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Children with Chronic Kidney Disease: A Closer Look at Calcium, Phosphate and Vascular Calcification

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Abstract

Calcium and phosphate are normal constituents to maintain healthy bones. But in kidney failure, they get turned into hidden and dangerous assassins, ready to cause serious damage to the kidneys, bones and the vasculature. How these previously normal elements become so dangerous and how to reduce these threats will be the focus of this communication. Finally, we shall highlight recent data concerning arterial wall stiffness and the risk of vascular calcification in children with chronic kidney disease.

Keywords: Chronic kidney disease; Hypertension; End-stage kidney disease; Anaemia

Causes of Chronic Kidney Disease (CKD) in Children

The major causes of chronic kidney disease (CKD) in adults are hypertension and diabetes mellitus, but the causes are different in childhood. Foreman et al. [1] examined data of over 4000 infants and children from North American, Europe, and Japan, in whom renal functions were less than 25% of normal. They found 33% of childhood CKD resulted from glomerulonephritis, followed by obstructive uropathy 25%, hereditary nephropathies 16%, and hypoplastic dysplasia 11%, with less common conditions rounding up the rest. Later experiences [2] continue to confirm these early findings.

Morbidity of CKD

CKD is silent in early stages in both children and adults [2,3]. There are few signs or symptoms. Urine and blood chemistry are often normal early on. Hence, it is difficult to make timely diagnosis. What makes it even more complicated is that CKD progresses at variable rates. Surely, kidney damage results from diverse causes. But, even if it is from the same etiology, the extent of kidney injury can be different. Promoters of progression are central in determining the rate of CKD progression. Without intervention to rein in the progression promoters, many patients can be expected to end up with end-stage kidney disease, whose survivals become dependent on dialysis and transplantation [2].

So, why is CKD a silent disease in the early stages? Why is it asymptomatic? The answer lays in the kidneys' ability to adapt. This adaptive hyperfiltration [4] requires the remaining nephrons to work harder, resulting in normal serum creatinine, blood urea nitrogen, electrolytes, calcium, phosphate and parathyroid hormone (PTH). But, as CKD progresses to a more advanced stage, typically when 50% of kidney functions are lost, this adaptive hyperfiltration becomes insufficient to maintain mineral and electrolytes balance. From this point on, the patients will show rapidly rising serum creatinine and blood urea nitrogen. Simultaneously, serum phosphate and PTH will escalate in parallel.

CKD Progression

In addition to adaptive hyperfiltration pushing progression [5], there are other hyperfiltration promoters. These include: hypertension, anaemia, diabetes, obesity, high protein intake, and pregnancy. The point to remember here is hyperfiltration from any source, in overworking the nephrons, eventually wears them out. If we can offset these promoters, we can check the on-going damage and slow down the accelerated progression.

Along with hyperfiltration, there is a long list of additional promoters of CKD progression. Amongst these are vascular calcifications, calcium and phosphate dysfunctions. Again, if we can neutralize these promoters, we can slow down the rate of CKD progression.

Arteriopathy and Vascular Calcifications

First, we are going to focus on arteriopathy (thickened and stiff arterial wall) and vascular calcification as promoters of CKD progression [6-8]. In the past, we often regard vascular calcification as something, which happens in older people [7,8], who are at risk of life-threating strokes and heart attacks. But

new evidence compels us to look for vascular calcifications hiding in children with renal disease [9-12].

Normal stem cells differentiate into chondrocytes to form bones. Stem cells also normally differentiate into vascular smooth muscle cells (VSMC) to form blood vessels. Moe et al. [13] highlighted how these VSMC can be transformed to chondrocyte-like cells by CKD-induced up-regulation of transcription factors. These chondrocyte-like cells then incorporate calcium and phosphate, in the setting of CKD, to mineralize the vessels. Whether an artery calcifies or not, ultimately depends on the strength of the inhibitors inside and outside the blood vessels, working against calcification.

Ultrasonography of the easily accessible carotid arteries in the neck, can detect thickened arterial wall (arteriopathy) long before radiographic documentation of vascular calcification. London et al. [11] emphasized that vascular calcification is a marker of reduced survival in adult dialysis patients. In children, we do not have vascular calcification data, but we have carotid intimal-media thickness data [9,10], measured by ultrasonography. Litwin et al. [10] documented extensive carotid arteriopathy in a high proportion of children, at 12 years of age and moderate CKD (50% renal functions remaining). Recently, Aytac et al. [14] underscored the importance of modifying arteriopathy in childhood CKD, by early vitamin D treatment.

Calcium and Phosphate

Central to calcium, phosphate and bone health is vitamin D. We are all familiar with vitamin D, from dietary sources or sunlight on the skin, being converted to its 25 hydroxylated form in the liver [3,15,16]. This is further hydroxylated in the kidneys to 1,25 dihydroxyvitamin D (1,25-D). 1,25-D is the active form of vitamin D, promoting dietary calcium absorption. Sooner or later, CKD patients cannot make enough 1,25-D, resulting in mal-absorption of dietary calcium. The ensuing hypocalcemia promotes secondary hyperparathyroidism. High PTH levels increase the risk of arterial calcification [7].

With PTH hypersecretion, bone reabsorption may become unrelenting in children with CKD, causing fracture rates to rise to thrice that of the general pediatric population [17]. This is the burden of renal failure we need to curb in childhood CKD.

Phosphate together with calcium is closely connected, in maintaining healthy bone and normal growth [3,15]. The dietary intake of phosphate can be high or low, which is adjusted by the kidneys: filtering, reabsorbing and excreting the right amount: to maintain phosphate homeostasis. However, this becomes complicated as CKD progresses. For one, when the kidneys fail, phosphate cannot be excreted adequately and its retention begets hyperphosphatemia. The serum phosphate concentration keeps rising as CKD progresses. This steadily rising hyperphosphatemia becomes a big problem, because if the serum calcium and phosphate product gets exceedingly high, extra-skeletal precipitation of calcium phosphate will follow.

The tipping point for signs and symptoms to appear is a 50% kidney functional loss [3,15,16]. At the earlier stages of CKD, when kidney function is better than 50% of normal, any small mineral electrolyte retentions are compensated for by adaptive hyperfiltration, resulting in transient changes in mineral electrolytes, and not detectable by routine laboratory tests. Still, this silent hyperfiltration overworks the kidneys and is harmful in the long run. Certainly, earlier diagnosis and treatment can control this major promoter of progression.

Remarkable and exciting progress has been made on upstream regulators of calcium and phosphate, such as FGF23 [15,16], klotho [18], and sclerostin [19]. But, these developments are beyond the scope of this communication.

Treating Renal Osteodystrophy/Metabolic Bone Disease

Rickets, demineralization, bone deformities, bone fragility, growth retardation, extra skeletal vascular calcifications and arteriopathy characterize metabolic bone disease (MBD). We are in a transitional period in the usage of the term MBD [16], replacing the previous descriptor of renal osteodystrophy [20].

There is a broad array of treatments available to treat MBD and curbing progression of vascular calcifications and arteriopathy [21,22]. To achieve such end-points, efforts must be made to control hyperphosphatemia. When serum phosphate concentration is markedly elevated, the calcium x phosphate product becomes excessive, leading to significantly increased mortality risks in elderly CKD and dialysis patients [23,24].

To treat hyperphosphatemia, first avoid high phosphate food. Second, remove dietary phosphate with phosphate binders [16,17]. This treatment modality is bittersweet. Bitter: because phosphate is so abundant in our favorite sodas and foodstuff, making compliance difficult. Sweet: because it usually works, if the patient has the encouragement and discipline to comply.

Soft drink beverages are high in phosphate. It is a good idea to start here and cut back on consumption. Phosphate binders can be calcium based and non-calcium based phosphate binders. Recent data [24] suggest that non-calcium based binders are non-inferior to calcium-based phosphate binders. Importantly, the risk of hypercalcemia associated with calcium-based binders is minimal with non-calcium based binders.

The mainstay in treating MBD continues to be 1,25-D. The criteria for starting 1,25-D vary and guidelines for its pediatric use are being developed [20]. Certainly, in the presence of CKD hypocalcemia, no one questions the use of 1,25-D to bring serum calcium concentrations to normal values, both for total calcium and for ionized calcium.

CKD-induced hyperparathyroidism is a compelling reason to use 1,25-D. The question is when to start treatment? When is PTH elevated in children with CKD? To answer these questions, earlier studies [3] showed that when the serum creatinine exceeds 1.5 mg/dl (132 µmol/L), PTH becomes consistently elevated. At this point, start 1,25-D therapy to reverse secondary hyperparathyroidism [25-27].

With increasing frequency in advanced CKD, despite all our efforts, the elevated PTH persists. This resistance to treatment is referred to as “refractory hyperparathyroidism.” When this is

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encountered, either surgical, or medical parathyroidectomy becomes necessary. Medical parathyroidectomy with calcimimetic agents is worth a try before surgical parathyroidectomy. Cinacalcet, the approved calcimimetic agent, operates by binding to parathyroid calcium sensing receptor to increase sensitivity to ionized calcium and successfully reduces secondary hyperparathyroidism [28,29]. Cinacalcet's efficacy and safety profiles are good. Its oral route of administration increases patient acceptability. The combined use of vitamin D and calcimimetic agents to suppress PTH in dialysis patients showed good potential in reducing cardiovascular risks in elderly patients but not in younger patients [29].

Summary

CKD is asymptomatic in its early stages. This signature feature comes about because of renal adaptive hyperfiltration. Initially, hyperfiltration succeeds in maintaining fluid-electrolyte and mineral balances. However, longstanding hyperfiltration becomes too heavy a burden, and together with other factors, turn into hidden assassins inflicting injuries to the kidneys, vasculature and bones.

Vascular calcification is a major morbidity and mortality risk in adult CKD. New awareness of this risk in children is highlighted by the findings of extensive arteriopathy in pediatric CKD.

Finally, elevated phosphate and parathyroid hormone levels are associated with significantly increased risk of bone fractures in pediatric CKD. Hence, for patient survival and quality of life, it is critically important to treat hyperphosphatemia and secondary hyperparathyroidism, early in the course of CKD.

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