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Changes in DXA and Quantitative CT Measures of Musculoskeletal Outcomes Following Pediatric Renal Transplantation

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Abstract

This prospective study evaluated changes in DXA whole body bone mineral content (WB-BMC) and spine areal bone mineral density (spine-BMD), and tibia quantitative CT (QCT) trabecular and cortical volumetric BMD and cortical area in 56 children over 12 months following renal transplantation. At transplant, spine-BMD Z-scores were greater in younger recipients (<13 years), vs. 898 reference participants ($p < 0.001$). In multivariate models, greater decreases in spine-BMD Z-scores were associated with greater glucocorticoid dose ($p < 0.001$) and declines in parathyroid hormone levels ($p = 0.008$). Changes in DXA spine-BMD and QCT trabecular BMD were correlated ($R = 0.47$, $p < 0.01$). At 12 months, spine-BMD Z-scores remained elevated in younger recipients, but did not differ in older recipients (≥ 13) and reference participants. Baseline WB-BMC Z-scores were significantly lower than reference participants ($p = 0.02$). Greater glucocorticoid doses were associated with declines in WB-BMC Z-scores ($p < 0.001$) while greater linear growth was associated with gains in WB-BMC Z-scores ($p = 0.01$). Changes in WB-BMC Z-scores were associated with changes in tibia cortical area Z-scores ($R = 0.52$, $p < 0.001$), but not changes in cortical BMD Z-scores. Despite resolution of muscle deficits, WBBMC Z-scores at 12 months remained significantly reduced. These data suggest spine and whole body DXA provide insight into trabecular and cortical outcomes following pediatric renal transplantation.

Keywords

Bone mineral density; nutrition; renal transplantation; pediatric

INTRODUCTION

Children with chronic kidney disease (CKD) have multiple risk factors for impaired bone accrual including growth failure, abnormal mineral metabolism, malnutrition, muscle

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DISCLOSURES

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deficits and secondary hyperparathyroidism. Successful renal transplantation corrects many of the abnormalities contributing to bone disease; however, glucocorticoid therapy and persistent hyperparathyroidism may impair recovery. Dual energy x-ray absorptiometry (DXA) is widely available for bone health assessment. The International Society for Clinical Densitometry (ISCD) recommended lumbar spine and whole body (WB) DXA scans for children with chronic diseases that impact bone metabolism.(1) However, ISCD and Kidney Disease Improving Global Outcomes (KDIGO) guidelines(2) cautioned against the use of DXA in CKD for two reasons. First, DXA is a two-dimensional technique that summarizes superimposed trabecular and cortical bone mass within the projected bone area and may not capture opposing parathyroid hormone (PTH) effects to increase and decrease trabecular and cortical bone mass.(3) Second, the utility of DXA to predict fracture in advanced CKD remains unproven.(4)

In contrast, peripheral quantitative computed tomography (pQCT) is a three-dimensional technique that distinguishes between cortical and trabecular bone and provides measures of volumetric bone mineral density (vBMD) and cortical dimensions. We recently reported changes in tibia pQCT outcomes in pediatric renal transplant recipients.(5) At transplantation, trabecular vBMD was elevated in younger recipients and decreased significantly in association with greater glucocorticoid exposure. Cortical vBMD increased significantly in association with greater glucocorticoid exposure and greater improvements in PTH levels. The baseline deficits in cortical dimensions did not improve, despite rapid recovery of muscle deficits and significant improvements in PTH levels. DXA scans were also obtained in this cohort.

The objectives of these analyses were to 1) assess changes in DXA measures of spine-BMD, WB bone mineral content (WB-BMC), and body composition [lean mass (LM) and fat mass (FM)] in children and adolescents over 12 months after transplantation, 2) examine associations between DXA measures, disease characteristics, PTH levels and glucocorticoid exposure, 3) examine correlations between pQCT and DXA results, and 4) examine relations between changes in WB-BMC and LM as an index of the functional muscle-bone unit.(6) These analyses employed a novel method to adjust for the short stature that frequently confounds DXA measures in childhood CKD.(7, 8)

MATERIALS AND METHODS

Study Participants

This prospective study was part of a larger study of bone health in children with CKD, ages 5-21 years, at the Children's Hospital of Philadelphia (CHOP) and Cincinnati Children's Hospital Medical Center (CCHMC).(5, 8-13) Patients were ineligible if they were non-ambulatory or had developmental disorders preventing completion of study procedures. Baseline visits were completed within 2 weeks of transplantation and follow-up visits 3, 6 and 12 months after transplantation.(5) PQCT and vitamin D results were reported.(5, 12) Sixty-one recipients were enrolled and these analyses are limited to the 56 with >2 DXA scans; 53 completed the 12-month visit.

Transplant recipients were compared to a reference sample of 964 healthy children, ages 5-21 years (898 at CHOP, 66 at CCHMC) recruited from general pediatric practices. Participants were excluded for a history of illnesses or medications potentially affecting growth, maturation, and nutrition.(14) A subset of 224 at CHOP enrolled in a longitudinal study with a 12 month visit.(5)

The study protocol was approved by the CHOP (#01-002565) and CCHMC (#01-12-25) Institutional Review Boards. Informed consent was obtained from participants > age 18, and assent and parental consent from those <18 years.

Anthropometry and Physical Maturity

Height was measured using a stadiometer and weight with a digital scale. Pubertal development was classified according to Tanner by self-assessment questionnaire.(15)

CKD Disease Characteristics and Medications

Medical charts were reviewed for disease and treatment characteristics. Renal disease was categorized as congenital anomalies of the kidney and urinary tract (CAKUT), focal segmental glomerulosclerosis (FSGS), systemic inflammatory disease (Wegener's granulomatosis, systemic lupus erythematosus) and other (cystinosis, tubulointerstitial nephritis, Alports, etc.).

Dual Energy X-Ray Absorptiometry

The ISCD Official Positions state that lumbar spine and WB (excluding the head) scans are the preferred DXA sites in children.(16) Spine (L1-4) and WB DXA scans were performed using a Delphi/Discovery (Hologic, Bedford, MA) densitometer in array mode and analyzed using software versions 12.3 and 12.4, to generate spine-BMD (g/cm^2) and WB-BMC (g). WB-BMC, as opposed to BMD, was used in this study because CKD results in cortical bone loss through decreases in both density and dimensions, and the ISCD recommends WB-BMC due to better reproducibility. DXA WB body composition measures included fat mass (FM) and LM (kg). A spine phantom and WB phantom were scanned daily and weekly, respectively. The in vivo percent coefficient of variation (CV) was 0.85% for spine-BMD, 1.06% for WB-BMC, 0.48% for WB LM and 1.61% for WB FM.

Peripheral Quantitative Computed Tomography

Tibia pQCT scans (Stratec XCT2000 12-detector unit, Orthometrix, Inc) were obtained at the 3% site for trabecular vBMD and 38% site for cortical cross-sectional area and vBMD, as described.(5) The hydroxyapatite phantom was scanned daily and our CV for short-term precision ranged from 0.5% to 1.6% for pQCT outcomes.

Laboratory Studies

Serum creatinine (mg/dL) was measured by spectrophotometric enzymatic assay (Vitros, Johnson & Johnson, Rochester, NY) with a CV of 1-5%. Estimated GFR (eGFR) ($\text{ml}/\text{min}/1.73\text{m}^2$) was calculated using the CKiD pediatric estimating equation.(17) Plasma intact PTH (iPTH) was measured by ^{125}I radioimmunoassay (Scantibodies Clinical Laboratory); CV 3-5%.(18) It was not possible to obtain informed consent and research specimens before transplantation in 38 recipients. Therefore, a clinical iPTH obtained within 3 months before transplantation was utilized in recognition of the rapid declines in iPTH after transplantation. Eighteen participants had a study iPTH drawn prior to or at transplantation, 31 participants had a iPTH result available in the medical records within three months prior to transplantation. The remainder ($n=5$) did not have a iPTH level prior to transplantation; therefore, the analyses included the research iPTH drawn a median of 10 days after transplantation.

Statistical Analysis

Statistical analysis were performed using Stata 11.0 (Stata,Corp., College Station, TX). A p-value <0.05 was considered statistically significant and two-sided tests used throughout. Continuous variables were expressed as means $\pm$ standard deviation (SD) or median (IQR,

interquartile range) for skewed distributions. Group differences between transplant recipients and healthy reference subjects were assessed using Student's *t* test or the Wilcoxon rank sum test. Changes within transplant recipients were tested using the paired *t*-test or the Wilcoxon signed rank test. Differences in proportions were tested using the chi-square test. Correlations between continuous variables were assessed by Pearson product moment correlations or Spearman's rank correlations.

Sex- specific Z-scores for height and body mass index (BMI) were calculated relative to age using national reference data.(19) In addition, BMI Z-scores were calculated in transplant recipients relative to height-age ($BMI_{\text{height-age}}$) as recommended in CKD.(20) DXA and pQCT results were converted to sex- and race- (black vs. non-black) specific Z-scores relative to age using the LMS method (LMS Chartmaker version 2.3) (21),as described.(8) This method accounts for the non-linearity, heteroscedasticity,and skew of bone and body composition data with age. The CHOP reference sample was used to generate the LMS curves. The median (range) age in the reference participants was 11.6 (5.0 to 21.9) years with a mean (SD) of 11.9 (4.9) years. While the reference participants were younger than the transplant recipients, on average, the LMS curves provided robust estimates of the distribution of each outcome across the entire age range of the transplant recipients. The reference participants were 48% male and 39% black. The mean (SD) height and BMI Z-scores were 0.36 (1.00) and 0.27 (0.92), respectively.

DXA Z-scores for spine-BMD, WB-BMC, LM and FM were generated relative to age and were then adjusted for height Z-score according to the method by Zemel et al.(7) This method uses prediction equations that adjust for height Z-score and interactions between age and height Z-score. The impact of this adjustment was recently reported in children with pretransplant CKD: the mean WB-BMC Z-score relative to age was -1.31 whereas the result adjusted for height Z-score was -0.36.(8) Zemel et al, demonstrated that this method provides an unbiased adjustment. In contrast, the assessment of BMC relative to height or height-age results in a systematic bias as older healthy children with lower height Z-scores are compared with younger children and appear to have greater BMC or BMD than expected. An alternative approach is to assess DXA results relative to bone age; however, this does not address the impact of bone size, especially among mature participants. The pQCT cortical area Z-scores were similarly adjusted for age and tibia length for age Z-score.

We previously reported that pQCT trabecular vBMD Z-scores were markedly elevated in younger children at transplantation.(5) Those data were presented separately for younger (<13 years) and older (>13) participants. Similar patterns were observed for DXA spine-BMD Z-scores here and results are presented according to the aforementioned age strata and comparisons with reference participants were performed within these two strata.

Changes in DXA Z-scores within transplant recipients over 12 months were assessed with quasi-least squares (QLS) regression using the Stata xtqls function.(22, 23) QLS models allow for a variable number of measurements per participant and the implementation of the Markov correlation structure that is appropriate for modeling associations among measurements that are unequally distributed in time. The QLS models include changes within each interval as the outcome (i.e. baseline to 3 months, 3 to 6 months, and 6 to 12 months). In each model, the following covariates were tested and adjusted for if statistically significant: DXA Z-score at interval start, age, sex, race (black versus non-black), and study location (CHOP vs. CCHMC). Additional covariates hypothesized for the bone models were interval glucocorticoid exposure, interval increases in height, eGFR at 3 months, iPTH at interval start and changes in iPTH, calcium and phosphorus levels over each interval (adjusted for the value at the beginning of each interval). The effect of calcineurin inhibitors or steroid free protocols were not tested in the models given the vast majority of participants

received tacrolimus and glucocorticoids. The models for body composition tested for relations with interval glucocorticoid therapy and eGFR.

To determine if gains in WB LM Z-scores were associated with expected gains in WB-BMC Z-scores after transplantation, the 12-month changes in WB-BMC Z-scores relative to gains in LM Z-scores were compared in transplant recipients and the subset of reference participants enrolled in the longitudinal study using multivariable linear regression analysis.

The Tables and Figures reporting DXA outcomes were restricted to participants with data at noted visits in order to facilitate comparisons over time within the same individuals.

RESULTS

Participant and Disease Characteristics

The characteristics of the 56 participants at the time of transplantation are summarized in Table 1.(5, 12). Height and BMI Z-scores were significantly lower in transplant recipients compared to reference participants (both $p<0.01$). Thirty-six (64%) recipients were on dialysis prior to transplantation

Clinical Course after Transplantation

The laboratory parameters, eGFR and medications are summarized in Table 2.(5, 12). Serum iPTH levels declined significantly 3 months after transplantation, with a median (range) decrease of 178 pg/ml (−1438 to +49; $p<0.001$). iPTH levels were within normal range (66 pg/ml) in 81% of recipients at 6 months and 78% at 12 months. The average eGFR did not change between 3 and 12 months following transplantation, with 24 (45%) participants having an eGFR below 60 ml/min/1.73m² at the 12-month visit. The majority of transplant recipients were treated with a combination of glucocorticoids, tacrolimus and mycophenolate mofetil. Two were treated with a steroid-free protocol.

DXA Bone Outcomes

Table 3 summarizes DXA and anthropometric Z-scores at transplantation and 12 months among the 45 participants with results at both visits.

Lumbar Spine DXA BMD—At transplantation, spine-BMD Z-scores were inversely associated with age ($r=-0.34$, $p=0.02$), but were not associated with PTH levels. The results in Table 3 are stratified according to age. Baseline spine-BMD Z-scores were significantly greater in younger transplant recipients ($n=20$) compared with reference participants ($p<0.001$). Spine-BMD Z-scores decreased over the 12 months in the younger ($p=0.006$) and older ($p=0.06$) participants (Table 3 and Figure 1). At the 12-month visit, spine-BMD Z-scores in younger participants ($n=23$) remained significantly higher than reference participants ($p=0.005$). The 12-month results in older participants ($n=28$) did not differ from the reference sample.

In the QLS models for changes in spine-BMD Z-scores in all transplant recipients combined, greater glucocorticoid exposure [β (95% CI) = −1.87 (−2.65, −1.08) per mg/kg/day, $p<0.001$] and greater decreases in iPTH levels [β (95% CI) = 0.05 (0.01, 0.09) per 100 pg/ml $p=0.008$] over the intervals between visits were independently associated with greater declines in spine-BMD Z-scores. The results did not change when limited to the participants with pre-transplant iPTH levels only. Changes in spine-BMD Z-scores were not associated with eGFR, calcium or phosphorus levels or linear growth following transplantation.

Whole Body DXA BMC—At transplantation, WB-BMC Z-scores were significantly lower in transplant recipients (n=48) compared with reference participants (p=0.02). Although there was a decline in WBBMC Z-scores over the first 3 months following transplantation [mean change $\pm$ SD (-0.11 $\pm$ 0.29, p=0.02)], the decline over the 12 month study was not statistically significant (Table 3, Figure 2). At the 12-month visit WB-BMC Z-scores (n=53) remained lower compared to reference participants (p=0.02).

In the QLS model, linear growth and glucocorticoid exposure were significantly and independently associated with changes in WB-BMC Z-scores: greater glucocorticoid exposure [β (95% CI) = -0.75 (-1.16, -0.35) per mg/kg/day p<0.001] over the intervals was associated with greater declines in WB-BMC Z-scores, while greater linear growth [β (95% CI) = 0.035 (0.007, 0.062) per cm p=0.01] was associated with greater increases in WB-BMC Z-scores. Changes in WB-BMC Z-scores were not associated with eGFR, baseline or changes in iPTH, calcium and phosphorus levels.

Whole Body Lean Mass and Fat Mass—At transplantation, LM Z-scores were significantly lower in transplant recipients (n=48) compared to reference participants (p=0.004) and FM Z-scores (n=48) were not significantly different (p=0.07). Over the 12 month study, both LM and FM Z-scores increased significantly. At the 12-month visit, LM Z-scores did not differ between transplant recipients (n=53) and reference participants, whereas FM Z-scores were greater in transplant recipients (n=53) (p<0.0001).

The QLS model for changes in body composition Z-scores demonstrated that greater increases in FM Z-scores over each interval [β (95% CI) = 0.32 (0.20, 0.44) p<0.001] were associated with greater increases in LM Z-scores. Greater glucocorticoid exposure over each study interval was associated with greater increases in FM Z-scores [β (95% CI) = 2.08 (1.37, 2.79) per mg/kg/day p<0.001]. Glucocorticoid exposure was not associated with changes in LM Z-scores, independent of changes in FM Z-scores.

Changes in WB-BMC Relative to Changes in WB LM Z-scores—In order to determine if the gains in WB LM after transplantation were associated with expected gains in WB-BMC (i.e. the “functional muscle-bone unit”), the 12-month changes in WB LM and WB-BMC Z-scores were compared in the 45 transplant recipients and the 224 reference participants enrolled in the longitudinal substudy. The models were adjusted for baseline WB-LM and WB-BMC Z-scores. WB-BMC Z-scores increased with increasing LM Z-scores in both transplant and reference participants. However, the increase in WB-BMC Z-scores for a given increase in LM Z-score was significantly less in transplant recipients compared with reference participants [β (95% CI) = -0.17 (-0.27, -0.08) p<0.001].

Correlations between DXA and pQCT Outcomes—The Pearson correlations between tibia pQCT trabecular vBMD and DXA spine-BMD Z-scores were 0.45 (p<0.01) and 0.36 (p=0.02) at baseline and 12 months, respectively. The changes in each parameter over 12 months were also correlated (r=0.47, p<0.01). The decrease in pQCT trabecular vBMD Z-score was significantly greater than the decrease in spine-BMD Z-score (-1.06 $\pm$ 1.29 vs. -0.43 $\pm$ 0.77, p<0.01).

The Spearman correlations between tibia pQCT cortical area and DXA WB-BMC Z-scores were 0.77 (p<0.001) and 0.71 (p<0.001) at baseline and 12 months, respectively. The correlation between changes in each parameter over 12 months was significant (r=0.52, p<0.001). In contrast, the DXA WB-BMC and pQCT cortical vBMD Z-scores were not correlated at either visit, nor were the changes correlated (all r<0.1, all p>0.4). The changes in pQCT cortical area Z-score and changes in WB-BMC Z-score did not differ (-0.04 $\pm$ 0.62 vs. -0.05 $\pm$ 0.42, p<0.48).

DISCUSSION

DXA is the most widely used method to assess bone health. However, DXA has unique limitations in the setting of CKD. The wide spectrum of bone turnover abnormalities in CKD may differentially affect the superimposed trabecular and cortical compartments in the two-dimensional DXA image, yielding potentially misleading results. For example, PTH excess has generally catabolic effects on cortical bone with decreases in cortical vBMD and cortical thickness, and generally anabolic effects on trabecular bone with increases in trabecular thickness.(3, 24) Accordingly, KDIGO guidelines recommended against routine DXA BMD testing in patients with CKD stages 3 to 5 because “BMD does not predict the type of renal osteodystrophy”.(2) However, KDIGO did recommend measuring DXA BMD in the first three months after kidney transplantation in patients with an eGFR > 30 ml/min/1.73m² if treated with glucocorticoids.

Poor growth and decreased LM in pediatric CKD pose additional challenges in the interpretation of DXA areal BMD results. DXA is a two-dimensional projection technique that does not account for bone depth; therefore, DXA areal BMD and BMC relative to age are systematically underestimated in children with low height-for-age Z-scores.(25) The ISCD recommends that DXA Z-scores should be adjusted for short stature.(16) This study used a novel unbiased method developed in the Bone Mineral Density in Childhood Study to adjust for the decreased height Z-scores in the transplant recipients.(7) The ISCD guidelines also noted that body composition measures in conjunction of WB-BMC results may be helpful in evaluating patients with chronic conditions. As muscles increase during growth, bones adapt by increasing dimensions and strength. This capacity of bone to respond to mechanical loading with increased bone strength is greatest during childhood.(26) Therefore, we examined the relations between changes in whole body LM and BMC in this cohort.

Prior DXA studies of bone health in pediatric renal transplant recipients yielded inconsistent results,(27-35) largely related to varying use of methods to adjust for low height Z-scores, lack of reference data, differences in measurement sites, and inclusion of participants at highly variable (and frequently unspecified) intervals following transplantation. To our knowledge, this is the first study to assess changes in DXA measures of bone health and body composition in an incident cohort of pediatric renal transplant recipients, with adjustment for low height Z-scores based on robust reference data and inclusion of measures of PTH levels and glucocorticoid exposure. The study is also the first to compare pQCT and DXA results in children or adults.

The greater decreases in spine-BMD Z-scores in association with higher glucocorticoid doses and greater declines in iPTH levels were consistent with known effects of glucocorticoids and PTH to decrease and increase trabecular BMD, respectively. The observation of higher spine-BMD Z-scores in the younger compared with older participants at the time of transplantation was consistent with our pQCT results in this cohort where the mean (SD) trabecular BMD Z-scores in the tibia metaphysis were +2.10 (1.97) and -0.16 (1.51) in those recipients < 13 and >13 years of age, respectively.(5) The significant, but smaller magnitude of the age differences for the baseline DXA results (Table 3) compared with pQCT results may be due to the superimposed cortical bone in the DXA image, potentially concealing PTH-induced increases in trabecular volumetric BMD. In our prior pQCT studies in pre-transplant CKD,(11, 13) we detected a significant interaction between PTH levels and age whereby the positive association between PTH levels and trabecular volumetric BMD was more pronounced in younger participants. Prior pQCT studies by other investigators also documented greater trabecular BMD in the younger participants with

CKD.(36) The reason is unknown, but may relate to impaired resorption of secondary spongiosa in advanced CKD.(37)

Despite high-dose glucocorticoid exposure in the majority, spine-BMD Z-scores remained significantly greater in younger transplant recipients at 12 months, compared with reference participants. The spine-BMD Z-scores in the older participants were similar to reference participants. In contrast, the pQCT results revealed significant trabecular deficits in the older transplant recipients at 12 months, with a mean vBMD Z-score of -0.54. The superimposed cortical bone (with significant increases in cortical vBMD following transplantation, as described below) may have concealed trabecular deficits in the DXA scans. The observation that the decreases in pQCT trabecular vBMD Z-scores were significantly greater than the declines in spine-BMD Z-scores in this study is consistent with this theory. Importantly, these explanations are speculative since the DXA scans were obtained in the spine and the pQCT scans in the tibia metaphysis. Future studies using spine QCT and DXA are necessary to provide comparisons at the same anatomic site.

Cortical bone comprises approximately 80% of the skeletal bone mass and thus DXA WB-BMC is largely a function of cortical vBMD and cortical dimensions. This study demonstrated that glucocorticoid exposure was negatively associated with changes in WB-BMC Z-scores. We conclude that this was due to glucocorticoid effects to impair bone formation and accrual of cortical dimensions. This is consistent with our pQCT data in this cohort demonstrating that greater glucocorticoid doses were associated with greater decreases in periosteal circumference Z-scores.(5) That is, periosteal surface did not contract; rather, the periosteal circumference did not expand to the extent expected relative to concurrent increases in tibia length. In contrast, greater glucocorticoid exposure was significantly associated with greater increases in pQCT cortical vBMD in this transplant cohort, as well as in other childhood diseases.(38-40) Glucocorticoids therefore have competing effects on total cortical bone mass due to increases in cortical vBMD but inhibition of cortical expansion. In order to assess the impact of these opposing effects, we assessed the relative contribution of cortical dimensions and vBMD to cortical BMC on pQCT scans using linear regression. Within our healthy controls, a 1.0 SD lower cortical vBMD Z-score was associated with a 0.20 SD lower cortical BMC Z-score, while a 1.0 SD lower cortical cross-sectional area Z-score was associated with a 0.97 SD lower cortical BMC Z-score. Therefore, we submit that WB-BMC provides an index of cortical dimensions with minimal impact of disease or treatment effects on cortical BMD. The highly significant correlation between changes in DXA WB-BMC and pQCT cortical area Z-scores (and lack of correlation with pQCT cortical vBMD Z-scores) following transplantation is consistent with this interpretation. The association between glucocorticoids and lower WB-BMC may also have been due to glucocorticoid effects to decrease the trabecular component that makes up approximately 20% of WB-BMC. The lack of an association between changes in PTH levels and WB-BMC Z-scores may also be due to the inability of WB-BMC to capture effects on cortical vBMD. Our prior pQCT data in these transplant recipients documented an association between declines in PTH and gains in cortical vBMD but no association between changes in PTH levels and cortical dimensions.

A novel finding in this study is the significant positive association between gains in height and WB-BMC Z-scores. The association was not observed for spine-BMD. Given that the WB-BMC Z-scores at each visit were adjusted for height Z-score, this indicates that greater linear growth is associated with greater gains in WB-BMC than can be explained by the gains in height alone. Periods of growth may provide a unique opportunity to recover cortical dimensions, such that strategies to promote accrual of cortical dimensions should target intervals of greatest growth. We previously reported that gains in calf muscle were not

associated with the expected gains in cortical structure following transplantation in this cohort.(5) The results reported here confirm these findings using WB DXA. The clinical significance of this observation is unknown; however these findings warrant further study. Potential mechanisms include physical inactivity, poor muscle quality and function, or glucocorticoid effects.

This study has multiple limitations. First, the absence of bone biopsy data prohibited any correlations of DXA results with bone microarchitecture, turnover or mineralization. Second, the DXA and pQCT scans were not obtained in the same anatomic location. Third, the study did not include lateral spine x-rays for the assessment of vertebral fractures. This is an important limitation in light of recent reports of vertebral compression fractures in pediatric solid organ transplant recipients.(28, 41) While the relations between DXA Z-score and fracture risk have not been characterized in pediatric renal transplant recipients, prospective studies have demonstrated that lower whole body BMC predicted fractures in healthy children(42) and lower lumbar spine BMD was associated with fractures in children treated with glucocorticoids.(43, 44). Furthermore, DXA studies in adult renal transplant recipients demonstrated that lower BMD was associated with increased fracture risk.(45). Additional studies are needed to determine if the DXA results observed here are associated with clinically important increases in short-term and long-term fracture risk.

In summary, these data suggest that both WB and spine DXA provide insight into bone health following renal transplantation in children and adolescents. The spine-BMD Z-scores captured the expected independent effects of PTH and glucocorticoids on trabecular bone. The WB-BMC results illustrated the utility of this outcome to monitor impairment of cortical bone accrual, particularly accrual of cortical dimensions. The recent availability of population based DXA reference data (46, 47) along with prediction equations to adjust WB and spine scans for short stature may pave the way for use of these outcomes in clinical practice.(7)

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Abbreviations

CKD	Chronic Kidney Disease
DXA	Dual energy x-ray absorptiometry
ISCD	International Society for Clinical Densitometry
WB	whole body
KDIGO	Kidney Disease Improving Global Outcomes
PTH	parathyroid hormone
pQCT	peripheral quantitative computed tomography

BMD	bone mineral density
vBMD	volumetric bone mineral density
BMC	bone mineral content
CHOP	Children's Hospital of Philadelphia
CCHMC	Cincinnati Children's Hospital Medical Center (CCHMC)
CAKUT	Congenital anomalies of the kidney and urinary tract
FSGS	Focal segmental glomerular sclerosis
LM	Lean mass
FM	Fat mass
CV	coefficient of variation
iPTH	intact PTH
IQR	interquartile range
QLS	quasi-least squares
CI	confidence interval

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Figure 1. Lumbar spine BMD Z-scores after transplantation according to age at transplantation. The data are limited to the 14 participants < 13 years of age and the 18 ≥ 13 years of age with spine-BMD Z-scores at all four visit to facilitate comparison within the same participants over time.

Figure 2. Whole body BMC and Lean Mass Z-scores after transplantation. The data are limited to the 35 participants with Z-scores at all four visits to facilitate comparison within the same participants over time.

Table 1**Participant Characteristics at Renal Transplantation**

N	56
Age, yr	14.2 (6.8 to 21.5)
Male, n (%)	34 (60)
Race, n (%)	
White	43 (77)
Black	10 (18)
Other	3 (5)
Tanner stage 1-2, n (%)	23 (41)
Height Z-score	-1.33 ± 1.37
BMI Z-score	-0.14 ± 1.28
BMI _{height-age} Z-Score	0.29 ± 1.20
Underlying renal diagnosis, n (%)	
CAKUT	36 (64)
FSGS	11 (20)
Other	9 (16)
Age at CKD diagnosis, yr	2.2 (birth to 17.7)
Interval since CKD diagnosis, yr	9.2 (0.4 to 21.4)
History of prior renal transplantation, n (%)	2 (4)
Deceased donor kidney n (%)	25 (45)
Pre-emptive transplantation n (%)	20 (36)
Duration of dialysis, months	7.3 (0.4 to 70)

Results are presented as the mean ± SD for normally distributions, or the median (range), for skewed distributions, or n (%).

CAKUT: Congenital anomalies of the kidney and urinary tract

FSGS: Focal segmental glomerulosclerosis

Table 2**Laboratory Parameters and Medications after Transplantation**

	Baseline	3 months	6 months	12 months
Laboratory parameters	n=48	n=46	n=49	n=53
iPTH (pg/ml)	243 [*] (9 - 1552)	45 (14 - 176)	44 (18 - 163)	40 (13 - 292)
eGFR (ml/min/1.73m ²)		64 ± 13	63 ± 15	64 ± 17
		45 - 93	28 - 107	28 - 108
Phosphorus, (mg/dl)	6.6 ± 1.8	4.0 ± 0.9	4.0 ± 0.8	4.0 ± 0.8
	2.6 - 10.8	2.0 - 5.8	2.2 - 5.6	2.0 - 5.3
Medications				
Glucocorticoids, n (%)	45 (94)	45 (98)	48 (94)	50 (94)
Interval glucocorticoids (mg/kg/day)		0.36 ± 0.11	0.15 ± 0.05	0.13 ± 0.07
		0.09 - 0.62	0.05 - 0.32	0.05 - 0.36
Tacrolimus n (%)		41 (89)	43 (88)	43 (81)
Mycophenolate mofetil, n (%)		38 (83)	37 (76)	39 (74)
Azathioprine, n (%)		2 (4)	3 (6)	4 (8)
Sirolimus, n (%)		9 (20)	13 (27)	16 (30)

Continuous data are presented as the mean ± standard deviation (range) for normal distributions and the median (range) for skewed. Categorical data are presented as n (%).

*The median (range) iPTH concentration in the 18 transplant recipients enrolled and tested before renal transplantation was 199 (44 to 1194 pg/ml). For participants whose baseline visit occurred after renal transplantation, a clinical iPTH drawn within 3 months before renal transplantation was available in 31 participants; the median pre-transplant clinical iPTH concentration was 312 (9 to 1552 pg/ml). In the n=5 participants without a clinical or research iPTH measurement before renal transplantation, the post-transplant baseline iPTH was 165 (63 to 237 pg/ml).

Table 3

DXA and Anthropometric Z-scores at Transplantation and 12 months

Z-Score	0 months	12 months	0-12 month change	p value for the change
LS BMD				
< 13 years	1.36 ± 1.48 ^b	0.68 ± 1.17 ^b	-0.68 ± 0.90	0.006
	1.59 (0.07, 2.27)	0.48 (-0.19, 1.54)	-0.65 (-1.16, -0.09)	
13 years	0.21 ± 0.80	-0.01 ± 0.76	-0.22 ± 0.54	0.06
	0.07 (-0.32, 0.77)	-0.01 (-0.79, 0.47)	-0.02 (-0.64, 0.25)	
WB BMC	-0.33 ± 1.10 ^a	-0.38 ± 1.03 ^a	-0.05 ± 0.41	0.43
	-0.28(-0.91, 0.34)	-0.23 (-0.80,0.20)	-0.03 (-0.26, 0.22)	
WB Fat Mass	0.29 ± 1.28	1.14 ± 1.24 ^c	0.85 ± 0.86	<0.0001
	0.13 (-0.75, 1.19)	0.99 (0.23, 1.95)	0.95 (0.27, 1.27)	
WB Lean Mass	-0.43 ± 1.00 ^b	-0.03 ± 1.02	0.40 ± 0.67	0.0002
	-0.19 (-1.27, 0.15)	0.23 (-0.89, 0.52)	0.35 (0.07, 0.64)	
Height	-1.17 ± 1.44 ^c	-1.22 ± 1.43 ^c	-0.04 ± 0.23	0.21
	-1.28 (-2.24, -0.11)	-1.24 (-2.07, -0.19)	-0.04 (-0.12, 0.08)	
BMI	-0.04 ± 1.33	0.72 ± 1.39	0.76 ± 0.85	<0.0001
	0.14 (-0.83, 0.73)	1.14 (-0.11, 1.71)	0.61 (0.20, 1.15)	
BMI_{height-age}	0.33 ± 1.26	1.18 ± 1.17 ^c	0.79 ± 0.81	<0.0001
	0.55 (-0.44, 1.17)	1.35 (0.21, 1.93)	0.72 (0.34, 1.17)	

These results are limited to the 45 transplant recipients with a DXA at transplantation and 12 months later. There are 53 transplant recipients with anthropometric data.

Z-scores are expressed as mean ± SD and median (interquartile range).

The p value was generated by paired t-test.

LS BMD; Lumbar spine Bone Mineral Density

WB BMC; Whole Body Bone Mineral Content

^a p<0.05

^b p<0.01

^c p<0.001 compared to reference participants