REVIEW

Dialysis Strategies to Improve Growth in Children With Chronic Kidney Disease

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Despite major advances in the understanding and management of uremic growth failure, 35% to 50% of children with chronic kidney disease still grow up to become adults of small stature. The final adult height achieved is correlated with the height deficit recorded at the time of kidney transplantation. A degree of catch-up growth does occur after kidney transplantation in childhood, but it is often limited. Growth retardation in children with chronic kidney disease causes significant difficulties in their daily lives, often limiting psychosocial integration. Additionally, growth retardation is associated with a greater number of hospital admissions and an increased risk of mortality. Growth failure is the common endpoint of a variety of pathologies, including growth hormone resistance. In children on chronic dialysis, linear growth may be improved by ensuring that optimal clinical care is provided. This includes maximizing nutritional support (e.g., tube feeding in cases of anorexia) so as to prevent malnutrition. Further management options include the administration of recombinant human growth hormone (rhGH) treatment and the use of more frequent and intensive dialysis sessions, such as daily on-line hemodiafiltration, which combines increased dialysis convective flow with ultrapure dialysate, to limit cachexia.

DESPITE MAJOR ADVANCES in the understanding and management of uremic growth failure, 35% to 50% of children with chronic kidney disease (CKD) still grow up to become adults of small stature, with a final height of 2 standard deviation scores (SDS) below the adult mean, as well as below their familial target height.[1–4] At the time of kidney transplantation, children with CKD are significantly shorter than their peers. Despite satisfactory graft function, spontaneous catch-up growth is often insufficient, and the final adult height achieved is correlated with the height deficit recorded at the time of kidney transplantation.[5]

Evaluation after 6 and 12 months of dialysis has demonstrated little or no improvement in height SDS during the dialysis period in children aged >2 years (for both hemodialysis [HD] and peritoneal dialysis). Moreover, with conventional dialysis regimes, there is often a loss in height SDS that can be correlated to the duration of dialysis, with a mean loss of 0.4 to 0.8 height SDS per year.[6] The growth retardation, which occurs over the dialysis treatment period, should be limited as much as possible because it is well known that there is rarely a significant change in height SDS after transplantation in the age groups of 6 to 12 and >13 years.[2]

Growth retardation in children with CKD causes significant difficulties in their daily lives, often limiting psychosocial integration. Poor growth in children with CKD is associated with an increased risk of hospital admission and mortality, with a 14% increased risk of death with each unit decrease in height SDS.[7] For a height SDS of <2.5, the risk of mortality is doubled.[8]

Growth failure is the common endpoint of a variety of pathologies (Table 1) associated with CKD.[9] Protein-energy malnutrition is an important cause of impaired growth, particularly in infants and young children. It comprises both malnutrition and cachexia (loss of protein stores),

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Table 1. Factors Causing Growth Retardation in Children With CKD

Age at onset of CKD, in younger age groups, the magnitude of both growth retardation and catch-up capacity is greater
Primary renal disease, for example, difficulties caused by the obligatory loss of salt and water in renal dysplasia (infants)
Acidosis, fluid, and electrolyte abnormalities (volume overload or excessive losses)
Decreased nutrient intake because of anorexia and vomiting, reduced appetite (dietary restrictions, multiple medications often given with meals, preference for water in polyuric children, abnormal sense of taste, gastroesophageal reflux, and delayed gastric emptying, filled abdomen in cases of peritoneal dialysis…): all are factors leading to malnutrition
Increased nutrient losses (dialysis procedure, peritonitis, sepsis)
Increased nutritional needs (inflammation, acidosis, volume overload, uremic toxin retention, i.e., inadequate dialysis): all are factors leading to cachexia
Bone disease: osteodystrophy (hyperparathyroidism, adynamic bone)
Disruption of the GH/IGF axis:
Growth hormone resistance: reduction in IGF-1 production
Increase in GH levels (reduction in renal excretion and increment in pulsatile GH secretion)
Reduced number of GH receptors
Reduction in transcription of IGF-1 gene expression with inhibition of JAK2/STAT5 transduction signaling, probably because of upregulation of the suppressor of the cytokine signaling family
IGF-1 resistance: reduction in free (bioavailable) IGF-1
IGFBPs levels are increased
Reduced IGF transduction (proinflammatory cytokines, metabolic acidosis)
Increased proteolysis of IGFBP resulting in fragments with an increased affinity for IGF-1
Genetic potential as determined by mid-parental height
Comorbidities that influence feeding and growth according to their capabilities

CKD, chronic kidney disease; GH/IGF, growth hormone insulin-like growth factor axis; GH, growth hormone; IGF-1, insulin-like growth factor 1; IGFBP, IGF binding protein.

which are important as malnutrition alone implies that adequate dietary supplementation could be curative.[10]

Muscle wasting in CKD occurs partly as a result of decreased nutrient intake because of anorexia; however, other contributing factors include the activation of the proteasome-ubiquitine pathway[11] and resistance to endogenous growth hormone (GH).[12] These processes are favored in states of chronic inflammation, metabolic acidosis, volume overload, and retention of uremic toxin.

There are various factors that may disrupt the growth hormone insulin-like growth factor (GH/IGF) axis[2,9] including GH resistance, IGF resistance, and impairment of the post GH receptor intracellular signaling process (JAK2/STAT5). The latter is probably because of upregulation of intracellular proteins that suppress the cytokine signaling family. These regulatory proteins are induced during inflammatory processes.

Therefore, growth could be used as a measurable parameter to assess the optimal balance between nutrition (both malnutrition and cachexia) and adequacy of dialysis in children.

The standard dialysis program used in children on chronic HD (4 hour sessions, thrice a week) is not sufficient to allow for normal growth; therefore, the option of increasing the frequency of and

Table 2. Etiology and Treatment of Growth Retardation in Young Children: Specific to Hemodialysis

Consider malnutrition and factors promoting cachexia (inflammation, acidosis, uremic toxins retention)
Diagnose and treat volume overload (angiotensin II and inflammation)
Provide an adequate dialysis dose, not limited solely to urea
On-line hemodiafiltration is superior to conventional hemodialysis (increased blood purification and use of endotoxins-free dialysate)
Apply a convective dialysis dose (convective flow) to ensure clearance of middle molecular uremic toxins
Verify the purity of dialysate, not only germ-free but also endotoxin-free, to reduce inflammation (backfiltration)
Consider more frequent and more intensive hemodialysis, not just as a rescue therapy. The treatment of choice is in-centre daily on-line hemodiafiltration, which provides "the optimum stimulus package" (blood purification capacity, purity of the dialysate, unrestricted diet)

Table 3. Etiology and Treatment of Growth Retardation in Young Children: Specific to Peritoneal Dialysis

Consider malnutrition and other factors promoting cachexia (inflammation, acidosis, uremic toxins retention)
Diagnose and treat volume overload (angiotensin II and inflammation)
Avoid alkalosis/acidosis and hyponatremia
Risk of protein loss in the dialysate, especially during episodes of peritonitis (consider use of amino acid based dialysate), or in case of an hyperpermeable exchange (adapt fill volume in mL/m^2)
Risk of a full abdomen (a factor of anorexia): prefer dry "day" in cases of APD, avoid too high intraperitoneal pressures (measure the IPP, an objective control of the amount of fill volume)
Provide adequate dialysis, not just limited to urea dialysis removal

APD, automated peritoneal dialysis; IPP, intraperitoneal pressure.

using more intensive HD was proposed.[10,13] By performing daily on-line hemodiafiltration (D-OL-HDF), catch-up growth was achieved in children on chronic dialysis.[14] The effect D-OL-HDF has on catch-up growth appears to be multifactorial. First, it results in less resistance to GH, possibly because of the fact that it provides an "optimum stimulus package,"[9] which includes dialysis modality, that is, OL-HDF (high convective dialysis flow and use of ultrapure dialysate); dialysis time and frequency, that is, dialysis on 6 days a week for 3 hours; and finally, the absence of malnutrition as a result of unrestricted diet, good appetite, and less protein wasting, that is, less cachexia. With the use of ultrapure dialysate, OL-HDF seems to be the optimal procedure for HD, at least in terms of uremic toxin removal and reduced inflammation, which are factors that potentially limit uremic protein wasting. Moreover, D-OL-HDF also allows for[14] optimal control of metabolic acidosis (an additional factor which promotes cachexia). In patients receiving D-OL-HDF, before and after dialysis bicarbonate levels have been found to be within the normal range, both during and between dialysis sessions. This is beneficial because it means that the acidosis–alkalosis wave, which usually occurs with conventional thrice a week HD, can be avoided.

In children on chronic dialysis (Tables 2 and 3), linear growth may be improved by offering a range of treatment including:

- Optimal nutrition, supported by tube feeding, in cases of anorexia.[15]
- Avoidance of cachexia, by taking into account the detrimental effects caused by acidosis, inflammation, uremic toxin retention, and volume overload.
- Administration of recombinant human growth hormone (rhGH) to compensate for resistance to the GH/IGF axis.
- More frequent and more intensive dialysis sessions, increasing convective flow, and using ultrapure dialysate, that is, daily on-line hemodiafiltration.
- Paying careful attention so as to not neglect the child's educational, developmental, and social needs.

In-center daily OL-HDF, the "complete treatment package,"[9] requires a multidisciplinary team approach, involving not only nurses and doctors, but also dieticians, social workers, and teachers, regardless of the financial costs involved.[13,14]

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