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Review Article

Children's Growth Failure And Chronic Kidney Disease.

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Abstract

Since children with chronic kidney disease (CKD) may exhibit a range of endocrine problems, treating CKD presents a substantial challenge for pediatric endocrinologists. The degree of renal insufficiency is connected with the severity of growth failure, which is prevalent in CKD. Addressing reversible comorbidities, improving diet, and maintaining metabolic control are examples of management techniques.Growth significantly improves with kidney replacement therapy, including transplantation. A new Consensus Statement states that recombinant growth hormone (rGH) can be used to treat persistent growth failure in children with CKD stage 3 or who are receiving dialysis and are older than six months. For people who have persistent growth retardation and height between the third and tenth percentiles, rGH treatment may be an option.considered for people who have a chronic slowdown in their growth and a height between the third and tenth percentiles. If spontaneous catch-up growth does not occur and steroid-free immunosuppression is not an option, GH medication should be started one year after kidney transplantation for children who still have growth insufficiency. GH therapy should be taken into consideration at every stage of chronic kidney disease (CKD) in children because of nephropathic cystinosis and prolonged growth failure. Throughout therapy, potential negative effects and advantages must be routinely evaluated. Children with CKD can safely receive GH treatment. Its overall effectiveness is still debatable, though. Every potential issue that could hinder growth should be promptly addressed and fixed, if feasible, using a patient-specific strategy.Children with residual growth potential may benefit from GH therapy in order to promote catch-up growth.To maximize growth results in this population, future research should concentrate on developing consensus guidelines and improving efficacious therapy approaches.

Keywords : *children chronic kidney disease; growth; growth hormone.*

CHRONIC KIDNEY DISEASE IN CHILDREN

For doctors, treating chronic kidney disease (CKD) in children presents a problem.The definition of chronic kidney disease (CKD), which is based on exact criteria, is the impaired kidney's capacity to effectively eliminate waste materials and extra water. With 74.4 cases per million of the age-related population, the prevalence of CKD in children is not insignificant [1,2].In this case, we referred to the KDIGO 2024 Clinical Practice Guideline for the description and categorization of CKD as well as for its assessment and management [3].For young patients to be managed effectively, a thorough grasp of the pathophysiology and etiology is necessary.Congenital abnormalities, hemolytic uremic syndrome, focal segmental glomerulosclerosis, lupus nephritis, secondary glomerulonephritis, and interstitial nephritis are among the causes of chronic kidney disease (CKD) [4].A range of symptoms affecting different organ systems make up the clinical presentation of chronic kidney disease (CKD) in children. While gastrointestinal symptoms can include nausea, vomiting, and anorexia, cardiovascular symptoms can include hypertension, congestive heart failure, and pericarditis. Neurologically, CKD might manifest as encephalopathy, disorientation, or lethargy. Endocrine/metabolic disorders may show up as growth failure, secondary hyperparathyroidism, hypocalcemia, hyperphosphatemia, decreased vitamin D, and hematologic problems such anemia and bleeding tendency. In children with CKD, all of these comorbidities may negatively impact growth (Table 1). Because CKD affects the hypothalamic-pituitary function, it can also have an effect on sexual and reproductive health. For children patients with CKD, prompt identification of these issues is essential to proper therapy [5].

GROWTH FAILURE IN CHILDREN WITH CKD

Children with chronic kidney disease (CKD) often experience growth failure, and the degree of renal insufficiency is connected with the extent of growth impairment. One-third

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of the 6907 children with CKD in the 2008 North American Pediatric Renal Trials and Collaborative Studies annual report had a height below −1.88 SDS. Just 17% of children with CKD of all ages had height SDS > 0 in the same study, indicating that younger children were more likely to be short [6,7]. According to data from a prospective study of patients from South East Europe, 29.3% of the CKD patients who were enrolled had growth failure [7]. Similar effects of chronic kidney disease (CKD) on final height have been assessed in adult studies, with decreased height relative to the genetic target in between 30 and 50% of cases [7–9].Growth failure in children with chronic kidney disease (CKD) is caused by a variety of causes, such as comorbidities, hematological abnormalities, dietary status, mineral and bone disorders, genetic background, and endocrine problems. Children with CKD frequently have anemia and metabolic acidosis, which impair appetite and lead to malnutrition. Nonetheless, the severity and age of CKD start have the biggest effects on growth [9].Insulin-like growth factor 1 (IGF1) bioactivity is decreased and GH resistance is brought on by CKD.This condition stems from aberrant GH receptor signaling mediated by the Janus kinase 2-signal transducer and activator of the transcription 5 (STAT5) pathway, as well as decreased GH receptor expression in the liver and other target organs [10]. Sulfate incorporation in a porcine costal cartilage experimental animal model [11,12] and an increase of IGF binding proteins (IGFBPs) [13] both indicate decreased IGF1 bioactivity. Specifically, it has been discovered that unsaturated IGFBP3, a subclass of the IGFBPs family, directly inhibits the action of IGF1 on growth plate chondrocytes and cartilage tissue in vitro. Additionally, it has been demonstrated that exogenous growth hormone promotes growth via raising IGF1 levels and its function at the growth plate level.The particular uremic condition that characterizes children with chronic kidney disease is the cause of all these abnormalities.The growth plate metabolism is directly impacted by CKD as well. When compared to healthy controls, the growth plate's overall height in CKD rats has been observed to be either decreased, increased, or constant. The hypertrophic zone's enlargement, which was unrelated to proliferative activity, was the cause of the growth plate's larger-than-normal size [14]. Furthermore, CKD rats' chondrocytes were smaller in size at the end than controls'. This is crucial since it has been demonstrated that the volume of chondrocytes in the terminal growth plate determines height growth in mammals [15]. The relative lack of bioactive IGF1 in the development plate in CKD may be partially responsible for the decrease in the final volume of chondrocytes. because chondrocytes cannot reach their normal ultimate volume without IGF1 [16]. Notably, it has been demonstrated that high-dose rGHtherapy improves damaged chondrocytes in animal models of chronic kidney disease (CKD), specifically in terms of chondrocyte proliferation and growth plate cellular architecture [17].Changes in bone development, remodeling, and modeling are determined by CKD in juvenile patients, and these changes show up early in the disease's course. Abnormalities in calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism are the hallmarks of CKD–mineral bone disorder (CKD-MBD), a systemic disorder brought on by CKD that causes abnormalities in bone histology, linear growth, and strength. Growth retardation is also influenced by secondary hyperparathyroidism.Setting the ideal PTH levels for kids at every stage of CKD is debatable, though. increased PTH values were linked to increased growth rates in moderate CKD in some research, but normal growth velocity was attained with PTH levels within the normal range in other studies [18,19]. In children on maintenance dialysis, PTH levels ≥100 pg/mL have been linked to growth failure and adynamic bone disease, suggesting that PTH levels should be managed in advanced chronic kidney disease [20]. Children with uremic syndrome frequently exhibit bone abnormalities as a result of altered skeletal remodeling. These can show up as genu valgum, slipped epiphyses, epiphyseal widening, and wrist and femoral abnormalities [21].Morbidity is also greatly increased by pathologic fractures, vertebral crush fractures, and avascular necrosis of the femoral head. The first line of treatment for skeletal malformations must involve normalizing serum levels of calcium, phosphorus, and PTH, followed by surgical correction if necessary once the biochemical anomalies have stabilized. In individuals with normal kidney function, the phosphaturic hormone FGF-23 is linked to osteomalacia, low serum 1,25(OH)D3 levels, and renal phosphate wasting. As renal disease worsens, FGF-23 levels rise, especially in patients on maintenance dialysis. In people with CKD stages 2 to 4, Yamazaki et al. [22] discovered that increased FGF-23 levels were associated with calcitriol insufficiency and that pre-treatment readings might indicate parathyroid gland resistance to vitamin D therapy.These results suggest that FGF-23 may be involved in the pathophysiology of secondary hyperparathyroidism as well as the metabolism of vitamin D and blood phosphorus [23, 24].The reproductive system is also damaged by CKD. The reproductive system's aberrant functioning is caused by a number of CKD-related conditions. Indeed, CKD is linked to decreased production of luteinizing hormone (LH) and decreased prolactin clearance, which leads to hyperprolactinemia [25]. Decreased testosterone production can result from both an increase in prolactin and a decrease in LH. Uremia can directly inhibit LH receptors in Leydig cells as chronic kidney disease (CKD) advances to a uremic condition, which hinders the generation of testosterone [26]. These changes result in hypogonadism and puberty delay in children with chronic kidney disease (CKD), which negatively impacts pubertal growth and may lower height of adults [27, 28]. Growth is negatively impacted by low calorie and protein

consumption. For children with CDK to have the best growth outcomes, calorie intake must be balanced. In order to do this, measurements of height standard deviation score (SDS), body mass index (BMI), transferrin, and albumin provide crucial information about the growth potential and nutritional health of kids with chronic kidney disease. A Korean study assessing the risk factors linked to low height has confirmed the significance of nutritional health for normal growth in patients with chronic kidney disease. According to the study, children with CKD had a significant frequency of underweight (14.1%) and short stature (23.4%), and underweight was found to be a modifiable risk factor for stunted growth [29].Additionally, research on rats has demonstrated that exogenous growth hormone improves lean body mass and calorie intake utilization [30]. Children with small height have been reported to have poor quality of life (QoL), particularly when they have transfusion-dependent β thalassemia, achondroplasia, or chronic renal illness.Despite the fact that it can be extremely burdensome for patients and their families, this aspect of CKD is frequently overlooked. It has been demonstrated that the strain on caretakers increases, especially for parents of small-framed children [31].

MANAGEMENT OF CHILDREN WITH GROWTH FAILURE AND CKD

Probably the most significant factor affecting growth and wellbeing is nutritional status. The methods for enhancing these kids' nutrition are shown in Table 2. Estimating the growth potential is crucial for the first growth evaluation. It is necessary to compute genetic target height (TH). Since adult height prediction algorithms have a tendency to overestimate adult height, they are often not recommended for use in CKD patients.Growth needs to be observed on a regular basis. It is advised to utilize established measurement methods, such as measuring the Frankfurt vertical plane using a wall-mounted stadiometer and measuring supine length with an infantometer prior to the age of two. Plotting height and weight on reference charts specific to age and sex from the same population should be done at six-month intervals. Since CKD may cause growth slowing in a patient with normal stature, it is important to carefully assess the rate of growth rather than stature. Growth is significantly reduced when the growth velocity falls below the 25th centile [27].Every potentially curable comorbidity that hinders growth needs to be carefully managed. This could eventually enhance rGH's effects.As soon as possible, especially in early children and infancy, nutritional interventions that are adapted to age, sex, and stage of chronic kidney disease (CKD) should be implemented in order to match caloric and protein intake with dietary reference intake requirements [32]. Oral bicarbonate preparations should be administered to treat metabolic acidosis and keep HCO3 levels above 23 mmol/L.Children with end-stage chronic kidney disease (CKD) typically see a marked improvement in growth after receiving kidney replacement therapy (KRT), which is accompanied by intense nutritional care and various dialysis modalities. For children with CKD and growth failure, KRT is the best treatment for catch-up growth, particularly when combined with immunosuppressants that spare corticosteroid use [33, 34].Clinical studies using steroid-sparing regimens such as calcineurin inhibitors and the antimetabolite mycophenolate mofetil have demonstrated better growth following KRT [35].

CLINICAL PRACTICE RECOMMENDATIONS

Regarding the use of rGH therapy in children with CKD and growth failure, there is no universal agreement. It is important to weigh the probable benefits of rGH therapy against any potential drawbacks and contraindications. Careful monitoring of calcium/phosphate metabolism is especially crucial because severe secondary hyperparathyroidism is linked to stunted growth and a higher incidence of slipping capital femoral epiphysis. Since rGH therapy may raise the risk of elevated intracranial pressure, fundoscopic examination is required to rule out the presence of pre-existing papilledema. Treatment is absolutely contraindicated for increasing heart hypertrophy and active known malignancies. Additionally, individuals with any acute, unstable, or severe conditions should not use rGH. It is necessary to assess the potential height increase benefit by analyzing the includes the assessment of pubertal state and the remaining potential for bone growth. Reduced or increased growth potential is indicated by advanced or delayed bone age and pubertal stage, respectively [27, 36]. In patients with CKD stages 3-5 who have growth failure (height velocity <25th centile for age and sex and height below the 3rd centile) that has persisted for more than three months in newborns and for more than six months in children and older patients, the 2019 Consensus Statement [27] suggests using rGH. However, height may gradually increase toward and below the third centile, as in children with CKD and a reasonably high genetic target; the Consensus Statements recommend rGH therapy in children and newborns with CKD stages 3–5, decrease in growth velocity, and between the third and tenth centiles in absolute height. rGH therapy before six months is not advised because to the paucity of safety data in very young infants. The Consensus advises waiting a year following KT for children who continue to have growth failure in order to monitor for eventual growth catch-up. If growth failure continues and steroid-free immunosuppressive medication is not an option, rGH therapy may be considered. Despite a little decrease in eGFR, patients with nephropathic cystinosis are more likely to experience growth failure, making them a unique illness. In this instance, the Consensus advises

initiating rGH therapy at any point during CKD when growth failure is evident.According to a recent summary of expert opinion, children with CKD should be treated regardless of eGFR if the underlying cause is not cystinosis but rather distal tubular acidosis, renal Fanconi syndrome, Bartter syndrome, or glomerular disease. Growth failure in CKD patients in their pubertal years is indicative of a specific circumstance. Starting GH therapy in these situations is advised only if bone aging is postponed by more than a year [37]. When administered regularly in the evening, the dose of rGH is between 0.045 to 0.5 mg/kg/day, which is more than what is typically utilized for individuals with GH deficiency [27]. Regular dosage adjustments should be made based on body weight and growth. The effectiveness and safety of the therapy must be routinely evaluated. It's critical to discontinue treatment and assess for intracranial hypertension if there is a prolonged headache or vomiting. The incidence of slipping capital femoral epiphysis may rise if GH medication is followed by rapid growth, particularly in CKD patients. Therapy must be stopped and a complete evaluation must be conducted if there is groin, inner thigh, or knee pain, as well as if a change in gait is noticed. Treatment should be continued until growth velocity drops below 2 cm/year (when additional bone growth is not anticipated) in the event of a positive growth response and the lack of side effects [27]. GH insufficiency is not the cause of growth failure in CKD, while relative GH and/or IGF1 insensitivity may be.Poor response to exogenous GH is therefore not uncommon. The criteria for stopping treatment in poor responders are not universally agreed upon. 52% of experts supported stopping rGH therapy if height velocity was less than 2 cm/year, citing the Summary of Expert Opinion [37]. Conversely, 32% of specialists supported the continuation of treatment if there were no clinical reasons why rGH should not be used. In this case, it is best to routinely weigh the benefits and drawbacks of rGH therapy, communicate with patients and their parents, and discuss any decisions to continue or discontinue treatment. Numerous studies have demonstrated the advantages of GH therapy for kids with stage 3–5 chronic kidney disease. The International Pediatric Peritoneal Dialysis Network has verified these findings [38]. Despite inadequate calorie intake, GH therapy was successful in improving weight and linear development in newborns receiving chronic peritoneal dialysis.This is especially significant because reaching a healthy weight is essential before receiving a kidney transplant [39]. In one study, the authors reported that adult height significantly increased in comparison to baseline height (Figure 1), demonstrating the effectiveness of the rGH treatment [40]. A meta-analysis of 16 randomized control trials (809 patients) in prepubertal children with severe, end-stage CKD and following kidney transplantation revealed that, following a year of treatment, patients on rGH had a better growth rate (+3.88 cm/year) and were taller (+0.91 SDS) than the untreated group. one [41]. According to estimates, the anticipated gain for boys and girls following two to five years of optimal treatment is 7.4 cm and 7 cm, respectively [27]. There is mixed evidence to support the use of rGH in pubertal patients. However, in most of them, a rise in adult height has been noted [42–44]. The use of rGH treatment is not common, despite clinical studies demonstrating that it has a good safety profile and promotes height gain in children with CKD from stage 3 to dialysis and transplantation.The lack of international consensus guidelines may be the cause of this. To determine the best course of treatment for each patient, a multidisciplinary approach to the management of children with CKD and growth failure is crucial.

CONCLUSIONS

More than thirty years ago, GH therapy was authorized for the treatment of low stature in children with chronic kidney disease.Even if the most recent recommendations advise rGH treatment for all kids with growth retardation and chronic kidney disease [27],7], there are still several unresolved questions about its use and actual effectiveness. The impact on adult height is erratic and inconsistent [37]. This is most likely because of the tremendous diversity of the patients. The etiology of CKD, its length, steroid treatment, diet, hormone resistance, and comorbidities are really some of the elements that contribute to the pathophysiology of short stature. Certain children may be more susceptible to some of these issues than others. Because of this, it has become necessary for these individuals to receive individualized care. There is ongoing debate on the ideal eGFR level for children older than one year with growth failure and chronic kidney disease prior to beginning rGH therapy. PTH levels ≥100 pg/mL are linked to growth failure in children receiving maintenance dialysis, which supports the idea that PTH levels in advanced CKD should be targeted [20]. The best level of PTH rGH therapy to start is still up for dispute, though. Last but not least, the choice of whether to begin or continue rGH therapy depends on the dosage of corticosteroid treatment, which should not interfere with rGH's ability to promote growth. Children who have had kidney transplants may also have a variety of other problems, many of which are specifically tied to the pre-transplant illness as well as any treatments and complications associated with the actual transplant. Every potential issue that could hinder growth should be promptly addressed and, if feasible, remedied using a patient-specific strategy. Children with residual growth potential may benefit from GH therapy in order to promote catch-up growth.

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T.T. and M.C. conceptualized and wrote; G.M.U. and C.B.

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Conflicts of Interest

Regarding this particular problem, the writers disclose no conflicts of interest.

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