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Growth in children on renal replacement therapy: a shrinking problem?

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Abstract

Growth failure has been almost inextricably linked with chronic kidney disease (CKD) and end-stage renal disease (ESRD) since initial reports of renal dwarfism dating back to the turn of the 20th century. Growth failure in CKD has been associated with both increased morbidity and mortality. Growth failure in the setting of kidney disease is multifactorial, and is related to poor nutritional status as well as co-morbidities such as anemia, bone and mineral disorders, and alterations in hormonal responses, as well as to aspects of treatment such as steroid exposure. In this issue of *Pediatric Nephrology*, Franke et al report on the gains made in growth and maturation in pediatric patients with ESRD in recent decades, particularly in Germany. Through advances in the care of CKD and ESRD over recent decades, the prevalence of growth failure appears to be decreasing. These findings, along with a recent report demonstrating decreases in mortality in childhood ESRD in the United States Renal Data System (USRDS), suggest overall improvements in the outcomes of care, perhaps reflecting improvements in the quality of care for children with kidney disease worldwide.

Keywords

Growth; Chronic Kidney Disease; Dialysis; Transplantation; CKD-MBD

Historical perspective

Growth failure has long been recognized in children with chronic kidney disease (CKD). Short stature in children with CKD was first described in 1897 [1], and publications dating to the early 1900s described cases of “renal infantilism” or “renal dwarfism” [2,3]. Through the 1920s, physicians continued to characterize the physiologic changes in children with growth failure and bone deformities as a result of renal disease. By 1927, British physician Leonard Parsons published results of his investigations of children with “renal rickets,” and presented his conclusions about the physiologic basis for these changes [4]. He postulated that “the primary cause of renal rickets is the inability of the kidney properly to excrete phosphate”. He recognized a possible role for parathyroid hormone, theorizing that “there is a washing out of calcium from bones” in order to maintain serum calcium and prevent tetany. He recognized the high prevalence of acidosis in these children and its role in mobilizing calcium from bones. He also reported that, in contrast to other forms of rickets, renal rickets did not respond to treatment with ultraviolet irradiation.

In the 1950s, West and Smith [5] noted that, even in the absence of overt rickets, children with renal disease frequently suffered from growth retardation. They concluded that the

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most significant factors contributing to growth retardation were chronic acidosis and inadequate caloric intake, and hypothesized that endocrine abnormalities could also play a role. By mid-century, growth problems in children with CKD had become well recognized, but it was not until the advent of renal replacement therapy (RRT) in the late 1960s, however, that clinicians started to examine interventions to improve patients' growth [6-8].

By the late 1970s, the availability of RRT had allowed many children with end-stage kidney disease to survive to adulthood. However, the final height achieved by these patients remained far below normal. In 1994, Hokken-Koelega et al reported the results of a 20-year retrospective of patients who had received renal transplants before 15 years of age. As they stated, final heights in these patients “surpassed [their] worst expectations” – in their cohort, 77% of males and 71% of females had a final height below the third percentile [height standard deviation score (SDS) < -1.88)] [9].

In more recent times, the association of growth failure with poor clinical outcomes in children with ESRD has been well documented. Short stature at dialysis initiation has been shown in the North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS) registry to be associated with a higher risk of hospitalization and death [10]. Similarly, analyses of children on RRT in the USRDS have shown that decreased height and growth velocity are associated with an increased risk of both hospitalization and death [11,12].

In this issue of Pediatric Nephrology, Franke et al report on the gains made in growth and maturation in pediatric patients on RRT in recent decades [13]. They compare data from the European Dialysis and Transplant Association (EDTA), which spanned an observation period from 1985-1988, with data from a German study from Hannover and Berlin, spanning the years 1998-2009. They report that the mean height SDS improved in those 20 years from -3.04 in the EDTA registry to -1.80 in the Hannover/Berlin registry. In addition to overall improvements in mean height, the authors demonstrate earlier age at onset of puberty and age at menarche, as well as a clear improvement in pubertal growth over the last 2 decades.

Improvements in growth over recent decades have also been documented by other groups. For example, in 2010, Fine et al reported on their analysis of 20 years of data from the NAPRTCS registry [10]. In this registry, height SDS at the time of transplant improved from -2.4 in 1987 to -1.4 in 2007. Final adult height SDS for patients transplanted at age >12 years improved from -1.75 in the 1987-1991 era to -0.92 in the 2002-2008 era.

While the exact numbers and patient characteristics differ between these two studies, both studies illustrate what seems to be a clear trend towards improvement in growth over recent decades. Improvements in treatment for a number of factors contributing to poor growth in children on RRT over the last decades may explain the improved growth documented in these registries. Franke et al point out the remarkably increased rate of living-related transplantations today compared with the late 1980s, as well as the increase in pre-emptive transplants by almost 3 fold since that time. Use of steroid-avoidance or early steroid withdrawal protocols has become more common; Fine et al reported a decrease in steroid use of almost 20% over the last 20 years [10].

While this study by Franke et al could not examine the contribution of specific factors to improvements in growth over the last 20 years, they do point to secular trends in the care of CKD and related co-morbidities, including specialized care in pediatric nephrology centers, that may contribute to improvements in growth. Poor nutrition, anemia of CKD, CKD-associated mineral and bone disorders (CKD-MBD), acidosis, alterations in the growth hormone/insulin-like growth factor (GH/IGF) axis, and exposure to steroids have all been linked with growth failure in CKD, and management of each of these has improved over

time. Indeed, a recent report by Mitsnefes et al [14] demonstrates significant decreases in mortality in childhood ESRD in the USRDS over the last 20 years, likely reflecting overall improvements in quality of care.

Nutrition

Increased recognition of the importance of optimizing nutritional intake may be one of the factors leading to improved growth of patients on RRT in the last 20 years. Inadequate nutritional intake is common in infants and children with CKD and ESRD, and mean caloric intake has been reported to range from 62-85% of recommended dietary allowance (RDA) [6,15,16]. Supplementation to achieve caloric intake of at least 100% of RDA has been shown to result in improved linear growth rates, particularly in infants [17,18]. Although Franke et al in this analysis could not directly assess changes in nutrition prescription over time, treatment guidelines over the last decade have standardized the approach to nutritional recommendations in children with CKD.

Anemia of CKD

Severe anemia (defined as Hgb < 10 g/dL) has been shown to be associated with short stature in pediatric renal transplant recipients [19] and the early use of erythropoietin has been associated with improved catch-up growth [20]. In the last 20 years, there have been clear trends towards greater use of erythropoietin in children with CKD. As Franke et al report in this issue, their EDTA cohort from 20 years ago showed a high prevalence of anemia and low rate of erythropoietin use (19-34%), while the more recent Hannover/Berlin cohort had near-universal erythropoietin use.

CKD-MBD

From the first descriptions of “renal rickets” in the early 20th century, renal bone disease (renal osteodystrophy) has been well known to be associated with growth failure through both secondary hyperparathyroidism or alternatively low levels of parathyroid hormone (PTH) associated with low bone turnover and adynamic bone disease [21,22]. Despite significant advances in our understanding of the pathophysiology of CKD-MBD, such as the role of phosphaturic hormone fibroblast growth factor 23 (FGF23), CKD-MBD remains prevalent and optimal clinical care remains controversial. Unfortunately the study by Franke et al could not assess changes in the treatment of CKD-MBD in the control of hyperphosphatemia or secondary hyperparathyroidism that may have contributed to improvements over time. Similarly, we can only assume that recognition of the role of aluminum accumulation in causing the osteomalacia subtype of renal osteodystrophy has contributed to efforts to decrease aluminum exposure and thus to improvements in growth [23].

Growth hormone/insulin-like growth factor (GH/IGF) axis

The increasingly widespread use of growth hormone therapy in ESRD over the last 3 decades may be one of the most important contributors to overall improvements in height and maturation. Although children with CKD have normal to high levels of circulating growth hormone (GH), they have impaired sensitivity to the actions of GH. This is related to decreased tissue expression of the GH receptor [24], abnormalities in post-GH-receptor signaling [25] and decreased bioactivity of insulin-like growth factor I (IGF-I) due to an excess of circulating IGF binding proteins (IGFBPs) [26]. Children with CKD treated with recombinant human GH (rhGH) demonstrate significant improvements in growth velocity and final adult height [27]. However, rhGH remains underutilized in children with CKD and on RRT in many areas. In the 2008 NAPRTCS registry annual report, for example, among pre-pubertal children with CKD and height SDS < -1.88, only about 20% were on rhGH

[28]. In the current study by Franke et al, they report rhGH use in more than one third of their recent Hannover/Berlin cohort, which may be an important contributor to the growth improvements they observed compared to the EDTA cohort from 20 years ago.

Conclusion

While growth failure remains a problem in children with CKD and on RRT, advances in the care of CKD-associated co-morbidities are leading to improved growth outcomes, as evidenced by the analyses of Franke et al. Similarly, overall decreasing trends in mortality seem to parallel these findings. Through further research into the pathophysiologic processes underlying growth failure, and improved early recognition and treatment of growth failure, there is hope that this problem will truly become a thing of the past.

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