Changes in bone structure and the muscle–bone unit in children with chronic kidney disease

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The impact of pediatric chronic kidney disease (CKD) on acquisition of volumetric bone mineral density (BMD) and cortical dimensions is lacking. To address this issue, we obtained tibia quantitative computed tomography scans from 103 patients aged 5–21 years with CKD (26 on dialysis) at baseline and 12 months later. Gender, ethnicity, tibia length, and/or age-specific *Z*-scores were generated for trabecular and cortical BMD, cortical area, periosteal and endosteal circumference, and muscle area based on over 700 reference subjects. Muscle area, cortical area, and periosteal and endosteal *Z*-scores were significantly lower at baseline compared with the reference cohort. Cortical BMD, cortical area, and periosteal *Z*-scores all exhibited a significant further decrease over 12 months. Higher parathyroid hormone levels were associated with significantly greater increases in trabecular BMD and decreases in cortical BMD in the younger patients (significant interaction terms for trabecular BMD and cortical BMD). The estimated glomerular filtration rate was not associated with changes in BMD *Z*-scores independent of parathyroid hormone. Changes in muscle and cortical area were significantly and positively associated in control subjects but not in CKD patients. Thus, children and adolescents with CKD have progressive cortical bone deficits related to secondary hyperparathyroidism and potential impairment of the functional muscle–bone unit. Interventions are needed to enhance bone accrual in childhood-onset CKD.

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Children with chronic kidney disease (CKD) have multiple risk factors for impaired bone accrual, including poor growth, delayed maturation, muscle deficits, decreased physical activity, abnormal mineral metabolism, and secondary hyperparathyroidism. We recently reported that childhood-onset CKD was associated with significant deficits in cortical volumetric bone mineral density (BMD), cortical dimensions, and muscle area, as measured by peripheral quantitative computed tomography (pQCT).[1,2] CKD was also associated with elevated trabecular BMD in the younger participants only. The cross-sectional design limited the assessment of determinants of bone abnormalities and associations between bone and muscle outcomes.

To our knowledge, longitudinal studies of bone accrual in childhood CKD, in the absence of intervening renal transplantation, are limited to a series of 7–18 participants.[3–6] These studies were further limited by the use of dual-energy X-ray absorptiometry (DXA) measures of areal BMD. DXA is a two-dimensional projection technique that obscures distinct CKD effects on trabecular and cortical bone,[7] and underestimates volumetric BMD in children with growth failure.[8]

The objectives of this prospective cohort study were as follows: (1) to assess changes in trabecular and cortical volumetric BMD and cortical dimensions over a 1-year interval in children and adolescents with mild-to-severe CKD; (2) to identify correlates of changes in pQCT parameters, including CKD progression, intact parathyroid hormone (iPTH) levels, and medications; and (3) to assess the relationship between changes in muscle area and bone dimensions (the functional muscle–bone unit) compared with longitudinal data in the healthy reference participants.

RESULTS

Participant characteristics

This report describes the 103 CKD participants with two pQCT scans, at a median duration of 12.5 months apart (interquartile range (IQR) 12.1–13.2), including 83 from the previous cross-sectional study.[2] The focus of this study is determinants of changes in bone; therefore, this cohort

includes an additional 20 participants who were ineligible for the previous study because of a history of solid organ transplantation. All previous renal transplant recipients in this study were on dialysis, with a median interval since transplantation of 5.1 (IQR 3.9–7.2) years and a median interval since starting dialysis of 11 (IQR 2–56) months. Baseline characteristics are summarized in Table 1. The reference participants have been described.[2,9,10]

Compared with the non-dialysis CKD, dialysis participants were significantly older, more likely to be of black race, and more likely to have focal segmental glomerulosclerosis.

Table 1 | Baseline characteristics in the chronic kidney disease participants

	Non-dialysis	Dialysis
N	77	26
Age, years	13.2 (9.5–16.7)	18.4 (13.6–19.3)
Male, *n* (%)	50 (65)	15 (58)
Race, n *(%)*		
White	62 (81)	12 (46)
Black	14 (18)	11 (42)
Other	1 (1)	3 (12)
Tanner stage 1–2, n (%)	35 (46)	4 (15)
Height *Z*-score	−0.57 ± 1.37	−1.19 ± 1.15
BMI *Z*-score	0.34 ± 1.24	0.25 ± 1.39
Underlying renal diagnosis, n *(%)*		
CAKUT	52 (68)	9 (35)
Focal segmental glomerulosclerosis	7 (9)	12 (46)
Systemic inflammatory	2 (3)	1 (4)
Other	16 (20)	4 (16)
Age at CKD diagnosis, years	2.5 (birth–8.4)	8.8 (1.5–12.9)
Interval since CKD diagnosis, years	7.1 (5.1–12.1)	8.5 (3.1–13.6)
Hemodialysis, *n* (%)		16 (62)
Duration of dialysis, months		4.5 (1.0–23.8)
History of previous renal transplantation, *n* (%)		14 (54)
History of previous cardiac or liver transplantation, *n* (%)	5 (6)	1 (4)

Abbreviations: BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease.
Results are presented as mean ± s.d., median (interquartile range), or *n* (%).

Clinical course

Laboratory results, estimated glomerular filtration rate (eGFR), and medications are summarized in Table 2. There was a significant decline in renal function over the study period in non-dialysis CKD participants with a median decrease of 2 (IQR −7 to 1) ml/min per 1.73 m^2. Two participants initiated dialysis. Serum iPTH and phosphorus levels increased significantly in the non-dialysis population. The proportion of non-dialysis participants above the normal iPTH range (>65 pg/ml) increased from 39% to 52% over the study. The mean iPTH was above the pediatric Kidney Disease Outcome Quality Initiative (KDOQI) CKD stage–specific target range in 32 (42%) and 13 (50%) of non-dialysis and dialysis participants, respectively, and above the lower European target range in 38 (49%) and 18 (69%), respectively.[11,12]

Among the 20 participants with a history of previous transplantation, 7 received glucocorticoids and 9 received calcineurin inhibitors during the study period. The remainder of participants treated with glucocorticoids had a diagnosis of focal segmental glomerulosclerosis, systemic inflammatory disease, or immunoglobulin A nephropathy.

Six CKD participants sustained a total of seven fractures (one tibia/fibula, one radius/ulna, and five foot/toe) during the study interval (57/1000 patient-years).

Peripheral QCT outcomes

Table 3 summarizes pQCT *Z*-scores in the CKD participants.

Trabecular BMD

Overall, trabecular BMD *Z*-scores did not change significantly in all participants combined, or within the non-dialysis and dialysis groups. The multivariate regression model for changes in trabecular BMD *Z*-score demonstrated

Table 2 | Laboratory parameters at baseline and follow-up and medication exposure over the study interval

	Non-dialysis			Dialysis		
	Baseline	Follow-up	*P*-value for change	Baseline	Follow-up	*P*-value for change
Laboratory results						
eGFR (ml/min per 1.73 m^2)	41 ± 14	37 ± 16	<0.001			
iPTH (pg/ml)	49 (27–84)	61 (30–119)	<0.01	146 (85–479)	183 (62–504)	0.85
Phosphorus (mg/dl)	4.4 (3.8–5.0)	4.5 (4.0–5.5)	<0.01	5.4 (3.9–6.5)	6.5 (4.9–7.7)	<0.05
Corrected calcium (mg/dl)	9.6 (9.3–10.0)	9.5 (9.2–10.0)	0.67	9.4 (8.6–9.6)	9.5 (8.9–10.1)	0.16
Bicarbonate (mmol/l)	24 ± 3	24 ± 3	0.56	24 ± 4	25 ± 5	0.52
Concurrent medications, n *(%)*						
Calcitriol	34 (44)			25 (96)		
Growth hormone	7 (9)			2 (8)		
Calcineurin inhibitor	0			9 (33)		
Glucocorticoid	4 (5)			8 (31)		
Phosphate binder	25 (32)			26 (100)		

Abbreviations: eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone.
Results are presented as mean ± s.d. if normal distribution or as median and (interquartile range (IQR)).
These results are limited to those who have baseline and follow-up results for each parameter.
Calcium was corrected for those with an albumin ⩽3.5 using Calcium + (0.8 × (4.0 − albumin)).
Phosphate binders include both calcium and non-calcium containing.