significantly associated with decreased length gain and increased protein breakdown in children with CKD [55–57]. Recent studies on metabolic acidosis in uremic animals revealed a complex pattern of interrelated pathophysiological reactions. An increased glucocorticoid production and protein degradation together with suppressed spontaneous pituitary GH secretion, decreased expression of the GH-receptor, and insulin-like growth factor I (IGF-I) receptor, and decreased IGF-I serum concentrations highlight the necessity for adequate control of metabolic acidosis [58–60].

Renal Osteodystrophy

Skeletal deformities due to renal osteodystrophy contribute to uremic growth failure [61]. Pronounced secondary hyperparathyroidism (sHPT) can interfere with longitudinal growth by destruction of the growth plate architecture, epiphyseal displacement, and metaphyseal fractures. Severe destruction of the metaphyseal bone architecture may result in complete growth arrest. Although treatment with 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) in principle should revert sHPT and thus preserve growth potential, clinical data are conflicting [62–64]. The situation gets even more complicated as skeletal growth is the net result of proliferation and differentiation of growth plate chondrocytes with subsequent mineralization of the extracellular matrix. According to current knowledge, this biological process is under the control of three hormones, namely, PTH, $1,25(OH)_2D_3$, and fibroblast growth factor-23, as well as numerous paracrine and autocrine signals [65–67].

The contribution of sHPT to uremic growth failure has not been fully elucidated. Under physiological conditions growth plate chondrocytes proliferate and differentiate under the influence of PTH, mainly mediated by induction of local IGF-I synthesis [68]. However, bones and growth plates are relatively resistant to PTH in chronic uremia [64]. Hence, low or normal PTH levels, which are indicative of low bone turnover in experimental uremia as well as in children with CKD, have been suspected to impair longitudinal growth [69]. However, direct histomorphometric assessment in children on dialysis showed no association of low bone turnover with statural growth [70]. Likewise, a recent study on longitudinal growth of a large cohort of children on peritoneal dialysis failed to show a relationship between growth and PTH levels between 50–400 pg/mL (Fig. 24.3). However, growth in patients with levels above approximately 400 pg/mL tended to be impaired [71].

Anemia

Longstanding anemia in CKD patients has profound systemic consequences including anorexia and catabolism due to altered energy turnover and multiple system dysfunctions. In fact, retardation of growth and development is a hallmark in patients with longstanding chronic anemia of non-renal origin, e.g., thalassemia major. From a theoretical point of view, anemia may suppress growth secondary to reduction of appetite, intercurrent infections, cardiac complications, and severely reduced oxygen supply to cartilage. The advent of recombinant human erythropoietin (EPO) and thus the possibility to correct anemia in CKD patients allowed to investigate the impact of anemia on longitudinal growth. Whereas partial correction of anemia improved exercise capacity, and decreased heart rate and resting oxygen consumption, no persistent catch-up growth of EPO could be demonstrated in several multicenter clinical trials in dialyzed children [72, 73] despite anecdotal reports of short-term growth promoting effects [73, 74]. However, a recent retrospective study suggests an association between early initiation of erythropoietin treatment and growth in children with pre-dialytic CKD [75].

Endocrine Changes

Uremia interferes with the metabolism and regulation of various peptide hormones, leading to inappropriate circulating hormone concentrations and/or altered hormone action. Distinct alterations of the *gonadotropic* and *somatotropic* hormone axes have been identified which are considered crucial pathomechanisms of uremic growth failure.

Gonadotropic Hormone Axis

Gonadal Hormones

Adolescents and adults suffering from ESRD usually show low or low normal total and free testosterone (T) as well as dihydrotestosterone (DHT) plasma concentrations, which are thought to be due to decreased synthesis and/or increased metabolic clearance [76–80]. The reduced conversion of T to DHT secondary to diminished 5α-reductase activity might explain at least partially the delayed pubertal development in boys with advanced renal failure [81]. In addition, the probably uremia-related decreased clearance of the sex hormone–binding protein lowers the serum concentration of unbound T [76, 78]. Beyond this, the plasma concentration of inhibin, a gonadotropin feedback inhibitor produced by Sertoli cells, is increased in pubertal boys with CKD [82]. In adult women, plasma estradiol levels tend to decrease parallel to GFR reduction and adolescent girls show low-normal or decreased estradiol levels in relation to pubertal age [83, 84].

Gonadotropins

Increased plasma concentrations of LH and FSH in combination with decreased or low-normal gonadal hormones suggest a state of compensated hypergonadotropic hypogonadism in uremia [77, 78, 83, 85]. However, in CKD patients the usually inadequate degree of hypergonadotropism relative to the degree of hypogonadism is compatible with an additional defect of pituitary gonadotropin release, and the analysis of spontaneous pulsatile LH secretion has provided new insights into the underlying pathophysiology [86]. In CKD, mean LH plasma levels are elevated despite significantly reduced pituitary LH secretion, due to the markedly impaired renal metabolic clearance of LH [87–89]. When renal function is restored by kidney transplantation, pulsatile LH secretion normalizes [88].

Since the onset of puberty is heralded by the appearance of nocturnal LH secretion episodes, the uremia-related impairment of pulsatile LH release suggests that the delayed pubertal onset in CKD is due to a primary hypothalamic defect. Indeed, experimental evidence suggests reduced release of hypothalamic gonadotropin-releasing hormone (GnRH) due to uremia-related inhibitory factors and/or to an increased tone of the inhibitory neurotransmitter gamma-aminobutyric acid [89–92]. Beyond the quantitative alterations of gonadotropin release, uremia affects also the

biological quality of circulating gonadotropins. In pubertal and adult CKD patients the proportion of bioactive LH in relation to the total immunochemically measurable amount of LH is reduced. This might be due to altered glycosylation and/or accumulation of less active isoforms [79, 88, 90, 93].

In summary, insufficient activation of the hypothalamic GnRH pulse generator, likely mediated via circulating inhibitors, appears to be the key abnormality underlying delayed puberty and altered sexual functions in CKD. The neuroendocrine pathology resembles the regression of the gonadotropic hormone axis to the prepubertal state in patients with anorexia nervosa.

Somatotropic Hormone Axis

Growth Hormone Secretion and Metabolism

In pediatric and adult CKD patients fasting GH concentrations are normal or even increased, depending on the degree of renal failure. GH, a 22-kilodalton protein, is almost freely filtered by the glomerulus (sieving coefficient ~0.82) and thereby ultimately cleared from the circulation [94]. Indeed, a linear relationship between GFR and the metabolic clearance rate of GH has been shown; GH clearance is reduced by approximately 50% in patients with ESRD [95, 96]. The prolonged plasma half-life of GH, rather than increased endogeneous secretion, explains the increased circulating GH concentrations in uremia. Pituitary GH secretion is unaltered in prepubertal patients but decreased in adolescents with CKD, suggesting insufficient stimulation by gonadal steroids during puberty [97–99]. In addition, malnutrition and metabolic acidosis negatively impact GH secretion rates in children with CKD [58].

Growth Hormone Receptor and GH Signaling

Studies in experimental uremia have considerably advanced our understanding of uremic GH resistance. GH-induced hepatic IGF-I synthesis is diminished, due to either a decreased expression of the GH-receptor (GH-R) and/or a postreceptor signaling defect [100, 101]. Whereas reduced expression of the GH-R encoding mRNA in liver and growth plate chondrocytes was consistently seen, hepatic but not growth plate cartilage GH-R protein levels were comparable in uremic and non-uremic animals when corrected for uremia-associated anorexia by pair feeding [100–105]. Thus, while decreased GH-R abundance in growth plate cartilage is likely to contribute to uremic growth failure, a postreceptor GH signaling defect was identified as cause of the diminished hepatic IGF-I secretion upon GH stimulation. In fact, aberrant GH-dependent JAK/STAT signaling has been noted (Fig. 24.4). Activation of the JAK-STAT cascade by tyrosine phosphorylation upon binding of GH to its receptor leads to transcriptional activation of IGF-I synthesis but also of proteins of the suppressor of cytokine signaling (SOCS) family. The latter are responsible for dephosphorylation of the GH-activated cascade and as such provide a GH-regulated negative feedback loop. However, under the conditions of chronic uremia the equilibrium between GH-induced transcriptional activation of IGF-I and SOCS is shifted toward SOCS overstimulation. Preliminary evidence suggests that the micro-inflammatory state associated with uremia might contribute to GH resistance, as SOCS are also induced by inflammatory cytokines [100, 106].

In humans, levels of circulating GH binding protein (GHBP), which in turn results from proteolytic cleavage of the extracellular receptor domain, are taken as a measure of GH-receptor expression. In line with the above described pathomechanism, GHBP plasma levels in CKD patients are decreased and related to the residual renal function [107, 108].

Insulin-like Growth Factor Plasma Binding and Tissue Action

Apart from GH resistance, insensitivity to IGF-I is also found in the state of uremia [109–113]. While serum concentrations of IGF-I and IGF-II are usually within the normal range in children

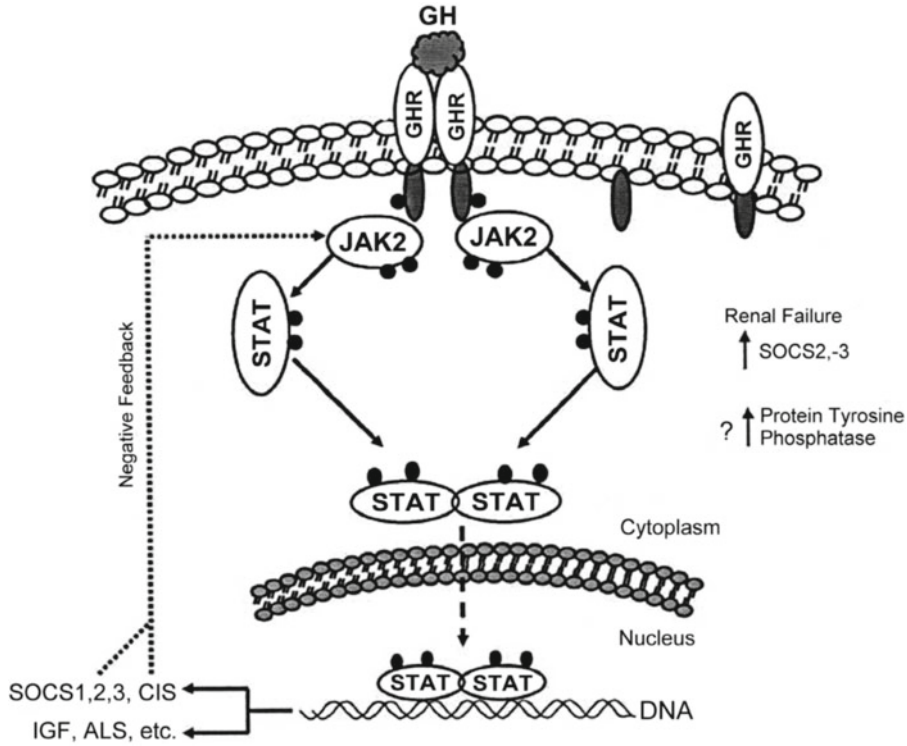


Fig. 24.4 Growth hormone (GH)-mediated JAK2/STAT signal transduction. GH activates several signaling pathways via Janus kinase2 (JAK2) including the JAK/STAT (signal transducer and activator of transcription) pathway. Binding of GH to its receptor (GHR) activates JAK2, which then self-phosphorylates followed by phosphorylation of the GHR and subsequently STAT 1a, 3, 5a, and 5b, members of a larger family of cytoplasmic transcription factors. These phosphorylated STATs form dimers that enter the nucleus where they bind to specific DNA sequences and activate their target genes including insulin-like growth factor-1 (IGF-1) and some suppressors of cytokine signaling (SOCS). Deletion of STAT5 expression leads to retarded body growth and STAT5b is required for GH-mediated IGF-1 gene expression. In renal failure phosphorylation of JAK2 and the downstream signaling molecules STAT5, STAT3, and STAT1 are impaired, as are the nuclear levels of phosphorylated STAT proteins. This important cause of uremic GH resistance may result in part from upregulation of SOCS2 and SOCS3 expression with suppressed GH signaling and also from increased protein tyrosine phosphatase activity, with enhanced dephosphorylation and deactivation of the signaling proteins (Reproduced with permission of Rabkin et al. [106])

with CKD, IGF-I levels are slightly reduced and those of IGF-II mildly increased in dialyzed patients [114]. In contrast to the unchanged total amount of circulating immunoreactive IGF, somatomedin bioavailability is reduced in uremia pointing to the existence of circulating inhibitors [115, 116]. A low-molecular weight somatomedin inhibitor (~1 kDa) was reported to circulate in uremic serum in an early study, but this has not been characterized further. Later studies focused on the accumulation of the specific high-affinity IGF-binding proteins (IGFBP1-6), which are normally cleared by the kidneys and are considered the main cause of diminished somatomedin bioactivity in uremia (Fig. 24.5). In particular, the concentrations of IGFBP-1, -2, -3, -4 and -6 increase as renal function declines and IGFBP-1, -2 and -6 have been shown to inhibit IGF-I bioactivity in vitro [114, 117–121]. By contrast, the serum concentrations of IGFBP-5 are normal and IGFBP-5 proteins undergo intense proteolytic cleavage in chronic uremia [120]. Likewise, the elevated level of IGFBP-3 is mostly due to the accumulation of proteolytic fragments whereas intact IGFBP-3 is markedly diminished [122, 123]. The molar excess of IGFBPs over

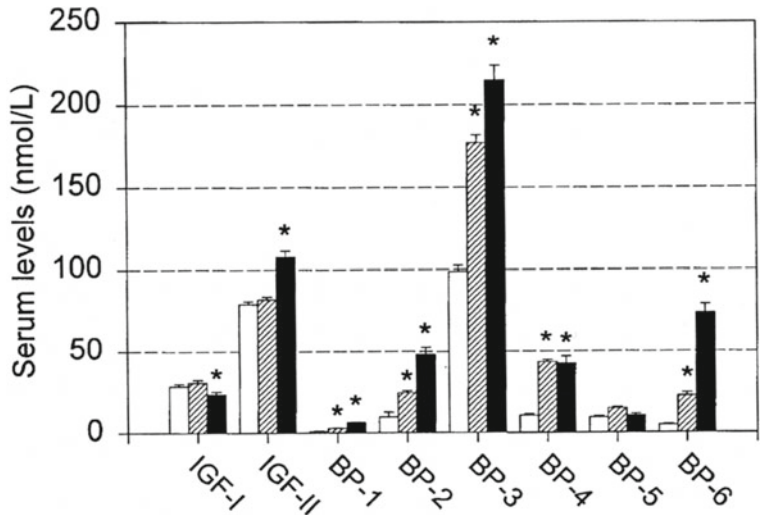


Fig. 24.5 Comparison of the molar serum concentrations of IGFs and IGFBPs in children with preterminal CRF (*hatched bars*) and children with ESRD (*filled bars*). The respective mean molar concentration in normal age-matched children is given in *open bars* for comparison. Data are means + SEM. *Significant ($P < 0.05$ by ANOVA) vs. control (Reproduced with permission of Ulinski et al. [120])

IGFs is approximately 150% in children with CKD and 200% in children on dialysis as compared to 25% in children with CKD. An inverse correlation between growth retardation and IGFBP-1, -2, and -4 serum concentrations has been described [109, 114, 120, 124]. Reduced IGF bioactivity can be returned to normal by removing unsaturated IGFBP [116]. These data are in favor of the concept that serum IGFBPs increase with declining renal function in CKD patients, and that the greater excess of IGFBPs in ESRD compared to pre-end-stage CKD patients contributes to the more severe growth failure and reduced response to rhGH therapy in these children. In addition cellular IGF signaling is impaired in the uremic state; it remains to be elucidated whether a postreceptor mechanism similar to the one observed for GH signaling is responsible for this phenomenon [110, 125].

In summary, the markedly deficient IGF-I synthesis and the modest elevation of GH levels, which is due to decreased metabolic clearance, in the presence of increased IGF plasma–binding capacity strongly supports the concept of a multilevel homeostatic failure of the GH-IGF-I system in uremia.

Treatment of Growth Failure in Chronic Kidney Disease

General Measures

In infants and young children with CKD the most important measure to avoid uremic growth failure is the assurance of *adequate caloric intake*. This often necessitates supplementary feeding via a nasogastric tube or gastrostomy. In a recent retrospective analysis of growth in 101 infants and young children with severe CKD, it could be demonstrated that persistent catch-up growth can be achieved in the majority of patients when measures like tube feeding are commenced instantly if expected growth is not achieved (Fig. 24.2) [21]. In later childhood, adequate nutrition is permissive although catch-up growth is rarely achieved by dietary manipulations alone [45, 126]. In general, the targeted caloric intake should be between 80% and 100% of the recommended daily allowance (RDA) of healthy children [52, 127, 128]. Caloric intake should account for growth failure and be related to "height age" rather than to chronological age. Caloric intake in

excess of 100% of RDA does not induce catch-up growth but rather results in obesity and may thereby negatively contribute to long-term cardiovascular morbidity in CKD patients [52–54]. Protein intake should be 100% of RDA. In patients on peritoneal dialysis, a slightly higher intake (+0.2 g/kg/day) is recommended to compensate for dialytic protein losses. Higher protein intake should be avoided since, despite many attempts, anabolizing or growth promoting effects of high-protein diets have neither been demonstrated in animal models nor in children with CKD. On the contrary, high-protein diets may be detrimental by aggravating metabolic acidosis and augmenting the dietary phosphorus load.

Metabolic acidosis should be vigorously treated by alkaline supplementation. In addition, supplementation of water and electrolytes is essential in patients presenting with polyuria and/or salt losing nephropathies [127, 129]. Supplementation of sodium chloride is also important in young children on peritoneal dialysis, since significant amounts of sodium chloride (i.e., 2–5 mmol/kg body weight) may be eliminated via ultrafiltration.

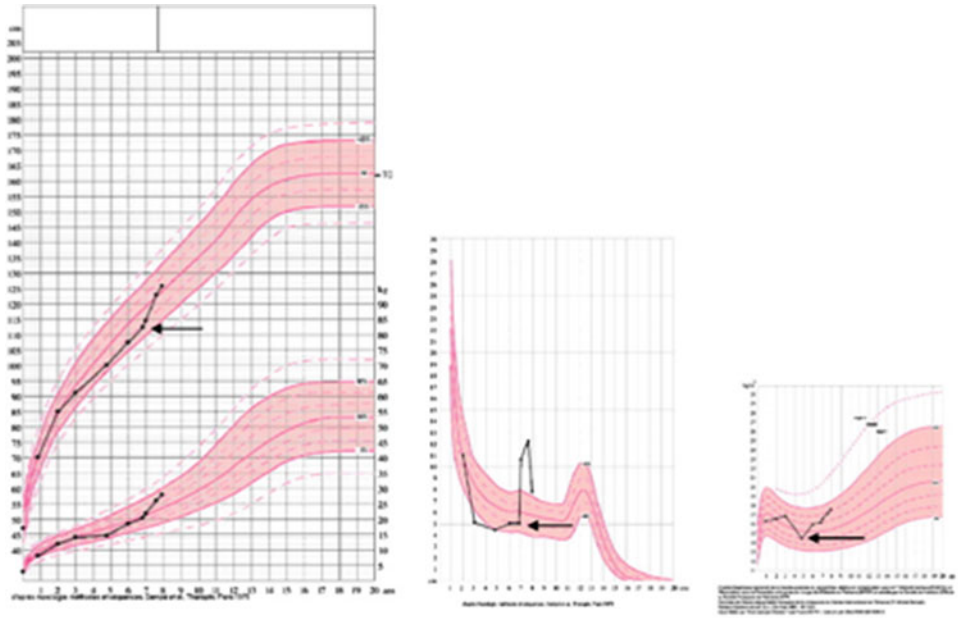
Dialysis and Intensified Dialysis

Although dialysis treatment attenuates the uremic state, longitudinal growth usually is not improved and long-term peritoneal or hemodialysis are associated with a gradual loss of standardized height in children and adolescents [15, 130–133]. In dialyzed infants, losses of up to 1 SD per year have been reported and even the utilization of high-flux hemodialysis and hemofiltration techniques does not improve the situation [22]. In fact, residual renal function appeared to be a better predictor of longitudinal growth than dialytic clearance [134, 135]. The same holds true for continuous peritoneal dialysis [134, 135]. Notably, a high peritoneal transporter status, a condition associated with increased morbidity and mortality in adults [136], is associated with poor longitudinal growth in children on chronic PD [134]. This might be due to the putative association of high peritoneal transport with micro-inflammation, which has been accused to suppress statural growth by interference with GH signaling (see above).

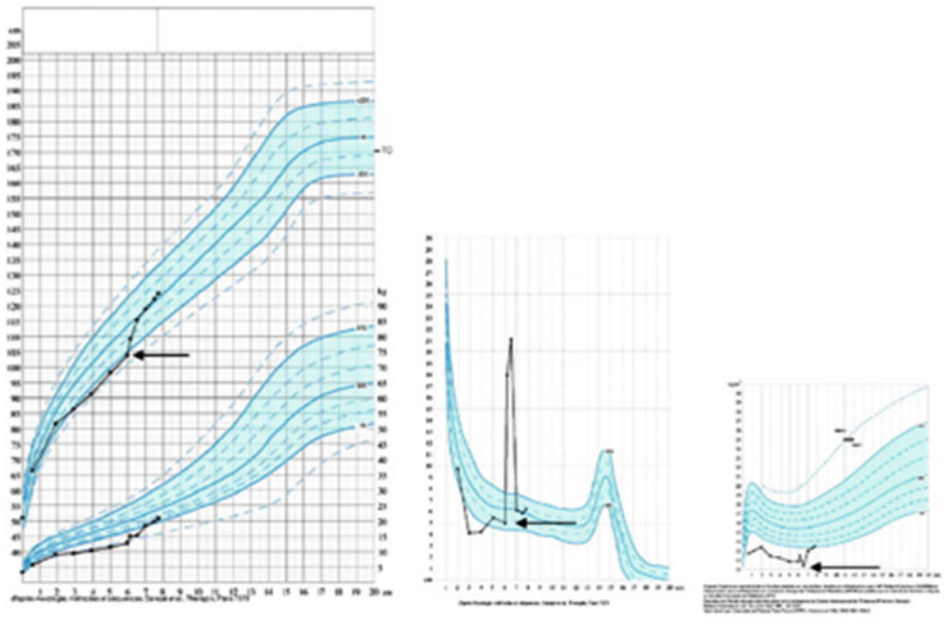
It has been suggested that intensified dialysis, achieved by either extended thrice weekly nocturnal or short daily sessions, might be able to induce catch-up growth [137–139]. According to a recent study, catch-up growth can be maximized when intensified hemodiafiltration (3 h, 6 times a week) and rhGH therapy are combined [140]. Using this approach in 15 mainly prepubertal children for an average observation time of 21 months, Fischbach et al. observed an average increase in growth velocity from 3.8 cm/year at baseline to 8.9 cm/year during the intervention (Fig. 24.6). This resulted in a mean 1.7 SDS gain of standardized height, representing complete catch-up growth according to the attainment of the target height SDS. From a pathophysiological point of view, intensified hemodiafiltration is a better substitute for physiological kidney function and may allow substantially better clearance of uremic toxins. As a result, micro-inflammation and metabolic acidosis may be abolished, leading to improved appetite and tissue anabolism. The improved removal of inflammatory cytokines might reverse growth hormone resistance and allow to exploit the full therapeutic potential of rhGH. However, the positive effects of this approach should be counterbalanced with the potential impact of intensified dialysis on psychosocial integration and augmented treatment costs. Prospective randomized trials appear required to provide definite proof to this promising concept.

Transplantation

Although many of the metabolic and endocrine disorders contributing to uremic growth failure are resolved by renal transplantation (RTx), post-transplant catch-up growth is usually restricted to young children and occurs far from regularly [9, 11–13, 141]. Beyond transplant function, age, and degree of stunting at time of transplantation, glucocorticoid dosage is inversely associated with longitudinal growth as well. While complete



Patient 14, a girl on daily on line hemodiafiltration
Protein diet intake(g/kg/d) : 2.4 ±0.4 ; protein nitrogen appearance(g/kg/d) : 1.3 ±0.14
Mean growth velocity (cm/year) : 9.6
Achieved height versus mid parental target height (SDS) : +0.3



Patient 1, a boy on daily on line hemodiafiltration.
Protein diet intake(g/kg/d) : 2.7±0.2 ; protein nitrogen appearance(g/kg/d) : 1.44 ±0.15
Mean growth velocity (cm/year) : 10.4
Achieved height versus mid parental target height (SDS) : +0.2

Fig. 24.6 Examples of growth charts (height and weight chart; growth velocity chart in centimeters per year; body mass under chart) of two patients on daily online hemodiafiltration (start indicated by bars) in addition to rhGH treatment. TC on height chart is the familial target height in centimeters (Reproduced with permission of Fischbach et al. [140])

steroid withdrawal was associated with unacceptably high rejection rates in children with azathioprine and/or cyclosporine A medication [142, 143], withdrawal appears much safer with the currently preferred immunosuppressants. In a recent randomized trial on late steroid withdrawal in patients on treatment with cyclosporine A, mycophenolate mofetil steroid-free patients showed improved growth compared to controls (i.e., change in height SDS; 0.6 ± 0.1 vs. -0.2 ± 0.1) within 27 months [144]. However, catch-up growth in pubertal patients was rather limited compared to that in prepubertal patients. Thus, efforts to avoid a height deficit before RTx, such as rhGH treatment, early (preemptive) RTx, and the use of efficacious immunosuppressive strategies for optimized graft function and early withdrawal or even complete avoidance of steroids are required to improve final height in children after RTx.

Endocrine Therapies

Calcitriol

Calcitriol deficiency is a major cause of sHPT and renal osteodystrophy. Although calcitriol supplementation reverses the biochemical, radiographic, and histological signs of high-turnover bone disease, neither experimental nor clinical studies provide consistent improvement of longitudinal height [145–147]. These conflicting results might be due to differences in the mode of administration and to the pleiotropic calcitriol-specific effects on growth plate chondrocytes. There is general concern that a low-turnover bone state induced by intense calcitriol therapy may compromise longitudinal growth. Therefore, plasma PTH levels should be kept at two–three times the upper normal range in patients with CKD stage 4–5, and within the upper limit of the normal range in CKD stages 1–3 [61]. Although not formally proven in prospective clinical trials, these target ranges are thought to allow sufficient control of sHPT and avoid adynamic bone disease, minimizing any interference of uremic bone and mineral disorder and its treatment with longitudinal growth [61, 148, 149].

Calcimimetics

Pilot studies have provided preliminary evidence that calcimimetics are an effective therapy of sHPT in pediatric dialysis patients [150, 151]. Calcimimetics suppress PTH secretion by activating the calcium-sensing receptor (CaR). The CaR is expressed by epiphyseal chondrocytes; its stimulation stimulates chondrocytic proliferation and differentiation. Thus, calcimimetics may affect longitudinal growth in uremia as well. In fact, calcimimetics (cinacalcet) was shown to improve food efficiency and body weight gain in uremic rats, but no effects on growth plate morphology and/or longitudinal growth were seen [152]. It is hoped that efficacy and safety will soon be further addressed in a carefully designed clinical trial.

Growth Hormone

The unraveling of the pathomechanisms by which chronic uremia impairs the action of endogenous GH paved the way for pharmacological treatment with recombinant human (rh)GH [153–155]. Administration of rhGH markedly stimulates IGF-I synthesis with only a modest effect on IGFBPs, thereby normalizing somatomedin bioactivity and promoting longitudinal growth (Fig. 24.7) [156, 157]. The efficacy and safety of long-term treatment with rhGH in children with CKD before and after renal transplantation have been established extensively.

Efficacy of rhGH in Prepubertal Children

In prepubertal children with pre-dialysis CKD, rhGH therapy typically doubles height velocity during the first treatment year [158–165]. Catch-up growth continues asymptotically during extended treatment. After 5–6 treatment years mean standardized height had increased from −2.6 to −0.7 SDS in North American, from −3.4 to −1.9 in German, and from −3.0 to −0.5 in Dutch patients [163–165]. In dialyzed children, the treatment response is significantly attenuated compared to children with pre-end-stage CKD (0.8 SD vs. 1.3 SD; [163]). RhGH responsiveness is similarly poor in children on peritoneal dialysis and standard hemodialysis, but can be markedly

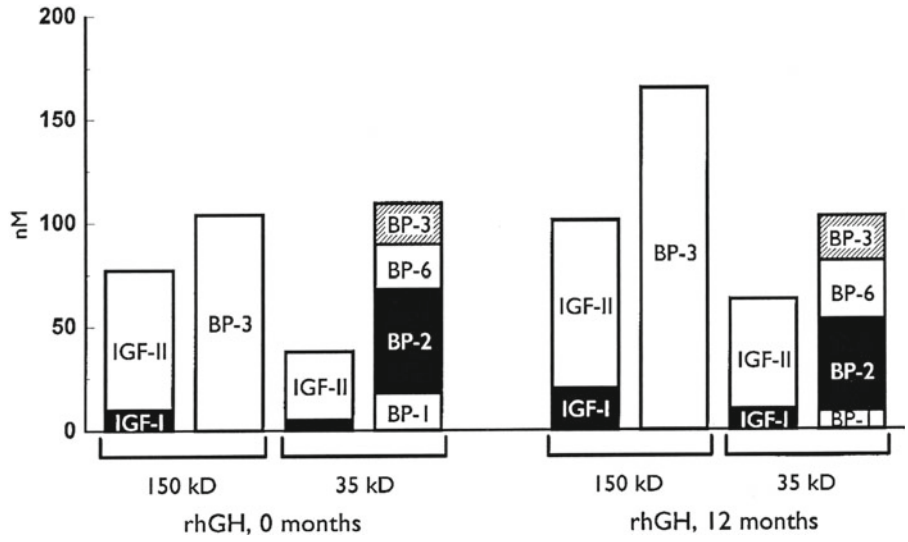


Fig. 24.7 Balance between IGFBPs and IGFs in serum of CRF children before and after rhGH treatment. Levels (nanomoles per L) of IGF-I, IGF-II, IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-6 in the 150- and 35-kDa fractions of CRF serum are presented. Protein levels were measured in whole serum of 30 CRF children before (0 months) and during (12 months) rhGH treatment. Mean IGFBP-1, IGFBP-2, and IGFBP-6 levels were assigned entirely to the 35 kDa serum fractions. The percentages of IGFBP-3 and IGFs at 150 kDa (fractions 23–27) and at 35 kDa (fractions 28–30) in sera from CRF children before and after 12 months of rhGH treatment were calculated; these percentages were then applied to the mean whole serum levels to calculate the amounts of each protein at 150 and 35 kDa. Both intact IGFBP-3 and IGFBP-329 were abundant in the 150-kDa fractions; IGFBP-329 was much more abundant than intact IGFBP-3 in the 35-kDa fractions (Reproduced with permission of Powell et al. [156])

improved when dialytic clearance is augmented by daily hemodialfiltration (vide supra) [163, 166–168].

Based on the current experience with rhGH in pediatric CKD patients, a model to predict growth response was developed very recently [169]. The prediction model was developed using a cohort of 208 prepubertal children on conservative or dialysis treatment followed in a pharmaco-epidemiological survey (KIGS), and validated in an independent group of 67 CKD patients registered at the Dutch Growth Research Foundation. The height velocity during the first rhGH treatment year (PHV) was predicted by the following equation: PHV (centimeters per year) = 13.3 – [age (years) × 0.38 + (weight SDS × 0.39)] – [hereditary renal disorder (0 when absent or 1 when present) × 1.16] + [Ln rhGH dose (milligrams per kilogram per week) × 1.04] + [GFR (milliliters per minute × 1.73 m^2) × 0.023]. This equation explains 37% of the overall variability of the growth response. The SE of the estimate or error SD of the prediction model was 1.6 cm and non-responders in the validation group were correctly identified. This model may help in predicting non-responders and in tailoring treatment strategies for growth retarded children with CKD.

Effects of rhGH on Pubertal Growth and Final Height

The evaluation of pubertal growth in CKD patients is complicated by (i) the delayed and shortened pubertal growth spurt compared to healthy children and (ii) changes in treatment modalities, i.e., start of dialysis, renal transplantation, and initiation and cessation of rhGH therapy [34]. In a study following patients with CKD and ESRD from late prepubertal age to final height, the average height increment in rhGH-treated patients was twice that seen in a matched control group. The main benefit for total growth and final height was achieved before the onset of

the pubertal growth spurt whereas no overall effect on the pubertal height gain was observed [16] (Figs. 24.8 and 24.9). The final height results from several clinical trials are given in Table 24.2 [165, 170–179].

Recently the determinants of final height were analyzed in 240 rhGH-treated children on conservative treatment, dialysis, or after RTx reported to the KIGS registry (Fig. 24.10). In children with normal pubertal timing, the mean increase in standardized height from prepubertal age to final height was 1.3 SDS. Patients with delayed onset of puberty achieved a significantly lesser increase in standardized height (+0.9 SDS). However, the mean age at initiation of rhGH treatment in these patients was 14.5 years and the mean duration of rhGH therapy was only 2.0 years. The average cumulative increase in height SDS was significantly greater in CKD patients who remained on conservative treatment throughout puberty (+1.5 SDS) than in those on dialysis and in renal allograft recipients (both +1.1 SDS). Adult height was independently positively predicted by the height attained at start of rhGH and the duration of rhGH treatment, and inversely by the time spent on dialysis, the age at onset puberty, and the age at start of rhGH. Altogether these parameters explained 61% of the overall variability of adult height. Hence, rhGH improves final height in prepubertal and pubertal patients, but the growth response is diminished in patients with delayed onset of puberty and those on long-term dialysis [177].

Efficacy of rhGH in Infants

According to standard concepts of the pathophysiology of uremic growth failure, malnutrition and fluid and electrolyte imbalances have a much greater impact on infant growth than alterations of somatotropic hormones. Consequently, correction

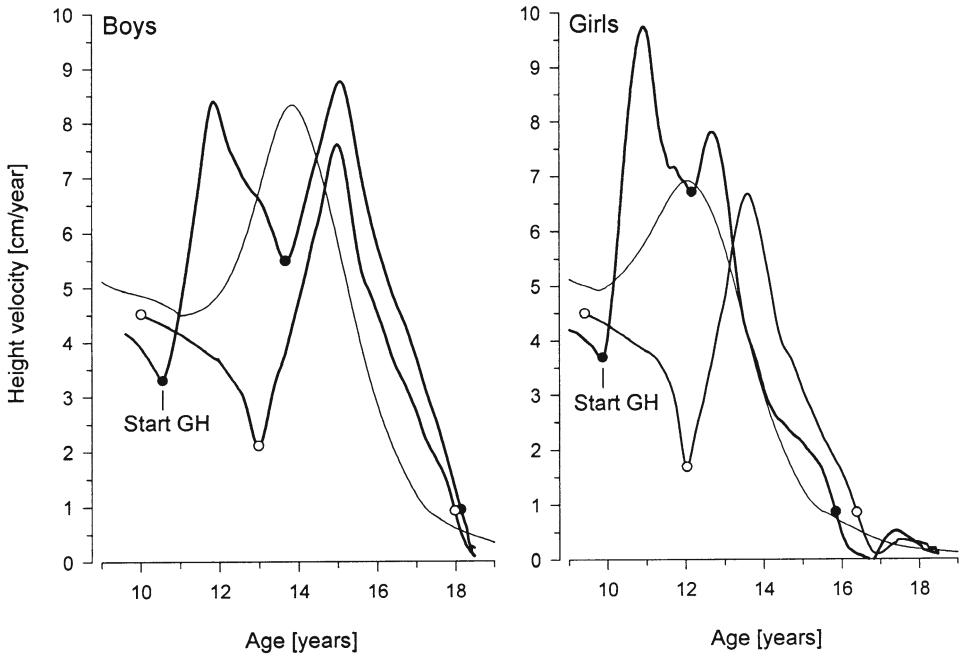


Fig. 24.8 Synchronized mean height velocity curves of 32 boys (*left panel*) and 6 girls (*right panel*) with CRF during rhGH treatment (*closed circles*), as compared with 50 children with CRF not treated with rhGH (*open circles*) and 232 normal children (*thin lines*). The *dots* indicate the time of the first observation, which corresponds to the start of rhGH treatment in the growth hormone–treated children, minimal pre-spurt height velocity, and the time of the end of the pubertal growth spurt (Reproduced with permission of Haffner et al. [16])

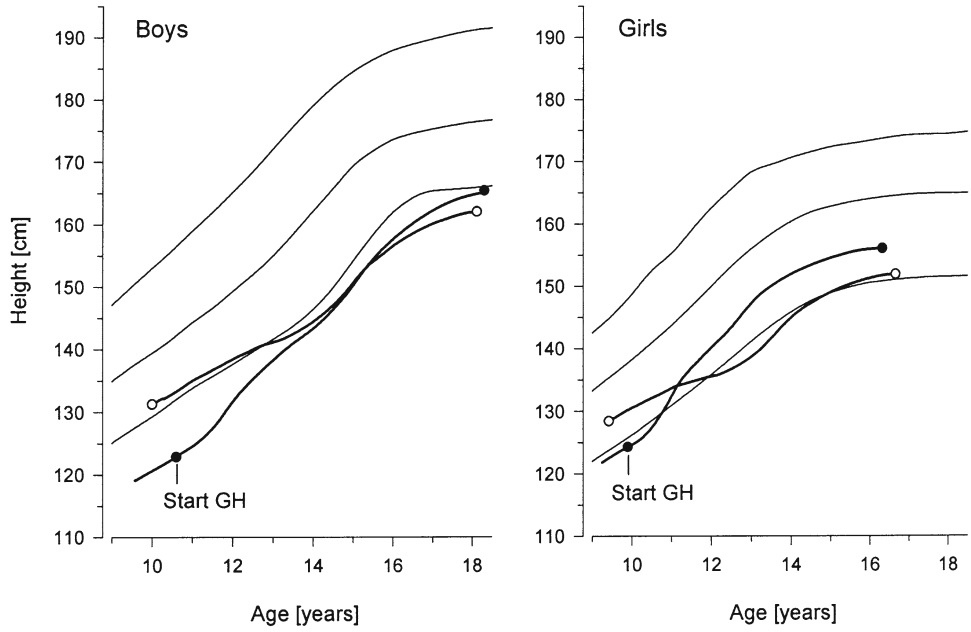


Fig. 24.9 Synchronized mean height curves of 32 boys (*left panel*) and 6 girls (*right panel*) with CRF during rhGH treatment (*closed circles*), as compared with 50 children with CRF not treated with rhGH (*open circles*). Normal values are indicated by the 3rd, 50th, and 97th percentiles. The *dots* indicate the time of the first observation, which corresponds to the start of rhGH treatment in the growth hormone–treated children, and the time of the end of the pubertal growth spurt (Reproduced with permission of Haffner et al. [16])

of the nutritional status has been considered the primary and sufficient measure to restore normal growth in growth retarded infants, postponing the option of endocrine therapeutic intervention to beyond the second year of life. Recently, this concept has been challenged by several reports initiating rhGH in growth retarded infants with CKD [180–182]. A randomized controlled study involving 30 growth retarded infants (mean age 16 months) with moderate CKD (mean GFR 25 mL/min/1.73 m²) observed excellent catch-up growth from −3.0 to −1.1 SDS within 24 months, in contrast to no significant change in controls. Unfortunately, the caloric intake of the children was not reported [180]. Likewise, Maxwell and Rees reported an increase in height SDS −3.3 to 2.2 within 12 months in 8 infants with a mean age of 22 months and CKD stage III–IV [181]. Very recently, Mencarelli et al. reported on a cohort of 27 infants with early onset CKD receiving either standard therapy or additional rhGH treatment [182]. Children treated with rhGH, but not patients undergoing close nutritional management only showed significant increases in both weight and height SDS (Fig. 24.11). Notably, two thirds of the patients receiving rhGH were on dialysis treatment. Hence, the results of these studies lend further support to the previous observation that the relative efficacy and cost-efficiency of rhGH is actually best when initiated at young age, i.e., during infancy and early childhood [163]. While the provision of adequate nutrition is certainly vital to growth and development of infants with CKD, some children show growth failure despite adequate calorie supply. In these patients, any further increases of energy intake typically lead to fat deposition but not catch-up growth. Early growth hormone therapy appears as an attractive option to accelerate length and weight gain in such infants since it helps accomplishing the body size required for renal transplantation without delay. This concept, which

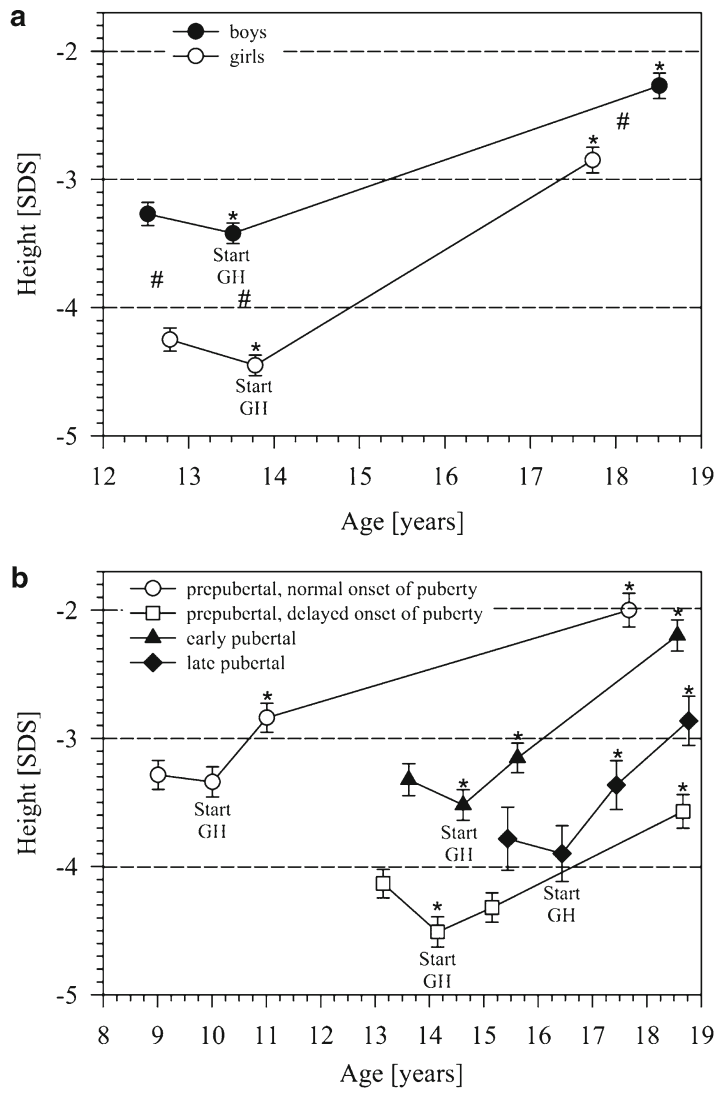


Fig. 24.10 (**a**) Mean height SDS of GH-treated boys (●; n = 193; aged 4.7–19.7 years) and girls (○; n = 47; aged 8.1–18.0 years) with CKD in the year before start of therapy until attainment of near-FH (data are given as mean ± SEM; #, P < 0.01 boys vs. girls; *, P < 0.01 vs. previous time point). (**b**) Mean height SDS of prepubertal CKD patients with normal (○, n = 68; aged 4.7–13.0 years) or delayed (□, n = 25; aged 10.1–17.1 years) onset of puberty and patients in early (▲, n = 112; aged 10.1–19.7 years) and late (◆, n = 35; aged 13.8–19.5 years) puberty in the year before start of GH therapy until attainment of near-FH (data are given as mean ± SEM; *, P < 0.003 vs. previous time point) (Reproduced with permission of Nissel et al. [177])

needs further elaboration in clinical trials, may include preemptive usage of rhGH in patients with still normal height but poor height velocity and downward crossing of percentiles.

General rhGH Treatment Strategies

The growth response to rhGH treatment is positively associated with residual renal function, target height, initial target height deficit and duration of rhGH treatment, and inversely with the age at start of treatment [163]. Daily dosing is more effective than three administrations per week and the optimal dose is 4 IU/m²/day (0.33 mg/kg/week) [183, 184]. Whereas discontinuation of rhGH results in catch-down growth in approximately 75% of CKD patients, this phenomenon is rarely observed when rhGH treatment is discontinued after transplantation, highlighting the close relationship between renal function and growth [174, 185]. Furthermore, although the absolute height gain achieved by rhGH is independent of age, the reference range increases

Table 24.2 Synopsis of studies reporting adult height data after rhGH treatment of growth failure in CKD patients

Study	No. of pts. studied	CRF treatment modalities	Age at start of rhGH (years)	Pubertal status at start of rhGH	Duration of follow-up (years)	Duration of rhGH (years)	Initial height SDS	Final height SDS	Change in height SDS
Dutch [175]	65	Cons Rx/ Dialysis	n.i.	Prepubertal	n.i.	5.8	−2.8.	−1.4	+1.4
KIGS [177]	108	Cons Rx	12.8	n.i.	4.9	>2.0	−3.2	−1.7	+1.5
	67	Dialysis	14.2	n.i.	4.0	>2.0	−4.0	−2.9	+1.1
	65	Transplant	13.7	n.i.	4.1	>2.0	−3.6	−2.5	+1.1
NAPRTCS [173]	9	Cons Rx	n.i.	n.i.	3.2	<3.2	−3.0	−2.2	+0.7
	22	Dialysis	n.i.	n.i.	4.1	<4.1	−3.6	−3.2	+0.4
	72	Transplant	n.i.	n.i.	3.7	<3.7	−3.0	−2.5	+0.5
German [16]	38	47% cons Rx 24% dialysis 29% transplant[a]	10.4	Prepubertal	7.6	5.3	−3.1	−1.6	+1.4
French [179]	35	Cons Rx	n.i.	n.i.	n.i.	n.i.	−3.0	−1.8	+1.2
	19	Dialysis	n.i.	n.i.	n.i.	n.i.	−4.1	−2.5	+1.6
	48	Transplant	n.i.	n.i.	n.i.	n.i.	−3.2	−2.2	+1.0
Belgian [171]	17	Transplant	n.i.	n.i.	n.i.	3.4	−3.0	−1.8	+1.2
Dutch [175]	18	Transplant	15.5	Pubertal	n.i.	n.i.	n.i.	n.i.	Total height gain 19 cm
NAPRTCS [176]	71	Transplant	n.i.	n.i.	n.i.	n.i.	−2.7	−1.8	+0.9

n.i. No information given

[a]Percentage distribution of patient years spent in each treatment category

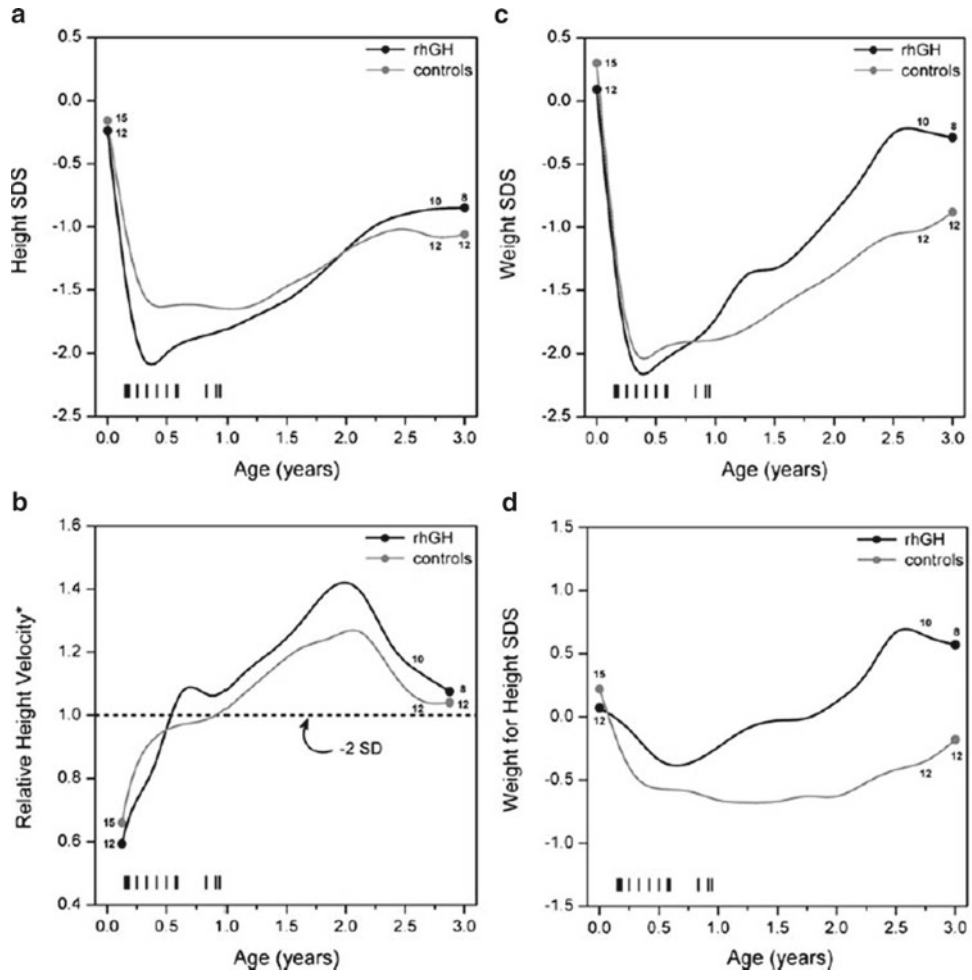


Fig. 24.11 Height and weight data. Recombinant human growth hormone (rhGH)-treated patients are shown in *black lines* and controls in *gray lines*. *Vertical bars* indicate the age at the beginning of rhGH therapy in individual patients. (**a**) Height standard deviation score (SDS), (**b**) growth velocity expressed as relative values to the −2 SDS channel for the normal population, (**c**) weight SDS, (**d**) weight for height SDS. Numbers indicate number of infants/children for which there were data at that time point (Reproduced with permission of Mencarelli et al. [182])

with age. Thus, rhGH treatment should be started as early as growth retardation becomes evident (i.e., height below 3rd percentile) (Fig. 24.12) [163]. It is still a matter of discussion whether a low growth rate (i.e., height velocity below the 5th percentile) is an indication to start rhGH even before height drops below the 3rd percentile. Such early, preventive therapy is probably more cost-effective than starting at a more advanced age when growth retardation has become evident and higher absolute rhGH doses are required.

Since rhGH is also effective in infants and young children with CKD, this treatment modality should not be withheld in this age group if malnutrition, metabolic acidosis, renal osteodystrophy, and electrolyte losses have been treated sufficiently [180–182]. The KDOQI guidelines for nutritional management in children with CKD suggest that rhGH should be initiated promptly if nutritional management has not induced catch-up growth within 3 months [128].

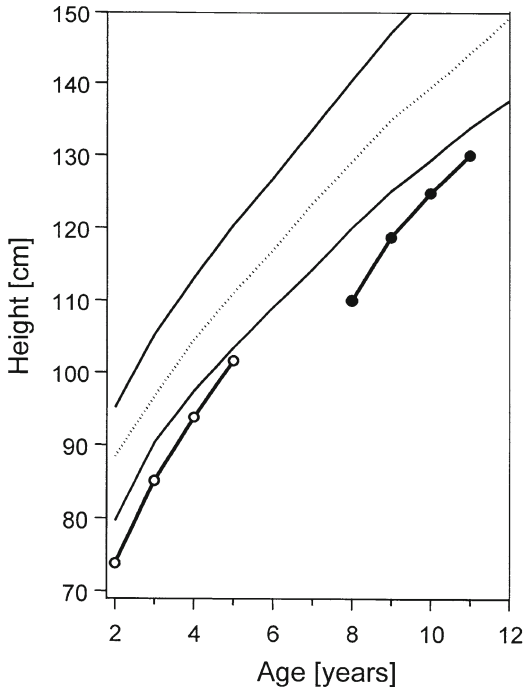


Fig. 24.12 Age-dependent efficacy of rhGH treatment exemplified by individual growth curves predicted for two patients of ages 2 and 8 years, started on rhGH at a basal height of −3.5 SD and a height velocity of −2.0 SD. The *dotted line* indicates the 50th percentile of a normal population, the *solid lines* bounding the *dotted line* denote the 3rd and 97th percentiles. Growth is accelerated over baseline height velocity in both patients by 4.5 cm in the first, 1.9 cm in the second, and 1.0 cm in the third years (empirical means of all patients on conservative treatment followed for 3 years). The young child reaches the third percentile within the third year, whereas the older child does not (Reproduced with permission of Haffner et al. [163])

The primary treatment target should be to return height into the patient's individual genetic percentile channel. Treatment may be suspended once this target is reached, but growth should be monitored closely as outlined above. In patients receiving rhGH while on conservative treatment, rhGH should be continued after initiation of dialysis; after renal transplantation rhGH should be stopped and spontaneous growth should be monitored for 12 months. If growth remains subnormal, weaning off glucocorticoids should be the first therapeutic consideration, and reinstitution of rhGH restricted to those patients with lacking or insufficient catch-up growth after steroid withdrawal or with a permanent need for maintenance glucocorticoid medication.

Potential Adverse Events Associated with rhGH Therapy

The safety of long-term rhGH treatment in CKD has been evaluated in several clinical studies and registries. A comprehensive comparison on the incidence of adverse events in large cohorts of CKD patients on conservative treatment, on dialysis, and after renal transplantation with and without rhGH treatment revealed no significant association between utilization of rhGH and the incidence of malignancy, slipped capital femoral epiphysis, avascular necrosis, glucose intolerance, pancreatitis, progressive deterioration of renal function, acute allograft rejection, or fluid retention [186]. Intracranial hypertension (ICH) in 3 out of 1,376 CKD patients was the only adverse event significantly associated with rhGH therapy. However, in all 3 instances ICH occurred after discontinuation of rhGH. In another survey ICH was noted in 15 out of 1,670 CKD patients on rhGH treatment (0.9%) [187]. Although the clinical symptoms weaned off after cessation of rhGH treatment, two patients had persistent blindness. In four patients symptoms of ICH recurred after reinstitution of rhGH treatment. Due to the potentially slightly increased risk of ICH in CKD a baseline fundoscopy is recommended and the rhGH starting dose should be 50% of the expected maintenance rhGH dosage for the first few weeks of treatment. Furthermore, hydration should be carefully monitored in CKD patients receiving rhGH since overhydration seems to be a predisposing factor for ICH. In the presence of symptoms like headache or vomiting an immediate workup for ICH including fundoscopy should be performed.

Although insulin secretion increases during the first year of rhGH treatment and hyperinsulinemia persists during long-term therapy, normal glucose tolerance is preserved during up to 5 years of rhGH administration in CKD patients on conservative treatment, dialysis, and after renal transplantation [188]. Hyperinsulinemia is most

pronounced in transplanted patients on concomitant glucocorticoid therapy. Hyperinsulinemia may, at least in theory, contribute to the development of atherosclerosis or induce diabetes mellitus by exhaustion of ß-cells. However, up to now this has not been observed in CKD patients receiving rhGH [186].

An aggravation of secondary hyperparathyroidism has rarely been reported in CKD patients on rhGH treatment, but the underlying pathomechanisms remain to be elucidated [189, 190]. GH might have a direct stimulatory effect on the parathyroid gland and/or might have subtle effects on calcium homeostasis which in turn stimulate PTH secretion. Finally, increased longitudinal bone growth by rhGH treatment may unmask preexisting renal osteodystrophy. Therefore, bone metabolism should be evaluated carefully and severe hyperparathyroidism and uremic bone disease should be treated before initiation of rhGH therapy in CKD patients. However, mild to moderate hyperparathyroidism should not be considered a reason to withhold rhGH from a poorly growing child.

Future Perspectives

Despite attention to nutrition and the availability of rhGH therapy, the problem of uremic growth failure has not been resolved in the majority of dialysis patients. The recently propagated concept of intensified hemodialysis combined with rhGH may be a promising option for patients suffering from growth retardation and GH resistance on conventional dialysis therapy [140] and deserves further investigation by controlled clinical trials. Another avenue of promising clinical research may be given by recombinant IGF-I administered as monotherapy or in combination with rhGH [191].

A particular challenge is given by the severely diminished pubertal height gain. In such adolescents, pharmacological inhibition of epiphyseal closure may allow an extended duration of the remaining growth period. Since the closure of the epiphyseal growth plate is induced by local estrogen action, inhibition of estrogen synthesis is a principal therapeutic option. GnRH analogues arrest pubertal progress, but the potential growth benefit would come at the psychological disadvantage of delayed sexual maturation. In boys, aromatase inhibitors, which suppress the local conversion of testosterone to estradiol, might extend the growth phase without affecting pubertal development and thereby increase the time window for rhGH therapy. An initial proof of this concept has recently been provided in short male adolescents treated with rhGH combined with the aromatase inhibitor anastrozole [192]. It will be fascinating to study its efficacy in adolescents on long-term dialysis.

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