Growth and metabolism in renal failure

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Chronic renal failure (CRF) is not a common condition in childhood in the United Kingdom. About 90 children per year may be expected to require treatment by dialysis or transplantation. The prevalence of chronic renal insufficiency in childhood is more difficult to determine but, in a survey in Switzerland, Leumann found 18 children per million child population to have a raised plasma creatinine; this suggests that about 500 children in the United Kingdom might be affected [1].

CRF causes growth retardation and this is associated with delay in both skeletal and sexual development [2]. These consequences in turn affect the emotional and social development of the child and inevitably both the condition and its treatment affect school attendance and performance. In addition, there is evidence that renal impairment early in life may directly affect cerebral function and development and lead to permanent mental retardation [3]. The cause of this is not known, but aluminium accumulation in the brain from the use of oral aluminium hydroxide as a phosphate binder to prevent the intestinal absorption of phosphorus is probably important [4] and because of this many paediatric units now use calcium carbonate as an alternative phosphate binder wherever possible.

The average height of young adults who have experienced chronic renal failure in childhood is 3 standard deviation (SD) below the mean, or a height of about 5ft 3in for boys and 5ft for girls; many, of course, are much smaller [5]. Most children with successful renal transplants have a normal growth velocity, but the accelerated growth necessary to restore normal height rarely occurs in older children receiving conventional immunosuppression with azathioprine and alternate-day steroids [6]. It is not yet clear whether very low-dose steroids and cyclosporin treatment will improve growth in these older children, but in infants with renal transplant growth is often better, and accelerated growth is more common.

The earlier the onset of the chronic renal insufficiency, the worse the height deficit at the time of transplantation [7]. A high proportion of children with end-stage renal failure suffer from congenital malformations of the urinary tract [2]. Thus, if permanent growth retardation is to be prevented, attempts have to be made to improve the growth of young children with renal insufficiency during early life when growth is normally at its maximum and before a renal transplant or dialysis is necessary.

Causes of impaired growth

There are many factors that contribute to poor growth associated with renal insufficiency. The fundamental reason is the disturbances in body composition caused by the renal failure. The main function of the kidney is the maintenance of body composition. All nutrients, other than energy, are usually consumed in excess of requirement and this excess is excreted in the urine. The alterations of body composition in renal failure are numerous and complex: thus external balance for sodium is maintained but hypertension occurs; external balance for protein is associated with a raised concentration of nitrogenous compounds such as urea in the body; the price paid for the maintenance of phosphate balance is hyperparathyroidism and so on.

The changes in body composition occur more rapidly and are more severe in children than in adults because their metabolic rate in relation to body mass is much higher; they eat relatively more than an adult and therefore have a higher intake of all nutrients. A 6-month-old baby requires about twice as much energy supply as an adult expressed as a function of body weight. In the healthy child, this is offset by the proportionately higher glomerular filtration rate.

In renal insufficiency, the strategy of reducing the intake of nutrients other than energy in order to minimise the changes in body composition is immediately apparent. It has its natural parallel in the first few months of life when glomerular filtration rate is normally only a quarter to a half that in adults and when the consumption of human milk and other nutrients provides the necessary energy for growth and development, but does not supply a large excess of nutrients to be excreted in the urine.

Table 1. Factors affecting growth and metabolism in renal failure.

| Glomerular osteodystrophy | Acidosis | Sodium | Energy and glucose malnutrition | Protein malnutrition | Hormonal alterations |
|---------------------------|----------|--------|---------------------------------|----------------------|---------------------|
Factors that more specifically affect growth and metabolism in renal failure are shown in Table 1.

Glomerular osteodystrophy

The first description of renal rickets has been attributed to Mr R. C. Lucas, Surgeon to Guy’s and the Evelina Hospital. In the *Lancet* in 1883 he reported four children with rickets associated with albuminuria [8]. Whilst it is true that the albuminuria was rightly attributed to renal disease, it nonetheless seems to be an arguable proposition that the cases Lucas described were suffering from nutritional rickets. He noted that the albuminuria disappeared with treatment with cod liver oil, and we can now surmise that this was perhaps because associated hyperparathyroidism was suppressed. What appears to be a true case of gross rickets associated with severe renal disease from pylonephritis was reported by Mr Davies-Colley in 1884 [9]. A full description of the case, along with the pathological specimens, can be found in the Gordon Museum at Guy’s. The ureters were found to be dilated at autopsy and it is possible that the patient was suffering from chronic pylonephritis associated with congenital vesicoureteric reflex leading to end-stage renal failure. In our experience of over 200 children treated by dialysis and transplantation, chronic pylonephritis secondary to vesicoureteric reflex and infection is the commonest single cause of end-stage renal failure in childhood [2]. In 1890, Dr J. F. Goodhart, during the course of a lecture on albuminuria, reported a number of children with chronic renal disease and noted that they were small and had rickets [10]. The importance of glomerular osteodystrophy in determining the small stature of children with CRF has been emphasised [11].

The importance of the kidney for the metabolism of vitamin D is well recognised and the production of the active metabolite 1,25 dihydroxycholecalciferol (1,25-vitamin D3) is affected early in chronic renal failure. Studies in children have shown a significant reduction in the plasma concentration of 1,25-vitamin D3 when the GFR falls below 50 ml/min per 1.73 m² body surface area [12-14]. Parathyroid hormone concentration is consequently raised, leading to increased fractional excretion of phosphate by the kidney, and the somewhat paradoxical but common finding of hypophosphataemia in early CRF. The production of 1,25-vitamin D3 is also affected by the dietary phosphate intake: a reduction in phosphate intake results in a rise in circulating 1,25-vitamin D3 with a fall in parathyroid hormone concentration [15].

We have treated children with long-standing chronic renal failure with a low phosphate diet supplemented with calcium carbonate or aluminium hydroxide as an intestinal phosphate binder whilst maintaining them on a constant dose of vitamin D given as dihydrocholesterol [16]. With this regimen their growth improved measured as the height velocity standard deviation score. Plasma phosphate fell, plasma calcium rose and there was a fall in urinary cyclic AMP reflecting parathyroid hormone activity, and a rise in the theoretical tubular threshold for phosphate reabsorption. These latter two measurements are indirect evidence of reduced parathyroid hormone activity and indeed parathyroid hormone levels were suppressed to within the normal range in children treated with aluminium hydroxide or calcium carbonate. Bone biopsy showed a significant reduction in osteitis fibrosa cystica, with a fall in total bone reabsorption surface, but there was no improvement in the osteomalacia expressed as the mineral appositional rate or the mineralisation lag time [17]. We are not sure why there was no improvement in the osteomalacia because the reduction in plasma phosphate was also associated with a rise in the concentration of 1,25-vitamin D3 which, as expected, correlated with the fall in dietary phosphate intake. None of the children had a plasma phosphate level below the normal range and therefore it seems unlikely that the poor mineralisation was due to hypophosphataemia. On the other hand, all the children had been on aluminium hydroxide during the study because the design of the trial involved a cross-over from aluminium hydroxide to calcium carbonate or vice versa after six months, and all of them had had raised plasma aluminium concentrations. Aluminium was detected in the bone biopsies of nine of 11 children and it is therefore possible that aluminium toxicity contributed to the poor mineralisation. We have also been able to show that the control of hyperparathyroidism with a low phosphate diet can be maintained for as long as three years [18], and that even gross lesions of osteitis fibrosa cystica in children can heal if the plasma calcium is kept at the upper limit of normal and the plasma phosphate concentration is correspondingly reduced so that the calcium phosphate product is kept within normal limits. The capacity to control secondary hyperparathyroidism has proved an important advance and has eliminated the need for surgical parathyroidectomy in our experience.

Acidosis

Hyperchloaemic metabolic acidosis is common in renal failure. Nitrogen metabolism is abnormal in experimental uraemia because of excessive catabolism of endogenous protein. The increase in muscle protein degradation can be eliminated by correcting the metabolic acidosis [19]. Acidosis is easily prevented by reducing the intake of animal protein and providing extra alkali, usually as sodium bicarbonate.

Sodium

Sodium retention and the consequent hypertension associated with CRF has already been referred to, but sodium wasting can also occur, particularly in infants with obstructive uropathy or congenital dysplastic kidneys. Chronic sodium depletion is an important cause of poor growth in infants with renal failure and sodium supplements should be given to the limit of tolerance. It should be suspected if there is evidence of chronic volume depletion with, for example, constipation or a high blood urea relative to the plasma creatinine concentration, or poor weight gain. Hyponatraemia with a urine sodium concentration of more than 40 mmol/l and a metabolic alkalosis are also features. Sodium should be adminis-
tered as sodium chloride, not as sodium bicarbonate unless a metabolic acidosis is present. Chloride deficiency is associated with growth failure in infants and children with Bartter’s syndrome or with familial chloride diarrhoea, and correction of the chloride deficiency is associated with a rapid improvement in growth [20].

Hypo-reninaemic hypoaldosteronism can occur in some children with CRF. The cause is not known, but it is characterised by hyperkalaemia and a metabolic acidosis. Overt salt wasting is uncommon and can be corrected by the administration of extra mineralocorticoid in the form of 9-alpha-fluorohydrocortisone with or without frusemide [21].

**Energy and glucose malnutrition**

Anorexia is common in renal failure and indeed the reduction in nutrient intake reduces the severity of the changes in body composition, but at the expense of energy malnutrition. This malnutrition is an important cause of death in adults on dialysis and contributes to the poor growth of uraemic children. It is important to ensure a normal energy intake, if necessary by giving energy supplements in the form of fat, using double cream or polyunsaturated fat emulsions such as prosparol, and with carbohydrate given as glucose polymer. This is particularly important in uraemic infants when spontaneous energy intake is frequently insufficient to match the high requirements at this age. In such children we frequently resort to feeding supplements through indwelling nasogastric catheters, often given overnight by the parents at home. The poor energy intake of some uraemic children is associated with poor growth, and improving energy intake improves the growth. However, uraemic children who have an adequate energy intake often continue to grow poorly.

**Glucose metabolism**

Uraemia is associated with major abnormalities in the metabolism of glucose for energy. A low molecular weight peptide which inhibits insulin mediated glucose uptake in muscle and adipose tissue has been isolated from uraemic serum [22].

We have studied glucose metabolism in uraemic children using the hyperglycaemic clamp method [23]. This involves raising the blood glucose concentration by 7 mmol/l with an intravenous injection of glucose and then maintaining the blood glucose at this raised level for 2 hours with a glucose infusion. Blood glucose is measured every 5 minutes and the infusion rate adjusted according ly. During the 2 hours of the study the rate of infusion has to be steadily increased as the pancreas responds to the hyperglycaemia by increasing insulin secretion. During sustained hyperglycaemia, hepatic glucose production is inhibited and the rate of glucose infusion is a measure of the peripheral uptake of glucose; the glucose disposal rate can therefore be calculated. The pancreatic response to hyperglycaemia is measured from the plasma insulin levels and the ratio of the glucose disposal rate to the plasma insulin response provides a measure of the body’s sensitivity to endogenously secreted insulin [24]. Glucose metabolism during hyperglycaemia is considerably reduced in uraemic individuals in spite of a normal or increased plasma insulin level, thus the tissue sensitivity to insulin is reduced [25].

Correction of hyperparathyroidism achieved either by surgical removal of the parathyroid glands or by reduction of the phosphate intake, restores glucose disposal rate to normal. This is achieved by an increase in plasma insulin concentration to above normal, but with no change in insulin sensitivity [26]. Dialysis is associated with an increase in glucose metabolism achieved by an improvement in insulin sensitivity [27]. The control of uraemia associated with a low-protein diet and an adequate energy intake also improves glucose disposal rate, again by improving insulin sensitivity [28].

It appears that there are two populations of uraemic individuals; those without hyperparathyroidism have a normal glucose disposal which is achieved by an increase in plasma insulin, whereas those with hyperparathyroidism have reduced glucose metabolism during hyperglycaemia because of an inappropriately low insulin output.

The site of the defect in glucose metabolism in uraemia is not known, but insulin binding to both monocytes and adipocytes is normal [24]. Other insulin actions, such as its antilipolytic action or promotion of branched-chain amino-acids uptake into cells, are not reduced. Defects in cellular glucose metabolism occur with decreased glycolysis due to inhibition of the activity of key glycolytic enzymes such as pyruvate kinase, phosphofructokinase and glucose-6-phosphate dehydrogenase [29, 30]. Defects of oxidative phosphorylation with uncoupling at site one in the respiratory chain have also been shown [31].

**Protein malnutrition**

Many abnormalities of protein metabolism have been demonstrated in uraemia. Cell mass is often reduced particularly in uraemic infants and not, surprisingly, correlates with their poor growth. Likewise, serum transferrin levels, as a measure of the adequacy of protein nutrition, also correlate with poor growth in uraemic infants [32]. Insulin stimulated protein synthesis is reduced and there is an increased tendency to protein catabolism [19, 33-35]. Uraemic children and adults have low plasma concentrations of the branched-chain amino acids — valine, leucine and isoleucine [36]. The cause and importance of this in not understood, but intracellular levels are close to normal and the low concentrations in plasma may in part be related to the hyperinsulinaemia [37]. Branched-chain amino acids are transaminated in muscle and can be metabolised to provide energy. Keto acids derived from the branched-chain amino acids are also reduced in uraemia and their reduction is, if anything, more profound than the reduction in the respective branched-chain amino acids [38]. It has been suggested therefore that the reduction in circulating keto acids may contribute to the energy deficit in uraemia. Perhaps more importantly, the reduction in keto isocaproic acid, the keto acid of leucine, which is a powerful inhibitor of protein degradation, may contribute

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to the increased protein catabolism of the uraemic state. Various attempts have been made in uraemic children and in adults to supplement the diet with keto amino acids, particularly keto isocaproic acid, in order to improve protein nutrition. We treated seven pre-pubertal growth-retarded children with severe chronic renal failure with a low-protein diet, supplemented with a mixture of keto and amino acids. The diet provided about 5 per cent of the total calories from the amino and keto acid mixture and from protein. Blood urea fell to below 20 mmol/l in all the children and stayed at that level throughout the study. Growth velocity increased in these children, with significant improvements in cell mass. In spite of these improvements, we found no change in plasma amino or keto acid concentration [39].

Hormones

The metabolism of a number of hormones other than insulin is also abnormal in uraemia [40, 41]. Growth hormone levels are high and paradoxically rise after an intravenous injection of glucose. The raised levels are due to increased secretion rather than reduced clearance. The pulsatility and amplitude of growth hormone secretion during sleep, however, is normal. No consistent abnormality of insulin-like growth factor one (somatomedin A) has been demonstrated. Prolactin levels are often raised, though this is not consistent. Reduced plasma testosterone concentrations are found in adult men on dialysis, with high basal levels of luteinising hormone and loss of pulsatile secretion. The cause and significance of these hormonal abnormalities and their relationship to poor growth are as yet poorly understood. We have found normal overnight hormone profiles for growth hormone, prolactin and gonadotrophin hormone secretion in children with chronic renal failure whose uraemia was controlled with a low-protein diet [41].

Conclusion

The cause of the poor growth in uraemia is to be found in the metabolic derangements that occur when the kidney is failing. The strategy for management is to minimise these derangements by controlling and modifying dietary intake. Energy intake must be maintained, but the intake of protein should be reduced to maintain the blood urea below 20 mmol/l. Protein intake can be reduced to provide not more than 6–8 per cent of total calories from protein. To put this in perspective, the normal protein intake in our society often provides as much as 18 per cent of total calories from protein, whereas breast milk provides about 6 per cent of calories as protein.

The necessary dietary modifications should be achieved with the minimal upset to the nutritional habits of the child and family. Special foods should be avoided. We concentrate initially on providing sufficient energy by giving energy supplements with meals, rather than directly attempting to reduce protein intake. Special diets and anxiety and tension over food intake are too often associated with a refusal by the child to eat. By giving energy supplements with meals, ordinary food intake is naturally reduced and this means that the intake of protein falls. Further modifications can be achieved by the dietician working closely with the individual child and family to introduce the necessary modifications in ways which are acceptable.

The elimination of dairy products from the diet and the avoidance of foods that contain large amounts of phosphate, such as some cereals, is important and phosphate binders are used to reduce intestinal phosphate absorption further. The child with a high plasma phosphate is initially started on aluminium hydroxide, but once the plasma phosphate has been controlled, calcium carbonate is substituted because of the risk, particularly in infants, of aluminium accumulation leading to brain damage and bone disease. The absorption of calcium from the calcium carbonate tends to offset the reduction in calcium intake which follows the removal of dairy products from the diet. Plasma calcium levels are kept at the upper limit of normal with extra vitamin D3, usually in the form of 1,25 dihydroxycholecalciferol or 1-alpha-vitamin D3. The acidosis is controlled with sodium bicarbonate and sodium chloride intake is increased as necessary to the limit of tolerance.

We have been applying this strategy now for the last few years in our chronic renal failure clinic and it is encouraging that many of the children are now growing normally, even in the presence of advanced renal insufficiency. This is particularly so in the infants, but accelerated growth has also occurred in the older children [42]. Recently there has been much interest in the causes of progression of renal failure. It has been shown both in animals and in humans that a low protein, low phosphate diet will slow down the progression of renal failure in a number of individuals with a variety of renal diseases [43]. It is therefore interesting that the glomerular filtration rate has been stable in the large majority of the children attending our clinic, though the fact that many of them have congenital structural urinary tract lesions, such as dysplasia or hypoplasia, rather than acquired renal disease is obviously important.

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