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REVIEW

Nutritional management and growth in children with chronic kidney disease

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Abstract Despite continuing improvements in our understanding of the causes of poor growth in chronic kidney disease, many unanswered questions remain: why do some patients maintain a good appetite whereas others have profound anorexia at a similar level of renal function? Why do some, but not all, patients respond to increased nutritional intake? Is feed delivery by gastrostomy superior to oral and nasogastric routes? Do children who are no longer in the 'infancy' stage of growth benefit from enteral feeding? Do patients with protein energy wasting benefit from increased nutritional input? How do we prevent obesity, which is becoming so prevalent in the developed world? This review will address these issues.

Keywords Growth · Gastrostomy · Diet · Dialysis · Height · Obesity · Chronic kidney disease · Progression

Introduction

The relationship between chronic kidney disease (CKD), reduced dietary intake and growth has been recognised for many years. In a seminal paper in 1974, Betts and Magrath studied the growth pattern and dietary intake of 33 children with varying degrees of CKD and identified then the principles that we now take for granted, namely that: growth in CKD is most severely affected in infants; a reduction in growth velocity may occur once the glomerular filtration rate (GFR) falls below 25 ml/min/1.73 m^2; there is a decrease in the energy, protein and vitamin D intakes in children with CKD compared with those recommended for their age, and of energy intake compared with that of normal children of their own height; reduced growth velocity occurs when the energy intake falls below 80 % of that recommended; the decrease in the intake of energy and nutrients in these children may in part be responsible for their growth retardation [1]. It is interesting to reflect on how far we have advanced since that time. This review will discuss the questions that remain unanswered in the management of nutrition in children with CKD.

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Epidemiology of growth

Conservatively managed CKD

Most descriptions of growth patterns in children with CKD are in the dialysis and transplant populations, primarily because the majority of the large registries concentrate on data collection from these relatively well-defined groups. However, it has to be remembered that large databases are based on voluntary reporting and, therefore, reporting bias may exist. The principal registry providing data on growth in children with conservatively managed CKD is the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). In their 2006 report [2] the findings by Betts [1] were confirmed: of 5,615 children with a GFR of <75 ml/min/1.73 m^2 over 10 years between 1994 and 2004, the most growth retarded were the youngest children (Table 1), but mean height standard deviation score (HtSDS) was reduced at all ages, with 37 % overall being less than −1.88 standard deviation score (SDS). Also as predicted, HtSDS worsened with progression of CKD, such that the NAPRTCS study was able to identify a strong association between GFR and HtSDS ($p<0.001$) (Table 2).

It might be expected that over the years there would have been an improvement in the HtSDS for children entering renal replacement therapy (RRT) programmes. Reports of the successful use of nasogastric feeding in children with

Table 1 Effect of age on height standard deviation score in 5,165 children with a glomerular filtration rate of <75 ml/min/1.73 m^2 [2]

HtSDS, Height standard deviation score

Age (years)	Mean HtSDS
0–2	−2.3
2–6	−1.7
6–12	−1.4
>12	−1.0

CKD began in the 1980s, and even these early studies demonstrated benefits to growth [3–5]. The subsequent use of gastrostomies [6], which may be superior to nasogastric tubes due to a reduction in vomiting events, and newer feed supplements and treatments for anaemia, a better understanding of the effects of acidosis and renal bone disease on growth and the use of recombinant human growth hormone (rhGH) should have improved things even further. However, it is only in the youngest children that an improvement in growth over the years has been demonstrated: those who started dialysis at <18 months of age between 1983 and 1995 had a HtSDS of −3.0 compared to −1.4 between 1996 and 2008 [7]. Part of the reason why any improvement may be difficult to demonstrate can be explained by the changing epidemiology of the patient population: most centres are now accepting challenging patients that would not have been treated at the inception in the early 1980s of RRT programmes for children; for example, infants, including those who may be premature or small-for-dates, and children with syndromes and comorbidities that may affect growth in their own right, now represent a large proportion of children on RRT in the developed world [8–10]. What this means is that many children, and particularly the very young, are already short at the time of entry to RRT programmes. NAPRTCS data for 2005 found that the mean HtSDS at the start of dialysis in 3,910 children was −1.66, i.e. well below that of the normal population [11].

Dialysis

Comparable to NAPRTCS, the United States Renal Data System (USRDS) collects data on patients on RRT programmes in the USA. Its 2007 report shows that the height and weight of approximately half of children on dialysis were below the 20th centile for the normal population [12]. The International Pediatric Peritoneal Dialysis Network (IPPN) collects data from more than 1,800 children on peritoneal dialysis (PD) from around the world and is, therefore, able to provide comparisons of all aspects of PD according to region in the largest cohort of children to date. Currently, the mean HtSDS at commencing PD is −2.35 SD, which is below normal worldwide, but there is a large variation, ranging in 21 countries from −1.3 in the UK, to −3.5 in Brazil. The mean body mass index (BMI) SDS is −0.01 and does not parallel the HtSDS; however, it shows less variation from normal. BMI has a wide range throughout the world, varying from a high incidence of obesity in the USA, where the mean BMI SDS is 0.8, to malnutrition, with the lowest BMI being in India, where it is −1.4 [13]. Regional variations in resources are likely to contribute to these differences [14]. The British Association for Paediatric Nephrology (BAPN) reports that in 2006, of 105 dialysis patients, 61 % were below the tenth centile and 44 % below the second centile [15].

Table 2 Effect of glomerular filtration rate (GFR) on height standard deviation score (HtSDS) in 5,165 children with a GFR of <75 ml/min/1.73 m^2 [2]

GFR (ml/min/1.73 m^2)	HtSDS
0–10	−3.1
10–25	−1.9
25–50	−1.5
>50	−0.9

Registry data on longitudinal growth on dialysis are available from NAPRTCS, the IPPN and the BAPN. The NAPRTCS (2006) reports a decrease in HtSDS from −1.64 to −1.71 after 1 year and −1.84 after 2 years [16], and in the 2011 report, the mean HtSDS of 3,292 children commencing chronic PD was −1.71; this was −1.77 after 2 years in 781 children still receiving PD [17]. The weight (Wt) deficit was not as bad as the height deficit, with a mean of −1.13 SD. Younger children and those with the lowest body mass index standard deviation score (BMISDS) were most likely to have an increase in their weight standard deviation score (WtSDS). Of 407 haemodialysis (HD) patients, the mean change in HtSDS/year was −0.10. Growth retardation was most pronounced in patients who were young, male, had longer durations on HD and higher normalised protein catabolic rate and baseline HtSDS [18]. Patients in the IPPN show a decrease in HtSDS that correlates with time on PD [13]. In the UK between 1999 and 2008, HtSDS has remained remarkably stable, at a median of −1.4 to −1.9 SD. Weight too has remained stable, at −0.9 to −1.6 SD [19].

There is no evidence that growth differs with dialysis modality. NAPRTCS compared HD with PD over 2 years.

Table 3 Change in height standard deviation score (HtSDS) from the start of dialysis[a]

Time from the start of dialysis	Peritoneal dialysis		Haemodialysis	
	n	HtSDS	*n*	HtSDS
After 1 year	1,320	−0.04	573	−0.14
After 2 years	525	−0.09	276	−0.43

n, Number of paediatric patients

[a] Source of data: North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS 2006) [16]

Table 4 Age and height standard deviation score (HtSDS) at transplant and 3 years post-transplant [11]

Age at transplant (years)	HtSDS at transplant	HtSDS at 3 years post-transplant
0–1	−2.06	−1.86
2–5	−2.37	−1.95
5–12	−2.09	−2.16
13–17	−1.49	−1.76
>17	−1.86	−2.01

Although the decline in HtSDS was greater in the children on HD, this did not reach statistical significance [16] (Table 3).

Post transplant

The NAPRTCS database for 2005 describes the mean HtSDS at transplant and over the next 3 years according to age [11]. These data demonstrate the importance of height achievement before transplant, because only the youngest children showed any improvement in growth post transplant (Table 4).

NAPRTCS data also suggest that HtSDS at the time of transplant has improved over the years, from a mean HtSDS of −2.4 in 1987 to −1.4 in 2007 (Table 5) [20]. UK data, however, are not so positive: between 1999 and 2008, HtSDS has remained remarkably stable, at a median of −1.2 to −1.4. Weight too has remained stable, at a mean SDS of around 0 [19].

Comparison of heights of dialysis and transplant patients

Figure 1 shows the distribution of heights in 2005 in the UK dialysis population compared to those with renal transplants. The cumulative frequency distribution of height in 273 patients with a functioning allograft for at least 1 year and between 2 and 16 years of age at the time is shown together with the data from 105 dialysis patients. Although the transplant patients are taller than those on dialysis, both groups are well below the normal range. As well having a reduced overall mean, some children were very small. For the transplant patients, 48 % were below the tenth centile with 39 % being below the fifth centile and 27 % below the second centile. The corresponding figures for dialysis patients were 61 % below the tenth centile, 54 % below the fifth centile and 44 % below the second centile [15].

Final height

Most reports of final heights do not discriminate according to the patient characteristics. For example, registries do not separate out children with co morbidities that affect growth. Also, inevitably, they reflect treatment that commenced 20 years previously in many cases. They also include a mixture of patients in CKD stage 5 from birth and those who are already well grown before they develop CKD in later childhood. Patients may have been managed with dialysis, transplant or, most likely, both. With this in mind, mean final heights vary from 148 to 158 cm for females and 162 to 168 cm for males (second centiles 151 and 163 cm, respectively [8, 21–23]. There is evidence that over the years, final height post transplantation is improving (Table 5) [20]. This is likely to be due to a combination of factors, such as an improvement in the growth attained pre-transplant, pre-emptive transplantation (thus avoiding dialysis) and the development of protocols that minimise the use of corticosteroids.

Why do some patients maintain a good appetite whereas others have profound anorexia at a similar level of renal function?

This is a question for which there is no answer at present. Anorexia and vomiting are well recognised as features of infant CKD, and the benefits of enteral feeding are best established in this age group. There is a clinical impression that infants with severe CKD do not establish an appetite until they have undergone renal transplantation. However, in the older age group it remains a mystery as to why some children continue to eat and others do not. Logically, correction of ketosis, the acid–base balance and anaemia should help to restore appetite, and all clinicians have seen

Table 5 Mean height standard deviation score (HtSDS) of those patients over the age of 19 years who received transplants at different ages during different eras[a]

Age at transplantation (years)	Transplantation era			
	1987–1991	1992–1996	1997–2001	2002–2008
>12	−1.75	−1.31	−0.99	−0.92
6–12	−2.06	−1.81	−1.63	
2–5	−1.42	−1.20		

[a] Data are used with permission from Fine at al. [20]

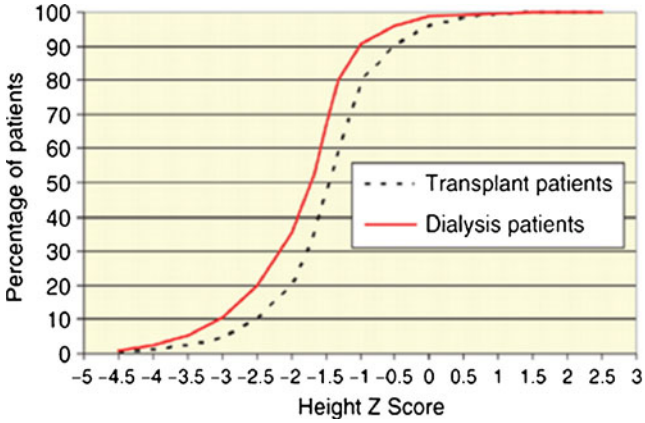

Fig. 1 Distribution of the height standard deviation score (HtSDS) in children on dialysis and post transplant (used with permission from Lewis et al. [15])

children who gain weight after the start of treatment for undiagnosed CKD. However, not surprisingly, there are no reports in the literature of this rather difficult-to-measure phenomenon. We do know, however, that taste sensation is reduced early in CKD and worsens as CKD progresses in some patients [24]. Other factors affecting appetite include the requirement for multiple medications, the high fluid requirement in the polyuric child and elevated circulating cytokines, such as leptin [25], tumour necrosis factor-gamma (TNF-α) and interleukin (IL)-1 and −6, which act through the hypothalamus to affect appetite and satiety [26]. Vomiting may result from gastro-oesophageal reflux and delayed gastric emptying in association with a decreased clearance of polypeptide hormones, and during PD, it may arise from raised intra-abdominal pressure [6]. Insufficient dietary intake may be due to episodes of fasting surrounding surgical procedures and episodes of sepsis. Some of these children may respond to prokinetic agents [14, 27]. Many children with CKD have associated comorbidities that influence feeding (and growth) in their own right [14].

Why do some but not all patients respond to increased nutritional intake?

There are many influences on nutrition and growth, some of which are potentially remediable and others of which are not.

Irremediable factors

Birth weight and gestation

Several studies have shown that both prematurity and low birth weight are common in young children with CKD. In one study, the incidence of prematurity was 26 % in 101 infants with CKD 4/5, with 18 being small for gestational age and 10 of these being preterm and SGA, with a mean HtSDS of −0.42 at birth [8]. Figures from the Chronic Kidney Disease in Children (CKiD) prospective cohort study are similar, even for children with a mean GFR of 43 ml/min/1.73 m^2, being 12, 14 and 17 %, respectively. The incidence of requirement for neonatal intensive care was 40 % [10]. Infants in the IPPN database had a mean length at birth of −0.47SD [28]; this was −0.69 in Finnish infants requiring PD in infancy [29]. The comparable overall incidence of abnormal birth history in the U.S. population is 7–8 %. Although many otherwise normal infants born prematurely grow normally, many of those who are also SGA remain below the normal range for height into adulthood [10]. In the CKiD study, it was possible to demonstrate a negative effect of low birth weight and SGA on subsequent growth in children with CKD, such that those born with a birth weight of <2.5 kg, or a birth weight below the tenth centile, were significantly short in later childhood. It is recognised that in otherwise normal infants who are SGA, most of the catch-up occurs in the first 6 months of life [10]. This is just the time when infants with severe CKD are at their most vulnerable to nutritional deficiencies, and loss of height has been reported to be as high as 2 SD in the first 6 months of life [30].

Comorbidity

The incidence of comorbidity has been reported to be as high as 50 % in infant studies and 30 % in older children on dialysis [31, 32]. These can be syndromes and major comorbidities in other organs that can affect both nutritional intake and growth in their own right. In some registry data this effect is not well-captured. In one study, children with CKD 4/5 in the first 2 years of life were categorized according to the presence or absence of comorbidity. Those without comorbidity were found to have a normal length at birth, superior growth throughout childhood and a final height that is within the normal range [8].

Potentially remediable factors

Residual renal function

Residual renal function (RRF) increases clearance and growth. In one paediatric patient cohort, HtSDS improved from −1.78 to −1.64 over 1 year of PD in 12 patients with RRF but declined from −1.37 to −1.90 in 12 patients without RRF. The weekly Kt/V was not different among the two groups of patients, and only the native kidney Kt/V and creatinine clearance correlated with growth, suggesting that clearance obtained by PD cannot be equated with that obtained by native kidneys. In 11 of 20 patients on PD with a minimum Kt/V of 2.1 and daily protein intake of 3.25 g/kg/

day, the HtSDS improved from −2.3 to 0.55, while in the other nine patients with a Kt/V of <2.1, the HtSDS declined by −0.50. Variables affecting growth were nitrogen balance and residual Kt/V [27]. A retrospective analysis of 30 children on chronic HD showed that RRF positively affected nutrition independently of HD efficiency and rhGH treatment [33]. These results reinforce National Kidney Foundation Disease Outcomes Quality Initiative (NKF/DOQI) guidelines which suggest that avoidance of nephrotoxic agents and the use of biocompatible dialysis fluids which may help preserve RRF, may be of benefit for an improvement in nutritional status

Late referral

Early referral to a paediatric nephrology centre, followed by careful management, is important in the prevention of growth deterioration. It has been recognised for many years that the loss of HtSDS in the first 6 months of life can be as high as 2 SD [30]. Subsequent studies have verified this phenomenon: the loss of HtSDS from birth to onset of PD was −0.6 in a study on Finnish infants [29], −1.2 in the IPPN infant database [28] and −2.0 in UK infants [8]. Although infants are particularly likely to be affected because of their very rapid rate of growth, it is not just this age group which is affected by late referral or intensification of therapy: late referral has been shown to be associated with a BMI of less than the tenth centile more often than early referral, even in older children [34].

Sodium wasting

Requirements for sodium vary according to the type of CKD. With renal dysplasia there can be large obligatory urinary losses of salt and water (as well as bicarbonate). Such children may become chronically salt- and water-depleted. This can be expressed as failure to gain weight adequately despite good nutritional intake, and without sodium and water supplementation, the growth of these children will be impaired. An improvement in the HtSDS of as much as 1.8 SD over 2 years has been reported in 24 infants with polyuric CKD who received feeds supplemented with up to 4 mmol/100 ml sodium chloride or bicarbonate; this improvement in the HtSDS was significantly different to that of the controls [35].

Acidosis

Acidosis can occur as early as CKD stage 2 in young children with renal dysplasia, which has a dominant tubular component. It is common in all causes of CKD when the GFR falls below 25 ml/min/1.73 m^2 and is seen more often in children than adults because of the consumption of base due to the growth of bone and other tissues. As well as its effects on bone metabolism, acidosis causes increased muscle breakdown over synthesis, and the administration of base to patients on dialysis decreases protein degradation and urea generation [36]. Hypoalbuminaemia is also correlated with acidosis and improves with treatment [37].

Even moderate acidosis has been associated with poor growth. Animal studies suggest that the effect of acidosis on growth may be due to inhibition of the secretion of GH, or its action on peripheral tissues [36]. The KDOQI recommends raising the serum HCO^{3-} to ≥22 mmol/l. Of 430 children in the CKiD study, with a median age of 11 years and GFR of 45 ml/min/1.73 m^2, the median HtSDS and WtSDS were −0.70 and −0.08, respectively. When the children were categorized according to serum CO_2, those with a level of≥22 mEq/l compared to <18 mEq/l had a HtSDS that was on average 0.56 SD higher, although the WtSDS was similar (N. Rodig, personal communication, April 2012). However, there are no controlled studies of the benefits of correction of acidosis on growth.

Other haematological and biochemical factors

Owing to the multifactorial nature of growth failure in CKD, It is always difficult to separate out the relative importance of each of the different causes, particularly as poor management, for whatever reason, is likely to affect all aspects of care. Anaemia is one example, where, although intuitively it might be expected to interfere with growth, only registry data, with large numbers of children would be able to demonstrate such effects. The NAPRTCS CKD database identified that a haematocrit below 33 % was an independent risk factor for short stature [2], and treating anaemia early does seem to be associated with an improvement in growth [38]. Another aspect of nutritional care with potential effects on growth is calcium, phosphate and vitamin D management. Severe hyperparathyroidism is associated with impaired growth [39], and growth can be normal with parathyroid hormone levels within the normal range, even in children on dialysis [40].

Inadequate and prolonged dialysis

It would seem logical that inadequate dialysis would impair appetite, nutrition and growth, but the optimum dialysis dose to overcome this (and other dialysis-related morbidities) is unknown. Over 60 % of 21 children on continuous cycling PD (10 children aged <5 years and 11 aged >5 years) showed catch-up growth when the Kt/V was maintained at over 3, and they grew significantly better than historical controls with a mean Kt/V of 1.7. This group of children was also under careful nutritional management [41]. Catch-up in children under 2 years of age on PD has also been reported from our centre [42]. There is concern that

increasing Kt/V might increase albumin losses in the peritoneal dialysate, resulting in worsening malnutrition. One non-interventional study of 30 children did show an inverse correlation between Kt/V and albumin, particularly if the former rose above 2.75 [43]. However, increasing the Kt/V from 2.0 to 2.5 by adding a daytime dwell of icodextrin did not cause this effect in eight children on continuous cycling PD [44]. Although there was no correlation between growth and intensity of dialysis in the IPPN study, an interesting correlation did emerge: that infants managed with physiological pH dialysis solutions grew significantly better. Indeed, this correlation was stronger than the effect of gastrostomy feeding. The cause of this correlation is unclear, but one hypothesis would be that there is a reduction in the inflammatory stimulus in comparison to standard PD solutions, which contain relatively more glucose degradation products [28]. The Italian registry of 84 infants starting PD before the age of 1 year identified a positive correlation of growth with exchange volume and dialysis session length [32].

Without doubt, the greatest success in inducing catch-up growth has been seen in children on intensified HD programmes, including short sessions of haemodiafiltration (HDF) (2–3 h, 5–6 times per week [45]), and nocturnal HD [46]. Whether this success is due to an improved clearance of toxic molecules, reduction of inflammation or improved appetite and/or nutritional intake is not known. Of 15 children with a mean age of 8 years and 3 months managed with daily HDF for 3 h, 6 days a week, mean protein intake was high, at 2.5 g/kg/day, and the C-reactive protein level was low in 13 children, suggesting a combination of low inflammation and good dietary intake. Mean growth velocity increased from 3.8±1.1 cm/year at inclusion to 14.3± 3.8 cm/year during the first year of HDF, resulting in a dramatic change in the HtSDS over the 20-month follow-up period (from −1.5±0.3 to +0.2±1.1 SDS [45]). Studies of nocturnal HD are few in number as yet, with small numbers of patients [46]. The biggest study conducted to date had 16 patients with a mean age of 15 years on nocturnal HD. The protein catabolic rate increased from 1.2 g/kg body weight (BW)/day under conventional HD to 1.5 g/kg BW/day under nocturnal HD. Most of the patients had an improved appetite, and serum albumin and weight improved. The overall energy assimilation increased by 6.96 % [47].

Given our knowledge that in the majority of reports HtSDS declines with increasing time on dialysis [13, 16–18], the obvious key to the prevention of growth deterioration is pre-emptive transplantation.

Access to a paediatric renal dietician

The paediatric renal dietician is crucial to the successful management of nutrition in children with renal disease. To the best of our knowledge, there is only one study looking at the relationship between dietary contact time and growth in CKD. In this study, it was estimated that 5.9 contacts per patient (in clinic or by phone) per month in children under the age of 5 years and 3.1 in children older than 5 years were necessary to successfully support families of children on PD. This intensive input resulted in improvement of HtSDS and WtSDS from −1.20 and −1.32 to −1.14 and −0.73, respectively, over a 3-year period [48]. The KDOQI nutritional guidelines recommend a review of dietary intake every once to twice a month for those under 1 year of age in CKD stage 5, and every 1– 3 months in those over that age [49]; children entirely dependent on enteral feeds may need to be seen more frequently, particularly in infancy when feed adjustments may be necessary as often as weekly. The purpose is to prevent the development of malnutrition in preference to treating it once it has developed.

Is feed delivery by gastrostomy superior to oral and nasogastric routes?

Nutritional intake during the first 2 years of life is the most important influence on growth. It might be predicted, therefore, that careful dietary control, with the use of enteral feeding when necessary, would be able to maintain normal growth or even allow catch-up. Initial reports of enteral feeding and growth at this age have been variable [27], but more recent reports have shown clear benefits, and it is now generally accepted that early and intensive nutritional management is of benefit to both growth and nutrition in this group [50]. Indeed, this is the recommendation in the KDOQI nutritional guidelines [49].

The IPPN data substantiates this approach and, importantly, also demonstrate a benefit of gastrostomy over nasogastric tube feeding. Of 153 children in 18 countries who started PD before the age of 2 years, growth was found to vary worldwide. Patients in some countries showed a steady decline in HtSDS over 2 years, from a mean of −2.2 to −4 SD in Turkey, −1.9 to −2.8 SD in Latin America and −1.5 to −1.9SD in Europe. In contrast, in the USA, the children started PD at a HtSDS of only −3.8, but improved to −2.5SD on PD length SDS increased by 0.6 SD per year of gastrostomy feeding but did not change with oral or nasogastric feeding. One possible explanation for this is an increase in vomiting associated with a nasogastric tube, which can act as a stent passing through the gastro-oesophageal junction [6]. Only 41 % of the patients were enterally fed, and gastrostomy feeding was restricted almost exclusively to the USA and European centres. The reason for this marked global variation in feeding strategies is not clear [28].

Do children who are no longer in the 'infancy' stage of growth benefit from enteral feeding?

After the infantile phase of growth, the role of the GH axis becomes more important, so increasing nutrition may prevent further growth decline but may not enable catch-up. There is, however, no reason to believe that enteral feeding would not improve malnutrition and all if its consequences. Reviewing the literature on the effects of enteral feeding after infancy is not straightforward, since many cohorts in the published studies do not classify their outcomes by age [14, 27]. Some studies, each with small numbers of patients, have shown stabilisation of growth decline or a modest increase in HtSDS [3, 5, 8, 48, 51–53].

We have looked specifically at prepubertal children in our centre who started enteral feeding after the age of 2 years. We have identified 18 children to date, with a mean age of 7.1 (range 2.1–13.3) years and a GFR of 16 ml/min/1.73 m^2[4–46]. Nine were on dialysis at the time enteral feeding was initiated and four commenced dialysis during the first year of enteral feeding. The mean HtSDS and BMISDS were respectively −2.61 and −0.79 at the start of enteral feeding, −2.38 and 0.71 after 12 months [p=not significant (NS) for HtSDS, p=0.0005 for BMISDS] and −2.20 and 1.13 by 24 months (n = 11; 5 children received transplants before 2 years of age) (p=NS for HtSDS, p=0.0009 for BMI SDS) (Fig. 2a, b). The feeds administered provided a mean of 53 kcal/kg and 1.2 g protein/kg. Perhaps most importantly, albumin, which we know has a link with mortality and morbidity [14], improved from a mean of 34.8 g/l at the start of enteral feeding to 37.8 and 39.3 g/l after 12 and 24 months, respectively, of enteral feeding (though p=0.44 and 0.12, respectively) (Fig. 2c). Hypoalbuminaemia, a surrogate marker of protein energy wasting (PEW), has been associated with mortality in children initiating dialysis, such that each −1 g/dl difference in serum albumin between patients was associated with a 54 % higher risk of death [54]. On the other hand, a higher albumin (>4 g/dl) in adolescents on HD was associated with a 57 % reduced risk of death, as well as fewer hospitalisations [55]. Given the known deterioration in nutritional intake that occurs as CKD progresses, early nutritional intervention is important for both long-term survival and linear growth at all ages. On the other hand, these children did show a significant increase in their BMISDS, so care must be taken not to administer too many calories.

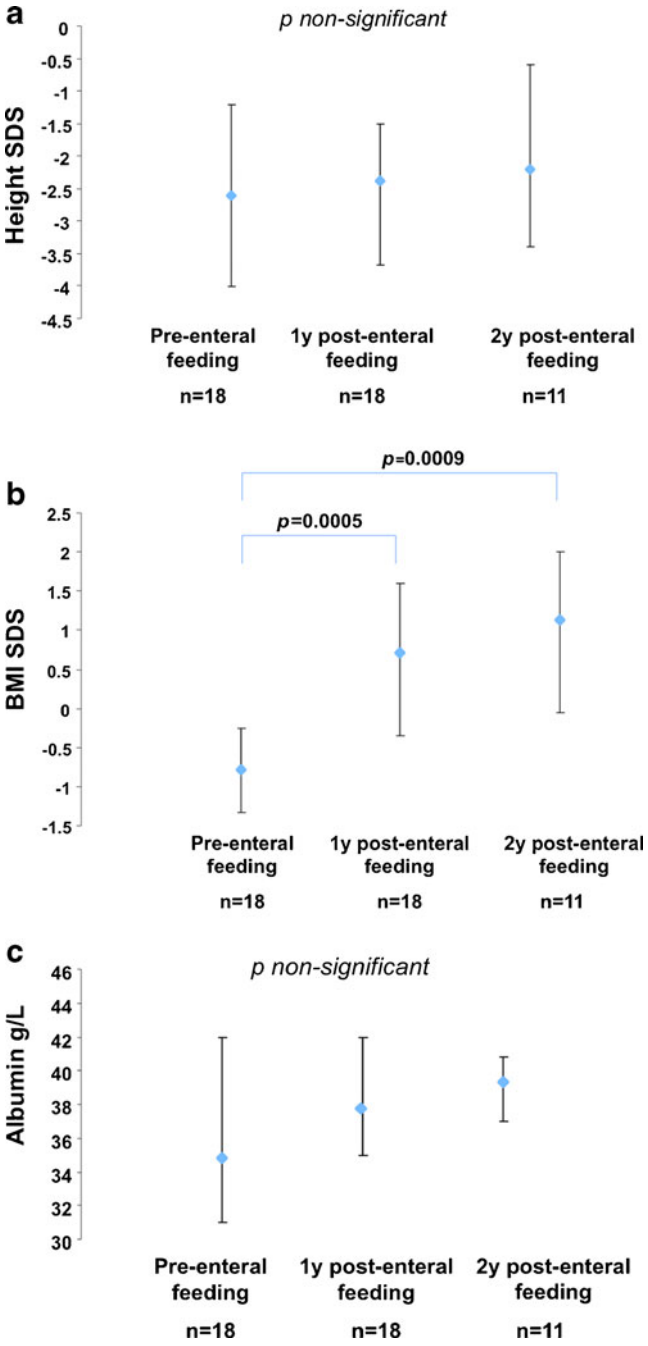

Fig. 2 **a** Mean and interquartile range (IQR) height standard deviation score (HtSDS) pre- and post-enteral feeding in chronic kidney disease (CKD) patients over 2 years of age (L. Rees and H. Jones, unpublished results). **b** Mean and IQR body mass index SDS (*BMI SDS*) pre- and post-enteral feeding in CKD patients over 2 years of age. **c** Mean and IQR serum albumin (g/L) pre- and post-enteral feeding in CKD patients over 2 years of age

Do patients with PEW benefit from increased nutritional input?

Protein energy wasting, or cachexia, differs from malnutrition (Table 6). Metabolic abnormalities, particularly acidosis, chronic inflammation (↑IL-1, IL-8, TNF-α) and decreased response to anabolic hormones (insulin, insulin-like growth factor 1, GH) are thought to contribute to maladaptive responses, such as anorexia, elevated metabolic rate, wasting of lean body mass and underutilisation of fat stores for energy [14, 56].

In a study of 548 children in the CKiD study whose median age was 12 years and GFR was 44 ml/min/1.73 m^2, 18 % had PEW defined as meeting two-thirds of the criteria, including low albumin or low cholesterol, weight loss (BMI <5th centile or decline in BMI of >10 % centile) and low protein intake (fair, poor or very poor self-reported appetite) (A. Abraham, personal communication, April 2012). Despite the differences in causation and phenotype between PEW and malnutrition, studies in adults have demonstrated that PEW can be improved substantially by an appropriate diet, and a recent review argues very strongly for the use of dietary interventions and nutritional support in mitigating or correcting PEW [57].

How do we prevent obesity, which is becoming so prevalent in the developed world?

Obesity is emerging as a new problem for children with CKD and seems to parallel the incidence around the world in the normal population. The IPPN database demonstrates this regional variation in BMI, from a mean BMISDS of 0.8 in the USA to −1.4 in India in children of all ages [13], and of infants, 26 % were obese in the USA and 50 % were malnourished in Turkey [28]. In the European Registry for Children on Renal Replacement Therapy (ESPN/ERA-EDTA), which includes 25 countries, of 5,199 patients below the age of 18 years the prevalence of underweight was 4.3 %, while 19.6 and 11.2 % were overweight or obese, respectively. Receiving steroid therapy and living with a renal transplant were independent risk factors for overweight. In North America, the frequency of obesity is increasing in the CKD population both before and at CKD stage 5 ([58, 59] and M. Bonthuis, personal communication, April 2012).

One important question is whether enteral feeding predisposes to obesity. It would seem logical that careful and frequent dietetic surveillance of the feed itself should be able to provide the optimum dietary intake on an individualised basis. Calorie requirements for children with CKD should not exceed those recommended for the general population. Indeed, many children with CKD may be relatively inactive in comparison to their peers and therefore need less calories. Also, special consideration needs to be given to children on PD, who may absorb as much as 10 calories/kg/day from their dialysate. On the other hand, protein intake in children on dialysis needs to exceed that recommended for normal children due to losses of protein in the peritoneal dialysate and of amino acids on HD [27, 49].

In a study in Canada, 33 % of 20 children with CKD stage 2–5 who had been gastrostomy fed were classified as overweight (BMI for age 85–95th centile) or obese (BMI for age ≥95th centile) by the time of gastrostomy removal. However, by this stage, 70 % of the patients had received steroid therapy post-transplant. The number of overweight and obese patients became even more evident at 5 years post-gastrostomy removal by which time 50 % were in this category. When this group was compared to a matched group who had not received enteral feeds, 36 % of the patients were classified as overweight or obese, and of these patients only 54 % had been transplanted, suggesting that factors other than tube feeding were responsible [60].

Obesity is a particularly a problem after renal transplantation. This has been studied in the NAPRTCS database in a retrospective cohort study of 4,326 children transplanted between 1995 and 2006, and followed up to January 2007. The median BMI of these children increased by 11 % at 6 months post-transplant but there were no substantial changes thereafter [61]. In Europe, children with the lowest BMI and those over 5 years of age at transplant showed the greatest increases in BMI post-transplant [58]. The use of steroid-sparing regimens may mitigate post-transplant obesity [62].

Table 6 Differences between malnutrition and protein energy wasting

Malnutrition	Protein energy wasting
Inadequate intake of nutrients	Inadequate intake of nutrients only partially responsible
Body fat is lost	Normal or even increased fat mass
Lean body mass initially preserved, later loss of muscle mass and protein stores	Loss of lean body mass
Low resting energy expenditure	High resting energy expenditure
Can be reversed by dietary supplements	Inadequate response to dietary supplements

Conclusion

Poor growth in children with CKD is widespread. Although many questions on nutritional management remain to be answered, and there are some irremediable factors that affect growth, careful surveillance of the dietary intake of children with CKD may prevent not only poor growth but also the high morbidity that is associated with both under- and over-nutrition.

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