

## Review Article

# Growth and body composition in children with chronic kidney disease

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Growth failure is a common yet complex problem of childhood chronic kidney disease caused by multiple factors encountered due to the primary disease or secondary to the renal impairment. This review seeks to describe the various patho-physiological mechanisms contributing to growth failure in the various stages of childhood with particular emphasis on nutritional problems and endocrine dysfunction encountered whilst managing these children. In addition, we shall examine the role of body composition in chronic kidney disease, their relationship with growth and nutrition and the potential effect of abnormalities in fat mass and lean mass on long-term morbidity and mortality.

### Growth: nutrition: Body composition: Chronic kidney disease

Childhood chronic kidney disease (CKD) represents a spectrum of conditions, which result in renal impairment varying from mild renal insufficiency to end stage renal failure (ESRF) (Table 1). CKD can be defined as either a glomerular filtration rate of less than 60 ml/min per 1.73 m<sup>2</sup> for greater than 3 months or kidney damage demonstrating pathological abnormalities or markers of damage – blood, urine or imaging investigations. Most studies in these children refer to those with moderate to severe CKD (stages 3–4) and ESRF (stage 5), which corresponds to a glomerular filtration rate being less than 15 ml/min per 1.73 m<sup>2</sup> and requires renal replacement therapy of either dialysis or renal transplantation. The incidence of children with ESRF has been reported as nine per million child population overall with the highest incidence of new patients occurring between 10 and 15 years of age (Ansell *et al.* 2003). Multiple aetiologies are responsible for CKD (Table 1), of which over 50% are due to congenital abnormalities with the remainder being mainly due to hereditary conditions, glomerulonephritis or multi-system disease.

The presentation of CKD can be varied, either due to the primary renal disease or as a consequence of impaired renal function, with onset sometimes being silent with an insidious progression and symptoms only developing late in its course (Table 1). Even with optimal care, many of these children go on to develop ESRF and require renal replacement therapy. Management of CKD prior to renal replacement therapy is thus conservative with the main aims being to slow down disease progression, optimise renal function and minimise complications secondary to CKD.

Growth failure is a significant problem in CKD with up to 50% of all patients with ESRF in childhood attaining adult heights below the 3rd centile (Fivush *et al.* 1998). The cause of growth failure in CKD is multifactorial with linear impairment being a final common pathway of various factors including the aetiology of CKD, hormonal dysregulation, nutritional deficiency, metabolic acidosis, uraemia, chronic anaemia and persistent micro-inflammation (Kuizon *et al.* 1997; Chan *et al.* 2002). Whilst optimal conservative management aimed at minimising these complications has been shown to improve growth, the impact of each factor on growth remains unclear.

In the present review we shall summarise the various patho-physiological mechanisms of growth failure in CKD. In particular, we shall examine the importance of endocrine dysfunction and nutrition in growth failure and, finally, look at the close association of these factors with abnormalities in body composition in CKD.

### Pathophysiology of growth impairment

#### Age of onset

CKD can result in impairment in each phase of development from *in utero* to adolescence, which can subsequently result in growth retardation, with studies suggesting that the degree of height deficit worsens with duration of disease (Norman *et al.* 2000). Intrauterine growth retardation is critical to linear growth and may occur in severe renal hypoplasia, whilst placental insufficiency causing intrauterine malnutrition may also affect renal

**Abbreviations:** CKD, chronic kidney disease; DXA, dual energy X-ray absorptiometry; ESRF, end stage renal failure; GH, growth hormone; IGF, insulin-like growth factor.

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**Table 1.** Stages, aetiology and modes of presentation of chronic kidney disease (CKD)

Stages of CKD	Description	GFR (ml/min per 1.73 m <sup>2</sup> )
Stages		
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with decreased mild GFR	60–89
3	Moderate decreased GFR	30–59
4	Severe decreased GFR	15–29
5	Kidney failure	< 15 or dialysis
Aetiology	Modes of presentation	
<b>Congenital abnormalities</b>	Antenatal ultrasound	
Aplasia/hypoplasia/dysplasia	Urinary tract infection	
Reflux nephropathy	Enuresis	
<b>Hereditary conditions</b>	Failure to thrive	
Medullary cystic disease	Short stature	
Polycystic kidney disease	Lethargy and pallor	
Cystinosis	Haematuria	
<b>Glomerulonephritis</b>	Abdominal mass	
Focal segmental glomerulosclerosis	Nephrotic syndrome	
<b>Multisystem</b>	Hypertension	
Lupus erythmatosus	Congestive cardiac failure	
Henoch-Scholein purpura	Seizure	
Haemolytic Uraemic Syndrome	Screening siblings of index cases	

GFR, glomerular filtration rate.

morphogenesis in the first trimester and therefore retard fetal growth (Bassan *et al.* 2000; Rodriguez-Soriano *et al.* 2005).

In infancy, untreated CKD is associated with severe growth retardation with loss in relative height being as high as SD 0.6 per month during the first year of life (Rees *et al.* 1989; Karlberg *et al.* 1996). Feeding problems experienced in these infants with its concomitant anorexia and uraemia results in protein–energy malnutrition, which in turn leads to increased protein catabolism and ultimately growth retardation, which may also explain the failure of some of these infants to exhibit catch-up growth.

After 2 years of age, children who develop CKD exhibit an initial loss of height followed by growth parallel to their percentile after the disease process is better controlled (Schaefer *et al.* 1996). The degree of growth retardation is closely associated to renal dysfunction with a decrease in height standard deviation scores occurring once glomerular filtration rate falls below 25 ml/min per 1.73 m<sup>2</sup> (Englund *et al.* 2003) Finally, in adolescence, onset of puberty may be delayed by up to 2 years in up to 60 % of affected children and the delay may correlate to the duration of CKD (Schaefer *et al.* 1990; Simon, 2002). Even when they do enter puberty, a sub-optimal peak height velocity and shorter pubertal phase may result in a sub-optimal final height (Kleinknecht *et al.* 1980).

#### Nutritional deficiency

Various studies have shown that these children frequently have protein, energy and nutrient-deficient diets regardless of the degree of renal impairment and this, in turn, can lead to both retarded growth and abnormal body composition (Salusky *et al.* 1983; Abitbol *et al.* 1990; Norman *et al.* 2000). An association between energy intake and growth has been shown in children receiving haemodialysis or peritoneal dialysis (Tom *et al.* 1999). Although energy requirements are aimed at 100 % of the recommended daily allowance for age, 120–140 % has been suggested for catch-up growth, but

achieving this is often limited by anorexia secondary to uraemia. Anorexia is further exacerbated by hyperleptinaemia, which is shown to have a hypothalamic effect to reduce appetite and food intake and to increase energy expenditure (Warady *et al.* 1999; Mak *et al.* 2006). Protein deficiency is common in untreated children, which contributes to acidosis, uraemia, catabolism and impaired growth (Greiber & Mitch, 1992; Meireles *et al.* 1999). This can remain a problem in children receiving peritoneal dialysis, where there is a significant loss of body protein into the dialysate effluent (Quan & Baum, 1996). Further nutrient deficiencies in phosphate, K, Na, vitamin C, vitamin B6 and folic acid resulting from dietary restrictions could also contribute to growth failure and may require individualised prescription depending upon stage of renal failure and haematological and biochemical changes. In the UK, nutritional recommendations are based on dietary reference values (Department of Health, 1991) for food energy and nutrients. In the presence of normal height (>2nd percentile), energy and micronutrient requirements are based on chronological age but if height falls below the 2nd percentile, requirements for height and age may be used as baseline values and adjusted accordingly, as recommended by Coleman (2001) (Table 2).

Infants and young children with CKD frequently suffer from recurrent vomiting, anorexia and feeding problems (Hellerstein *et al.* 1987). Gastro-oesophageal reflux, which can significantly impair nutritional and medicinal delivery in an already undernourished child, has been reported in over 70 % of these patients, with further studies observing gastro-oesophageal reflux to have significantly prolonged reflux periods and intra-oesophageal pH to be abnormally decreased (Ruley *et al.* 1989). This suggests the presence of both gastric and oesophageal dysmotility, further complicated by the presence of gastric dysrhythmias and delayed gastric emptying (Ravelli *et al.* 1992). The uraemic state may also interfere with extra-renal secretion and degradation of regulatory peptides within the gut, with increases in serum gastrin and

**Table 2.** Nutritional guidelines for the child with chronic kidney disease (CKD). Guidelines providing recommended ranges for energy and protein requirement. Further adjustment required based on individual nutritional assessment

Stage of CKD and age (years)	Energy/ kg body weight (kJ)	Protein/kg body weight (g)
<b>Pre-dialysis</b>		
Pre-term	500–750	2.5–3.0
0–0.5	480–630	1.5–2.1
0.5–1.0	400–630	1.5–1.8
1.0–2.0	400–500	1.0–1.8
2.0–puberty	Minimum EAR* for chronological age (use height age if < 2nd percentile for height)	1.0–1.5
Pubertal		1.0–1.5
Post-pubertal		1.0–1.5
<b>Peritoneal dialysis (CCPD/CAPD)</b>		
Pre-term	500–750	3.0–4.0
0–0.5	480–630	2.1–3.0
0.5–1.0	400–630	2.0–3.0
1.0–2.0	400–630	2.0–3.0
2.0–puberty	Minimum EAR* for chronological age (use height age if < 2nd percentile for height)	1.5–2.0
Pubertal		1.4–1.8
Post-pubertal		1.3–1.5
<b>Haemodialysis</b>		
Pre-term	500–750	3.0
0–0.5	480–630	2.1
0.5–1.0	400–630	1.5–2.0
1.0–2.0	400–630	1.5–1.8
2.0–puberty	Minimum EAR* for chronological age (use height age if < 2nd percentile for height)	1.0–1.5
Pubertal		1.0–1.5
Post-pubertal		1.0–1.5
<b>Guidelines for phosphate intake</b>		
Infants	< 400 mg/d	
Children < 10 kg	400–600 mg/d	
Children > 20 kg	< 800 mg/d	

\* Estimated average requirement (EAR) based on Dietary Reference Values (Coleman, 2001). CCPD, continuous cycle peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

other peptides resulting in altered regulation of gastrointestinal motility, modulation of hunger and satiety (Hallgren *et al.* 1988). Prolonged enteral feeding is therefore very common and needed in order to reach adequate nutritional requirements, although this can be associated with feeding difficulties and it is subsequently important to offer support on non-nutritive sucking in infants and encourage normal feeding behaviours in the older child (Dello-Strogolo *et al.* 1997).

#### Metabolic acidosis

Metabolic acidosis is common in CKD and often seen before glomerular filtration rate < 50%. It is essentially due to impaired NH<sub>3</sub> excretion, aggravated by nutritional protein load and altered electrolyte balance. This can then accelerate protein degradation by activation of the ubiquitin–proteasome pathway, stimulation of branched chain keto-acid dehydrogenase, stimulation of endogenous steroid synthesis and promotion of end-organ resistance to anabolic effects of growth hormone (GH) (Mitch & Price, 2003). Metabolic acidosis has also been shown to directly stimulate bone resorption, whilst correction of this abnormality has been correlated with an improvement in bone formation (Domrongkitthaiporn *et al.* 2002; Lemann *et al.* 2003).

#### Micro-inflammation

CKD is characterised by a chronic inflammatory state, with inflammatory cytokines being closely associated with protein

metabolism. Recent studies have shown the existence of a malnutrition–inflammation complex, in which chronic inflammation leads to protein–energy malnutrition (Kaizu *et al.* 1998; Kalantar-Zadeh *et al.* 2001). Malnutrition in CKD has been proposed to be a combination of uraemia and inflammation (Stenvinkel *et al.* 2000) with resultant severe catabolism and potential growth failure. The roles of IL-6 and C-reactive protein in adult studies have been shown to have a negative correlation with muscle mass in CKD and particularly haemodialysis (Kaizu *et al.* 2003) due to cytokine activation (Roccatello *et al.* 1998), which can induce protein catabolism and promotion of apoptosis (Carracedo *et al.* 1998) via ubiquitin and caspase-3 pathways (Carracedo *et al.* 2002; Raj *et al.* 2003). Strategies to reduce chronic inflammation, such as the use of regular L-carnitine in ESRF, may improve cellular defences, modulate the inflammatory cascade and, thus, indirectly maintain lean mass and growth potential (Pertosa *et al.* 2005).

#### Secondary hyperparathyroidism and renal osteodystrophy

Renal osteodystrophy develops as a result of the effect of impaired renal function on Ca, P, vitamin D metabolism and parathyroid hormone activity (Mehls *et al.* 1980). Impaired phosphate excretion results in an elevation of serum phosphate and a reciprocal drop in Ca, stimulating the development of secondary hyperparathyroidism and renal osteodystrophy. Histologically, renal osteodystrophy results in widening of the growth cartilage zone due to the development of

fibrochondroblastic, fibro-osteoclastic and woven bone resulting in narrowing of the cartilage layer and breakdown of the spongiosa layer. Although growth impairment does not occur initially, progressive destruction of the growth plate due to secondary hyperparathyroidism can lead to slipping of epiphyses and cessation of growth (Santos *et al.* 2005).

#### Growth hormone/insulin-like growth factor 1 axis

GH exerts its somatotrophic effects through both direct and indirect actions via insulin-like growth factor (IGF)-1 by inducing differentiation of epiphyseal growth plate precursor cells towards chondrocytes, which in turn become responsive to IGF-1 and concomitantly express IGF-1 mRNA resulting in proliferation of pre-chondrocytes, osteoblast hypertrophy, bone remodelling and net mineralisation (Ohlsson *et al.* 1998). IGF-1 affects somatic growth in fetal and postnatal development (Gohlke *et al.* 2005; Yakar *et al.* 2005) acting systemically as a classical endocrine hormone and locally as a paracrine/autocrine growth factor (Dupont & LeRoith, 2001), whilst being influenced to variable degrees by GH, nutrition and sex steroids (Straus & Takemoto, 1990; Thissen *et al.* 1994). Serum GH levels and secretory rates in CKD have been shown to be high-normal in pre-pubertal children, probably due to attenuated bioactive IGF-1 feedback and reduction in the metabolic clearance rate of GH (Haffner *et al.* 1994; Tonshoff *et al.* 1995). The paradox of normal or elevated GH levels in the presence of growth retardation has led to the concept of uraemic GH resistance (Kaskel, 2003). Despite increased GH concentrations, free IGF-1 levels and IGF-1 bioactivity are decreased in CKD due to the presence of IGF binding proteins, which have been shown to have multiple level interactions with the GH/IGF axis, which modulates their action (Frystyk *et al.* 1999; Kiepe *et al.* 2005).

#### Pubertal dysfunction

Delayed or abnormal pubertal progression in children with CKD further increases the risk of growth retardation. These children exhibit elevated gonadotrophins with decreased or low-normal gonadal hormones resulting in a state of compensated hypergonadotrophic hypogonadism (Marder *et al.* 1983; Schaefer *et al.* 1991). However, they may also have evidence

of hypothalamic-pituitary-gonadal dysregulation with blunted response of luteinising hormone to gonadotrophins and decreased luteinising hormone pulsatility and bioactivity (Blackman *et al.* 1981; Oertel *et al.* 1983; Giusti *et al.* 1991). Finally, oestradiol and testosterone are reduced due to uraemia, either through direct toxic effects or hyporesponsiveness of the gland, which can thus further effect pubertal growth (Karagiannis & Harsoulis, 2005).

#### Assessment of body composition

The complexity of nutritional management and its relationship to growth requires an accurate assessment of body composition in CKD and understanding of the potential problems of each method (Table 3). BMI was developed as a reliable method of assessing body fat and nutritional status in public health studies (Cole, 1997). However, its value in the setting of chronic disease, where children may also suffer from growth retardation, has been questioned (Schaefer, 2000). In addition to growth retardation, reduced levels of physical activity, ESRF with the need for dialysis and immunosuppressive therapy may further confound the interpretation of BMI. Furthermore, it is increasingly recognised that truncal obesity is associated with a higher risk of cardiovascular morbidity and that BMI, by itself, has limited value in assessing regional body composition (Bolton *et al.* 2003).

Assessment of skin-fold thickness as a marker of fat mass, whilst widely used, is prone to significant inter- and intra-observer variation. Similarly, whilst waist circumference measurements are closely correlated to both abdominal fat mass and insulin resistance syndrome (Hirschler *et al.* 2005), fluid overload in CKD can result in overestimation of fat mass whilst abnormal regional body composition or abnormal ratio of subcutaneous:visceral fat could be unrecognised (Odamaki *et al.* 1999).

Isotope dilution technique is often considered to be the gold standard for assessing body composition but this technique is not widely available and, in CKD, fluid overload may lead to inadequate equilibration with resulting underestimation of fat and lean mass (Wuhl *et al.* 1996). Densitometry estimates body composition from body density using either underwater weighing or air-displacement plethysmography (Sardinha *et al.* 1998; Fields & Goran, 2000) whilst neutron activation analysis

**Table 3.** Limitations of methods of assessing body composition in chronic kidney disease (CKD)

Method	Potential problem in CKD	Effect on assessment of nutritional status
BMI	Fluid overload increases weight. Unable to differentiate between lean and fat mass	Overestimation of nutritional assessment
Skin-fold thickness	Fluid overload increases subcutaneous tissue	Overestimation of nutritional assessment. Unable to recognise abnormal ratio of subcutaneous:visceral fat
Isotope dilution	Inadequate equilibration in fluid overload	Overestimation of fluid volume, with underestimation of fat mass and protein mass
Densitometry	Fluid overload	Overestimation of lean mass
Neutron activation analysis	Increased non-protein N (urea)	Overestimation of total body N and total body protein
Total body K	Increased tissue K concentration	Overestimation of body cell mass
Bioelectrical impedance	Fluid overload with abnormal fluid distribution	Unpredictable effect on estimation of fat mass and lean mass from total body water
Dual energy X-ray absorptiometry	Fluid overload	Overestimation of lean mass



provides a non-invasive analysis of the total body content of major elements by directing neutrons at the subject and then measuring the time of decay of the excited neutrons (Ellis, 2000). Fluid overload and raised K and urea in CKD are again limitations to these techniques. Total body K counting measures the naturally occurring radioisotope  $^{40}\text{K}$  to calculate total body cell mass. However, this method relies on estimating total body K in lean muscle, which may be abnormal in CKD resulting in an overestimation of body cell mass (Blumenkrantz *et al.* 1980). Bioelectrical impedance analysis has been widely used to examine nutritional status in children and body composition in CKD (Nagano *et al.* 2000; Schaefer, 2000). This method estimates body fluid compartment volume by measuring conduction of electrical current through body fluids and impedance by body components. However, concerns remain over the reliability, reproducibility and sensitivity to changes in regional composition of this method in individual children in these cohorts (Kyle *et al.* 2004).

Dual energy X-ray absorptiometry (DXA) involves two photon beams passing through a subject's body to create a two-dimensional projection of a three-dimensional structure. In CKD, in addition to assessing bone mineral content, whole body DXA can also provide reproducible estimates of fat mass and lean mass in children and adults by measuring the degree of dual photon attenuation produced by each tissue type (Goran *et al.* 1996; Azocar *et al.* 2004). Unlike the other methods described, DXA has the advantage of being more widely available in clinical practice. Furthermore, reference paediatric population data are increasingly becoming available for various populations and ethnicities (Ellis *et al.* 1997; Van der Sluis *et al.* 2000). The main concern over the accuracy of DXA is its failure to measure total body water. Instead, the software used to calculate lean mass assumes the total body water to be 73 % of lean mass (Pietrobelli *et al.* 1996). This is particularly pertinent to CKD, as in the presence of fluid overload there can be an overestimation of lean mass.

### Body composition in children with chronic kidney disease

There is increasing evidence that children with CKD have an altered fat mass and lean mass with nutrition, uraemia, chronic inflammation, physical inactivity and GH resistance contributing to the aetiology of abnormal body composition in these children (Axelsson *et al.* 2004; Pattaragarn *et al.* 2004). In affected adults, a high BMI has been reported with fluid overload and a low BMI has been associated with increased morbidity and mortality (Pifer *et al.* 2002). In children, similar studies have shown an inverse bell-shaped association between BMI and mortality risk with a change of more than 1 SD being associated with a 6 % increase in mortality (Wong, 2000). However, BMI when corrected for height age is only moderately raised in children with CKD (Schaefer, 2000). Measurement of skin-fold thickness in affected children has shown deficits in tricep skin-fold thickness (Orejas *et al.* 1995), but Zivicnjak *et al.* (2000) demonstrated that fat distribution in CKD was disproportionate with an increase in truncal fat in comparison with limbs. Such findings have also been reported in adults who had a significant increase in visceral fat and a decrease in subcutaneous fat when compared with healthy subjects (Odamki *et al.* 1999). Total body K, a potential marker of lean mass, is reported to be low in childhood CKD (Weber *et al.* 1980), whilst *in vivo*

neutron activation measuring total body N has also shown deficits in childhood CKD, although this change was not apparent when data were adjusted for height (Baur *et al.* 1994).

DXA data, corrected for height in children with CKD, demonstrated that BMI did not accurately reflect body composition, with patients exhibiting low lean mass with relatively high fat mass (Rashid *et al.* 2006). Johnson *et al.* (2000) also reported reduced lean mass and high fat mass in children with CKD and an increase in lean mass and a decrease in fat mass over a 6-month period of recombinant human GH treatment. Similar results have been reported in pre-pubertal children with CKD, confirming the lipolytic and anabolic effects of GH, although neither of these two studies adjusted the data for height or body size (Boot *et al.* 1998; Van der Sluis *et al.* 2000).

### Conclusions

The present review seeks to explain the different mechanisms that affect growth in childhood CKD. Endocrine disturbances and nutritional problems play major roles in growth failure. Children with CKD may have abnormalities of their body composition, which may not be apparent on simple measurement of BMI. Evaluation by methods such as DXA needs to be performed carefully with due consideration of the concurrent growth retardation and pubertal delay.

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