

## Growth hormone in chronic renal disease

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### ABSTRACT

Severe growth retardation (below the third percentile for height) is seen in up to one-third children with chronic kidney disease. It is thought to be multifactorial and despite optimal medical therapy most children are unable to reach their normal height. Under-nutrition, anemia, vitamin D deficiency with secondary hyperparathyroidism, metabolic acidosis, hyperphosphatemia, renal osteodystrophy; abnormalities in the growth hormone/insulin like growth factor system and sex steroids, all have been implicated in the pathogenesis of growth failure. Therapy includes optimization of nutritional and metabolic abnormalities. Failure to achieve adequate height despite 3–6 months of optimal medical measures mandates the use of recombinant GH (rGH) therapy, which has shown to result in catch-up growth, anywhere from 2 cm to 10 cm with satisfactory linear, somatic and psychological development.

**Keywords:** Chronic kidney disease, chronic renal failure, growth failure, growth hormone, short stature

### INTRODUCTION

Growth retardation in patients with chronic kidney disease (CKD), although poorly understood is thought to be multifactorial (under-nutrition, anemia, vitamin D deficiency with secondary hyperparathyroidism, metabolic acidosis, renal bone disease).<sup>[1,2]</sup> The presence of CKD compromises vertical growth with up to one-third children having severe growth delay (below the third percentile for height).<sup>[3]</sup> Despite optimal medical and nutritional therapy most children with CKD without supplemental growth hormone therapy are unable to reach their normal height.<sup>[4]</sup> This review focuses on use of growth hormone (GH) in patients with CKD.

### GROWTH HORMONE REGULATION

GH is important in regulating somatic growth, body composition, and intermediary muscle and bone metabolism.

Mature GH is a single-chain polypeptide that contains 191 amino acids with a molecular weight of 22,128 Daltons (22 kD). It represents approximately 21% of all circulating plasma GH. The next most common variant is the monomeric 20 kDa molecule, representing approximately 6% of all circulating plasma GH. GH may undergo further modification at the site of action and produce various dimers, trimers, pentamers, and oligomers.<sup>[5,6]</sup>

Its secretion from the anterior pituitary is regulated by growth hormone releasing hormone (GHRH), Ghrelin (Growth Hormone Secretagogue), and somatostatin. Mutations in GHRH receptor have been reported as isolated causes of growth retardation from the Indian subcontinent.<sup>[7-9]</sup> Ghrelin is a recently recognized regulator of GH secretion, which was isolated from the stomach. It acts as an endogenous ligand of the GH secretagogue receptor (GHS-R). The majority of circulating ghrelin exists as the des-octanoylated form, which has shown to stimulate GH release directly from the anterior pituitary.<sup>[10-12]</sup> Somatostatin has shown to directly inhibit GHRH secretion from hypothalamus, GH secretion from somatotrophs in the anterior pituitary and antagonize the GH secretagogue activity of ghrelin.<sup>[13]</sup>

Relevant to chronic kidney disease, GH is further regulated by:

1. Glucocorticoid (acutely – within 3 hours stimulates GH; chronically - by 12 hours suppresses GH secretion)<sup>[14]</sup>

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2. Neuropeptide Y – inhibits GH secretion<sup>[15]</sup>
3. Glucose - hypoglycemia stimulates GH secretion via GHRH agonism and/or somatostatin inhibition mediated via  $\alpha_2$  adrenergic receptors.<sup>[16,17]</sup> Hyperglycemia inhibits GH secretion.
4. Amino acids – L-arginine stimulates GH secretion via somatostatin suppression and GHRH augmentation.<sup>[18]</sup>
5. Leptin – exact role on GH regulation seems uncertain (leptin receptor has been detected in normal pituitary tissue).<sup>[19]</sup>

Most of the effects of GH are mediated by *insulin like growth factor-1* (IGF-I)/IGF system, in both the fetus and child/adult. In the fetus, GH is produced by the pituitary gland around 12 weeks of gestation.<sup>[20]</sup> *Growth especially around puberty needs the combined effort of thyroid and gonadal hormones<sup>[21,22]</sup> along with GH.*

The *IGF system* is composed of IGF-1, IGF-2, 2 specific receptor types, IGF-binding proteins (IGF-BP; total six identified; IGF-1 to 6) and acid labile subunit. *IGF-1* is a polypeptide of 70 amino acids being regulated exclusively by GH and to some extent by dietary energy and protein. It is encoded on the long arm of chromosome 12, produced by the liver<sup>[23]</sup> and most other human tissues (autocrine/paracrine effect) that *predominantly regulate linear growth.* *IGF-2* is a polypeptide of 67 amino acids thought to be GH independent. It is encoded on short arm of chromosome 11 (paternal imprinting) that predominantly regulates tissue growth, proliferation, differentiation, and apoptosis in concert with IGF-1. From this “original somatomedin hypothesis” a revised theory was entertained when studies suggested that the growth model of IGF-1 is not as straightforward as projected above, instead *GH has the ability to stimulate bone/cartilage tissue directly rather than via the IGF system.*<sup>[24,25]</sup> Of the IGF-BP's, only the promoter for the acid labile subunit (ALS) of the *IGFBP-3* complex has an identifiable GH-responsive element.<sup>[26]</sup> IGF BP3, although synthesized from the liver along with the IGF-1, is not co-localized within the same hepatocyte, instead IGF-BP3 exists within endothelial cells of hepatic sinusoids and is regulated indirectly by GH probably via IGF-1.<sup>[27]</sup>

## PATHOPHYSIOLOGY OF GROWTH FAILURE IN CHRONIC KIDNEY DISEASE

### Nutritional

Nutrition is important in all phases of human growth particularly so during infancy, because the rate of growth is highest and less dependent on growth hormone/IGF system. Growth velocity can be as much as >25 cm/year at birth to an average of 18 cm/year at age 1 year of age, so it is imperative that the correct nutrition is administered in

order to achieve the desired growth velocity. As mentioned earlier, the GH/IGF system is partially regulated by calorie and protein intake;<sup>[28]</sup> therefore inadequate nutrition can result in impaired growth.

Nutritional status can be measured by clinical, anthropometric, and biochemical parameters such as height, weight, BMI (weight/height<sup>2</sup>; kg/m<sup>2</sup>), skin fold thickness, hand-grip strength, and serum albumin and prealbumin. CKD is characterized by a wasting/cachectic syndrome. Although the mechanisms for cachexia are complex, contributory factors include:

1. anorexia, nausea, and vomiting (*uremic toxicity, metabolic acidosis*, imbalance of regulatory proteins of energy intake),
2. increased basal metabolic rate,
3. loss of lean body mass (muscle mass replaced with fat), and
4. declining serum proteins (albumin, transferrin {*anemia*}, prealbumin).

Inflammatory cytokines (TNF-[alpha], IL-1[beta], and IL-6)<sup>[29-31]</sup> and an imbalance of proteins (PR) (leptin, adiponectin, resistin, ghrelin) that regulate energy intake have been implicated in malnutrition and growth failure in children. Orexigenic neuropeptides such as agouti-related peptide and neuropeptide Y (NPY) (appetite stimulants) and anorexigenic neuropeptides such as proopiomelanocortin and  $\alpha$ -melanocyte-stimulating hormone (appetite suppressants) are primarily involved. As the arcuate nucleus of the hypothalamus lies outside the blood brain barrier it has direct access to the inflammatory cytokines pool.<sup>[32]</sup> Renal failure is associated with an altered clearance of several proteins PR (leptin, adiponectin, resistin, ghrelin) that influence energy intake:

- a. Leptin: Is a member of the IL-6 super-family of cytokines, a potent anorexigen that is associated with increased energy expenditure. Serum levels are inversely associated with renal function with high levels seen with declining renal function. It is also a marker of poor nutritional status.<sup>[33,34]</sup>
- b. Adiponectin: Is a small peptide (30 kDa) synthesized and secreted almost exclusively by adipocytes. It has anti-inflammatory and anti-atherogenic properties. It results in enhanced thermogenesis, weight loss, and improved insulin sensitivity. It is increased in patients with renal dysfunction undergoing dialysis<sup>[35,36]</sup> and although the exact mechanism of its effect on energy metabolism is debated, it clearly has an important role in uremic cachexia.
- c. Resistin: Is an adipokine produced by macrophages that has shown to contribute to insulin resistance and development of white adipose tissue with elevated plasma free fatty acids, in preclinical studies. Elevated

resistin has been associated with renal impairment and inflammation. Although its exact mechanism on energy metabolism is debated in humans, it is believed to bear a significant role in energy intake.<sup>[36,37]</sup>

- d. Ghrelin: Has shown to positively correlate to body mass index (BMI) and fat mass in patients with chronic kidney disease. Its administration has shown to increase energy intake and is being explored as a possible therapeutic option in the future.<sup>[38]</sup>

The energy intake in patients with CKD is greatly affected by nausea, vomiting, and anorexia, with most data showing a reduced calorie intake (approximately 10 kcal/kg/day below the recommended values). Despite this, the mean BMI reported was 28.7 by the United States Renal Data System in 2007, which is well in the overweight range.<sup>[39]</sup>

Although inconsistent among various studies, the total and resting energy expenditure is enhanced in CKD patients especially if they are on hemodialysis. Other factors that contribute to the cachectic state with reduced lean body mass are inflammation, insulin resistance, and hyperparathyroidism.<sup>[40,41]</sup> Adequate, yet caloric restricted diets (20% less than recommended) have shown to reduce inflammation and improve biomarkers of energy metabolism (resistin) that correlate positively with body fat, especially android fat.<sup>[42]</sup>

### Growth hormone/IGF system

Postnatal growth is dependent on the GH/IGF-1 system. Preclinical studies suggest that only 17% of postnatal growth occurs independent of the GH/IGF-1 axis. GH contributes to approximately 14% and IGF-I alone contributes to as much as 35% of linear growth.<sup>[43]</sup> The GH/IGF system is implicated in growth failure in patients with CKD via several proposed mechanisms.

#### Growth hormone insensitivity

GH levels are either normal or raised in most studies which when taken together with growth failure, suggests a peripheral tissue resistance.<sup>[44,45]</sup> This results from the following:

1. *Low GH receptor density in peripheral tissue* - serum high affinity GH-binding protein (GHBP) is the cleavage product of the extracellular domain of the GH receptor and is a good representative of GH receptor density especially in the liver. It correlates well with linear and somatic growth. It has been found to be in low concentrations in children with CRF, with the lowest values in children with end-stage renal disease (severe).<sup>[46,47]</sup>

#### 2. Reduced functional IGF - due the following reasons:

- a. Reduced total and free IGF-1 - free IGF-1 is reduced by up to 50% in children with severe renal disease.
- b. Increased immuno-reactive but bio-inactive IGF-BP's - Both IGF-BP3 and IGF-BP5 are GH dependent, growth promoting and meant to balance/buffer serum concentration of free IGF-1. They are severely affected in children with CKD. An increased concentration of low molecular weight 29 kDa IGF-BP3 (bio-inactive) and normal but fragmented IGF-BP5 is seen in the serum of CRF patients,<sup>[48,49]</sup> which are ineffective in augmenting the IGF-1 response on growth. Serum concentration of total IGF-BP's is increased in CKD patients, paralleling the degree of renal dysfunction, which might explain the greater degree of growth failure seen with end-stage renal disease compared to preterminal renal disease patients.<sup>[50]</sup> The elevated IGF-BP's might be explained by reduced renal clearance<sup>[51]</sup> and greater hepatic production. Hepatic production of IGF-BP 1 and 2 is enhanced by the increased GH production (negative feedback from peripheral resistance) and insulin resistance (insulin controls IGF-BP2 secretion).<sup>[52]</sup>

### Severity of renal disease and age of onset of renal disease

Growth of a child is affected as the glomerular filtration rate (GFR) declines to below 90 ml/min/1.73 m<sup>2</sup> becoming severe once the GFR falls below 25 ml/min/1.73 m<sup>2</sup>. Children with an early onset of CRF may suffer from prenatal and postnatal growth failure, leading to severe growth retardation even before the age of 3 years compared to older children, with the younger child affected more compared to the older for all age groups. Children with CRF stages 2–4 develop metabolic abnormalities that further negatively impacts growth. The severity of kidney disease relates directly to growth failure with patients with ESRD having the least height.<sup>[53,54]</sup> Once the GFR is <60 ml/min, metabolic complications worsen (anemia, metabolic acidosis, secondary hyperparathyroidism, renal osteodystrophy, naturessis) further compromising growth.<sup>[55-57]</sup>

### Nature of renal disease

Children with congenital disorders (renal dysplasia and obstructive uropathy) have the worst degree of short stature. Children with acquired diseases such as focal segmental glomerulosclerosis (FSGS) are more likely to have a normal growth pattern in the years before the onset of the disorder.<sup>[58]</sup>

### Others

#### Metabolic acidosis

Metabolic acidosis can directly stimulate bone resorption<sup>[57]</sup>

and impair function of growth plate cartilage.<sup>[58]</sup> It has been shown to do this via modulating the GH/IGF axis by the following mechanism:

- a. Inhibit pituitary GH secretion.<sup>[59]</sup>
- b. Reduce serum IGF-I levels (down-regulation of hepatic IGF-I and GH receptor mRNA expression)<sup>[60]</sup> causing resistance to the anabolic action of GH.

### Anemia

Although the relationship of anemia to GFR is less linear in children, compared to adults, the severity of anemia correlates positively to growth failure. Up to 54.1% of children on hemodialysis have hemoglobin < 11 g% while up to 69.5% have anemia while on peritoneal dialysis.<sup>[61,62]</sup> Anemia is defined as hemoglobin < 11 g% in children aged 6 months to 6 years and < 12 g% in children aged 6–14 years.<sup>[63]</sup> The main causes for the anemia in CRF are as follows:

- a. Reduced erythropoietin production – directly because of renal dysfunction and secondarily because of increased renal sodium loss. Patients with CKD that have a reduced GFR in turn have reduced sodium absorption and a net relative excess of oxygen which serves as a signal to decrease erythropoietin production.<sup>[64]</sup>
- b. Chronic inflammation.
- c. Chronic blood loss.
- d. Hyperparathyroidism.
- e. Aluminum toxicity.
- f. Hemoglobinopathies.
- g. Vitamin deficiencies (B12 and folate).
- h. Hemolysis.
- i. Adverse effects of cytotoxic or immunosuppressive drugs and angiotensin converting enzyme inhibitors.

Anemia is associated with transfusion dependence, decreased exercise tolerance, growth retardation, and delayed neurologic development.<sup>[65]</sup> Replacement therapy with the aim to correct hematocrit and hemoglobin has been associated with much improved linear growth, appetite, well-being, exercise tolerance, and cognitive function.

### Renal osteodystrophy

Renal osteodystrophy represents a spectrum of skeletal disorders ranging from high-turnover lesions (secondary hyperparathyroidism) to low-turnover lesions (osteomalacia and adynamic bone disease). Excess parathormone (greater than twice upper limit of normal) has been associated with a substantial delay in chondrocyte differentiation and ossification, which leads to impaired endochondral ossification of long bones. Treatment of secondary hyperparathyroidism with the aim to normalize parathormone (upper limit of normal) using dietary phosphate restriction, phosphate binders, and small doses

of 1- $\alpha$ -calcitriol levels has demonstrated good catch up growth in children.<sup>[66]</sup> Factors that contribute to adynamic bone disease in the absence of aluminum (excluded from dialysate fluid) are:

- a. Hypocalcemia,
- b. Impaired renal calcitriol production,
- c. End organ (skeletal) resistance to parathormone,
- d. Altered prepro-PTH gene transcription with attenuation of calcium-sensing receptor expression in parathyroid glands,
- e. Hyperphosphatemia.<sup>[67]</sup>

### Abnormalities with sex steroids

Patients with CKD demonstrate delayed or abnormal pubertal progression, which has been postulated secondary to

- a. Direct toxic effect of uremia on sex steroids (estradiol and testosterone),
- b. End organ resistance to effects of sex steroids,
- c. Hypothalamic-pituitary-gonadal dysregulation as evidenced by decreased luteinizing hormone pulsatility and bioactivity.

All have shown to cause growth failure<sup>[68-70]</sup>

### Treatment related to chronic kidney disease

Use of long-term steroid therapy may affect growth by

- a. Depressing pulsatile GH secretion,
- b. Inhibiting hepatic production of IGF- I,
- c. Peripherally interfering with cartilage metabolism, bone formation, nitrogen retention, and calcium metabolism.<sup>[71]</sup>

## CLINICAL PRESENTATION

Standard deviation score, or Z-score, provided, has been used to define height variations compared to their age adjusted counterparts. There are three distinct periods of growth for children. The first period is the first 2 years of life, when normal children usually grow about 37 cm in height. The second period is from infancy to adolescence, where children usually grow about 5–6 cm/year, and the third period is the adolescent growth spurt, which normally usually exceeds 25 cm (approximately 34 cm for boys, and 25 cm for girls). This would imply that the degree of growth failure should be greatest if renal impairment were to occur in the first 2 years of life.<sup>[72,73]</sup>

Congenital kidney diseases, severe renal impairment (GFR<10 ml/min), presentation at a younger age (particularly <2 years), white race, blood urea nitrogen <20 mg/dl, parathormone >2 times upper limit of normal, have been shown to have the greatest impact on the severity of short stature.<sup>[56]</sup> Anemia, acidosis, hypoalbuminemia, hyperphosphatemia, hypocalcemia, steroid therapy all have



shown to contribute to growth impairment, with mixed results in various studies.

## CLINICAL EVALUATION

A large percentage of children with CRF exhibit growth failure (58%, 43%, 33%, and 23% between aged 0–1 years, 2–5 years, 6–12 years, and more than 12 years, respectively). Children with clinically *defined CKD* (GFR <75 ml/min per 1.73 m<sup>2</sup> body surface area) and significant *growth impairment* defined as (height SDS <-1.88 {third percentile} or height velocity SDS <-2.00) should be evaluated and treated because affected children exhibit a range of potentially serious medical and psychological complications associated with an increased mortality. The 5-year mortality rate is higher (threefold) in children with severe (height velocity SDS <-3.0) or moderate growth failure, compared to patients with normal growth.<sup>[74,75]</sup>

For children with CRF presenting with short stature, a thorough evaluation of the pituitary gland needs to be undertaken before labeling the short stature as solely due to CRF. Because of the several abnormalities with the GH/IGF system in patients with CRF, it cannot be used diagnostically as it is in patients without CRF to assess GH status.

Baseline investigations should include the following:

1. Pituitary function tests ± dynamic tests (emphasis on thyroid function tests and gonadal hormones) correlating with a clinical evaluation (tanner stages). *Baseline IGFBP3* levels predict approximately 30% of the growth response to GH treatment in CKD. It serves as an indicator of sensitivity to exogenous GH and may be a useful clinical parameter to predict the growth response to rGH.<sup>[44,46]</sup>
2. Anthropometric markers of malnutrition (refer to malnutrition).
3. Biochemical tests covering (renal function (GFR),<sup>[76,77]</sup> hemoglobin, hematocrit; bicarbonate; vitamin D, calcium, phosphorous, parathormone; albumin/prealbumin).
4. Assessment of growth velocity, bone age (X-ray of wrist and elbow) and skeletal survey (X-ray of knee, hip).

## Therapy

The therapy is aimed at correcting linear and somatic growth. This can be achieved via the following plan. **Step 1:** Correct nutritional and metabolic abnormalities for at least 3–6 months before considering GH therapy.

- a. Nutritional replacement includes adequate intake of -
  1. *Calorie-energy* – Malnutrition is associated with

increased mortality and growth failure. At least 80% of the average energy requirements must be ensured to maintain nutrition in children with CRF. There is strong evidence for “catch up growth” especially in children under 2 years of age who are able to consume energy between 80% and 100% of the average recommendation. Feeding often has to be achieved via nasogastric or feeding tubes. Energy intake may need to be increased by up to 30% daily in patients who vomit. For children on peritoneal dialysis energy intake might have to be reduced by 8–12 kcal/kg/day in order to compensate for energy derived from the dialysate if there is excess weight gain. Children need the specialized input of a pediatric dietician. Children entirely dependent on enteral feeds may need to be seen weekly, particularly during infancy.<sup>[78-80]</sup>

2. *Protein* – adequate protein intake is as important as energy intake in the growth of children especially in those under 2 years of age. Protein and nutrient intake in children should be replaced according to requirements expressed as reference nutrient intakes (RNI), set at 2 SDs above the average.<sup>[81]</sup> Serum albumin is a valuable prognostic marker with predialysis values bearing a strong relationship to mortality. A fall in serum albumin by 1 g% at the start of dialysis for patients <18 years of age at the initiating of dialysis is associated with a 54% higher risk of death.<sup>[82]</sup>
3. *Water soluble vitamins* – Low levels are seen in children with CRF due to inadequate intake, increased loss as seen during dialysis and increased requirements. Replacement of serum folate is recommended to prevent hyperhomocytinemia. Recommended doses are 250 µg/kg to maximum of 2.5 mg daily for infants, 2.5 mg for children aged 1–5 years and 5 mg daily for children >5 years of age.<sup>[83]</sup> Other water-soluble vitamins (vitamin B12, vitamin C) should be adequately replaced which can very often be done by an adequate diet. Over-replacement of vitamin C can result in oxalosis, which could be potentially hazardous.<sup>[62]</sup>
- b. Correction of *anemia* – Iron deficiency is common in patients with CKD particularly in those on hemodialysis. Repeated blood sampling, surgical interventions, blood loss through the use of dialyzers and tubing, gastrointestinal loss, and shortened red blood cell lifespan are the main reasons for anemia in CKD patients. Chronic blood loss of approximately 6 ml/m<sup>2</sup> occurs in predialysis pediatric CKD patients and 11 ml/m<sup>2</sup> (gastrointestinal blood losses) and 8 ml/m<sup>2</sup> (per dialysis treatment)

occurs in hemodialysis patients. Adequate iron stores are imperative for success of Hb raising strategies. The aim is to achieve an Hb >11 g%, serum ferritin of >100 ng/ml and TSAT of >20% in pediatric hemodialysis, peritoneal dialysis and nondialysis CKD patients. This can be done via iron (intravenous more efficacious than oral), folate, and vitamin B12 replacement and optimal use of recombinant erythropoietin (dose approximately 150 U/kg per week) and darbepoetin (starting dose 1.6 µg/kg once weekly). Exacerbation of hypertension and paradoxically pure red cell aplasia (rare) can complicate erythropoietin therapy. Among available diagnostic tools for the assessment of anemia, serum ferritin and serum transferrin saturation (TSAT) is the most reliable in evaluation of anemia in children with CKD. The hematocrit is a less reliable diagnostic and prognostic tool as it is negatively influenced by factors such as body temperature, body water, hyperglycemia, and storage time prior to analysis, factors that are dynamically changing in children with CRF. The TSAT is calculated by dividing serum iron by total iron binding capacity and multiplying by 100. A TSAT of less than 20% is a significant predictor of iron deficiency.<sup>[62,76,84,85]</sup>

- c. Correction of *metabolic acidosis* – Up to 88% of children with CKD and growth retardation are acidemic. Serum bicarbonate should be maintained >22 mmol/l. Orally administered alkali therapy may be considered in children with metabolic acidosis (serum bicarbonate <22 mmol/l) (76).
- d. Correction of *vitamin D* - Vitamin D and calcium should be adequately replaced with the aim of keeping PTH in the upper range of normal in children with stage 1–3 CKD, and less than 3 times upper limit of normal in stage 4–5 CKD. Serum calcium should be maintained at levels <10.2 mg%. This can be effectively achieved using calcitriol (activated vitamin D3) and alfacalcidol. If the serum calcium stays persistently over 10.2 mg% (corrected) despite calcium withdrawal, vitamin D replacement often has to be held temporarily. If tertiary hyperparathyroidism is the cause for persistent hypercalcemia, cinacalcet (allosteric activators of the calcium sensing receptor) can be used. Low doses of vitamin D have shown to stimulate the growth plate but high doses of calcitriol have shown to inhibit cartilage proliferation *in vitro*. Over-suppression of bone with bolus doses of vitamin D is however not advisable as it may cause adynamic bone disease. Serum phosphorous should be maintained <1.5 times upper limit of normal for optimal growth. Serum phosphate levels can be controlled by dietary restriction, modification of dialysis prescriptions, and use of phosphate binders (non-calcemic probably better than calcemic).<sup>[56,76,86,87]</sup>
- e. Correction of *hypothyroidism* if present.

- f. Adequate *salt replacement* for salt wasters while maintaining adequate control on blood pressure. Salt wasters have been associated with hypercalciuria, bone loss and reduced erythropoietin production, all contributing to growth failure.<sup>[62,76]</sup>

**Step 2:** Failure to achieve adequate height despite 3–6 months of optimal medical measures mandates the use of *recombinant GH (rGH) therapy*, which has shown to result in catch up growth anywhere from 2 cm to 10 cm.

*rGH dose:* A meta-analysis that assessed 10 randomized controlled clinical trials has suggested that a dose of 28 IU/m<sup>2</sup>/week (0.05 mg/kg/day or 0.35 mg/kg/week; 1 mg = 3 IU) is optimal for children with CKD (76, 86, 88).

*rGH efficacy:* A far greater number of children (approximately 40%) reach their target adult height with an average gain in height of approximately 4 cm/year. The average increase in height varies from 1.0 to 1.4 SD in prepubertal patients. Greatest benefits are observed during the first year of use of GH therapy. Efficacy and compliance wane over time with up to 90% of patients reporting missing injections (waning compliance) in the first 2 years of receiving rGH therapy. Other parameters that show an improvement include body weight, mid-arm circumference, mid-arm muscle circumference, and psychological health (depression, phobic anxiety, sensitivity, and hostility).<sup>[76,88-93]</sup>

Factors influencing efficacy at presentation include the following.<sup>[62,76,94]</sup>

1. Degree of stunting (growth failure).
2. Bone age retardation.
3. Duration of GH therapy.
4. Time spent on conservative treatment (mean increase in height [+1.5 SD])/dialysis (mean increases in height [+1.1 SD]).
5. Severity of renal failure (end-stage renal failure and posttransplant children have a worse outcome).
6. Severe pubertal delay (height gain is twofold higher in patients with normal onset puberty).
7. Gender (girls gain more height compared to boys).
8. Age (<6 years of age; early pubertal and prepubertal patients, gain more cumulative height [+1.3 SD] versus late pubertal patients, where, cumulative height gain is approximately [+0.9 SD]).
9. High parathormone levels (intact PTH should be <500 pg/ml prior to starting rGH).
10. Younger age (<6 years, prepubertal or early pubertal), female gender, lesser time at dialysis, normal pubertal development and lesser degree of growth failure prior to starting GH therapy, all represent favorable factors predicting clinical response to GH therapy.

### Monitoring

Clinic visits every 3–4 months are recommended with assessment of the following:

1. Height, weight (appropriate GH dose modification), height velocity.
2. Occipitofrontal circumference (until 3 years of age).
3. Pubertal maturation.
4. Nutritional status.
5. Fundoscopic examination (raised intracranial pressure).
6. Serum chemistries, with special emphasis on thyroid function tests and parathormone.
7. Bone age (1 yearly) accompanied by hip and knee X-rays only if persistent hip or leg pain is present (avascular necrosis, slipped capital femoris).

### Growth hormone discontinuation [76]

1. X-ray for bone age suggests closure of epiphyses.
2. Height goal has been achieved (based on mid-parental height or 50<sup>th</sup> percentile for age).
3. Active neoplasia, slipped capital femoral epiphyses, benign intracranial hypertension, severe hyperparathyroidism (PTH >900 pg/ml for stage 5 CKD and lower values for early CKD), noncompliance or at the time of renal transplantation. GH therapy may be re-initiated at an appropriate time.

### Growth hormone safety

Most studies have established the relative safety of GH therapy with physical and psychological benefits. The main concerns include the following:

1. Skeletal abnormalities (slipped capital femoral epiphysis, avascular necrosis of hip, scoliosis).
2. Progression of renal failure or failure of transplanted renal graft.
3. Risk of malignancy.
4. Glucose intolerance (careful monitoring in patients preexisting hyperglycemia)
5. Hypothyroidism.
6. Raised intracranial pressure.
7. Hypertension.

While most studies (small numbers) are not powered enough to firmly attach the above-mentioned adverse effects to GH therapy, caution and regular monitoring is advised. Although no increased risk of malignancy has been associated with the use of GH therapy, a study that evaluated the use of rGH in cancer survivors (including 172 brain tumor patients) found an increased incidence of second neoplasms (all solid tumors) particularly in survivors of acute leukemia. The data raises concern; however, it needs to be interpreted with caution as most studies including the KIGS/KIMS database (the Pharmacia International

Growth Database started in 1987) do not suggest an increased risk of malignancy.<sup>[94]</sup>

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