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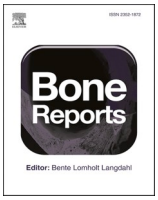

Bone health in autosomal dominant polycystic kidney disease (ADPKD) patients after kidney transplantation

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ABSTRACT

ADPKD is caused by pathogenic variants in *PKD1* or *PKD2*, encoding polycystin-1 and -2 proteins. Polycystins are expressed in osteoblasts and chondrocytes in animal models, and loss of function is associated with low bone mineral density (BMD) and volume. However, it is unclear whether these variants impact bone strength in ADPKD patients. Here, we examined BMD in ADPKD after kidney transplantation (KTx). This retrospective observational study retrieved data from adult patients who received a KTx over the past 15 years. Patients with available dual-energy X-ray absorptiometry (DXA) of the hip and/or lumbar spine (LS) post-transplant were included. ADPKD patients (n = 340) were matched 1:1 by age (±2 years) at KTx and sex with non-diabetic non-ADPKD patients (n = 340). Patients with ADPKD had slightly higher BMD and T-scores at the right total hip (TH) as compared to non-ADPKD patients [BMD: 0.951 vs. 0.897, $p < 0.001$; T-score: −0.62 vs. -0.99, $p < 0.001$] and at left TH [BMD: 0.960 vs. 0.893, $p < 0.001$; T-score: −0.60 vs. -1.08, $p < 0.001$], respectively. Similar results were found at the right femoral neck (FN) between ADPKD and non-ADPKD [BMD: 0.887 vs. 0.848, $p = 0.001$; T-score: −1.20 vs. -1.41, $p = 0.01$] and at left FN [BMD: 0.885 vs. 0.840, $p < 0.001$; T-score: −1.16 vs. -1.46, $p = 0.001$]. At the LS level, ADPKD had a similar BMD and lower T-score compared to non-ADPKD [BMD: 1.120 vs. 1.126, $p = 0.93$; T-score: −0.66 vs. -0.23, $p = 0.008$]. After adjusting for preemptive KTx, ADPKD patients continued to have higher BMD T-scores in TH and FN. Our findings indicate that BMD by DXA is higher in patients with ADPKD compared to non-ADPKD patients after transplantation in sites where cortical but not trabecular bone is predominant. The clinical benefit of the preserved cortical bone BMD in patients with ADPKD needs to be explored in future studies.

1. Introduction

Autosomal dominant polycystic disease (ADPKD) is the most common monogenic hereditary kidney disease and the fourth leading cause of kidney failure worldwide, accounting for 5–10 % of patients requiring kidney replacement therapy (Chebib and Torres, 2016; Perrone et al., 2001). ADPKD is caused mainly by pathogenic variants in the *PKD1* (~85 %) or *PKD2* (~15 %) genes (Torres et al., 2007), and is marked by

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an expansion of bilateral kidney cysts that progressively destroy kidney parenchyma and architecture, with 98 % and 78 % of male and female patients reaching kidney failure by age 80, respectively (Lavu et al., 2020). Nevertheless, ADPKD disease manifestations are not solely confined to kidneys as it affects other organs such as the liver, pancreas, and cardiovascular system (Chebib et al., 2016; Cornec-Le Gall et al., 2019). Polycystin-1 (PC1), encoded by the *PKD1* gene, functions as a G protein-coupled receptor (Hughes et al., 1995). Functional PC1 protein level is associated with ADPKD onset and progression (Hopp et al., 2012). Polycystin 2 (PC2), encoded by the *PKD2* gene, acts as a calcium channel (Mochizuki et al., 1996). Both proteins co-localize to the primary cilia of the kidney tubular epithelial cells forming the PC1/PC2 complex, which has a role in intracellular calcium regulation and its signal transduction cascade (Hughes et al., 1995; Tsiokas et al., 1997; Yoder et al., 2002). Moreover, PC1 and PC2 are expressed in various tissues, including the brain, heart, muscle, and bone (Peters et al., 1999; Markowitz et al., 1999). PC1 and PC2 are expressed in osteoblasts, osteocytes, and chondrocytes (Ecder and Schrier, 2009; Li et al., 2017; Lu et al., 2001; Xiao et al., 2010; Xiao et al., 2008). Experimental models with global, conditional loss or reduced dosing of the *Pkd1* or *Pkd2* genes in bone exhibit intramembranous and endochondral bone defects, decreased trabecular volume, low bone mineral density (BMD), osteopenia, reduced cortical thickness, and the development of craniofacial anomalies (Supplemental Table 1) (Li et al., 2017; Lu et al., 2001; Xiao et al., 2010; Xiao et al., 2008; Khonsari et al., 2013; Hou et al., 2009; Boulter et al., 2001; Xiao et al., 2014; Xiao et al., 2006; Qiu et al., 2012).

Despite the reported findings of the lower BMD and skeletal deformities associated with *Pkd1* and *Pkd2* loss in animal models, the effect of polycystin reduction on the human skeleton in the ADPKD population remains elusive. A recent cross-sectional observational study in patients with kidney failure reported that ADPKD has a unique bone phenotype, including lower turnover rates and a preserved cortical bone mineral density (Evenepoel et al., 2019). In addition, Gitomer et al. studied the bone phenotype in ADPKD patients during early CKD stages and demonstrated lower total alkaline phosphatase, higher circulating intact fibroblast growth factor 23, and decreased bone formation rate without evidence of higher rates of fractures when compared to other causes of kidney failure (Gitomer et al., 2021). Moreover, compared to healthy individuals, patients with ADPKD demonstrated significantly lower osteoid volume/bone volume and bone formation rate/bone surface (Gitomer et al., 2021).

The aim of the present study is to compare, using bone density scans, whether the phenotype of ADPKD patients differs from non-diabetic non-ADPKD patients after kidney transplantation.

2. Materials and methods

2.1. Study design

This retrospective study was performed with adherence to the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board (IRB#: 18-009199; date of approval: 11/14/2018). Adult patients who received a kidney transplant at Mayo Clinic between January 2005 and March 2020 were retrieved from the Mayo Clinic Kidney Transplant Database. We applied the following inclusion criteria: (i) kidney transplant from January 2005 to March 2020, (ii) available DXA of hip and/or spine post-transplant. The exclusion criteria included: (i) multiple kidney transplants, (ii) diabetes mellitus, autoimmune disease (e.g., primary FSGS), and extra-genitourinary malignancies. After applying the inclusion and exclusion criteria, 680 out of 1097 patients were matched 1:1 for age at kidney transplant (±2 years) and gender. Patients were divided into cases (ADPKD; n = 340) and controls (non-ADPKD; n = 340) (Fig. 1).

2.2. Data collection

Data regarding clinical and demographic information, including date of birth, date of transplant, sex, race, height, weight, the primary cause of kidney failure, estimated glomerular filtration rate (eGFR) using the CKD-EPI formula (Levey et al., 2009), creatinine, medications

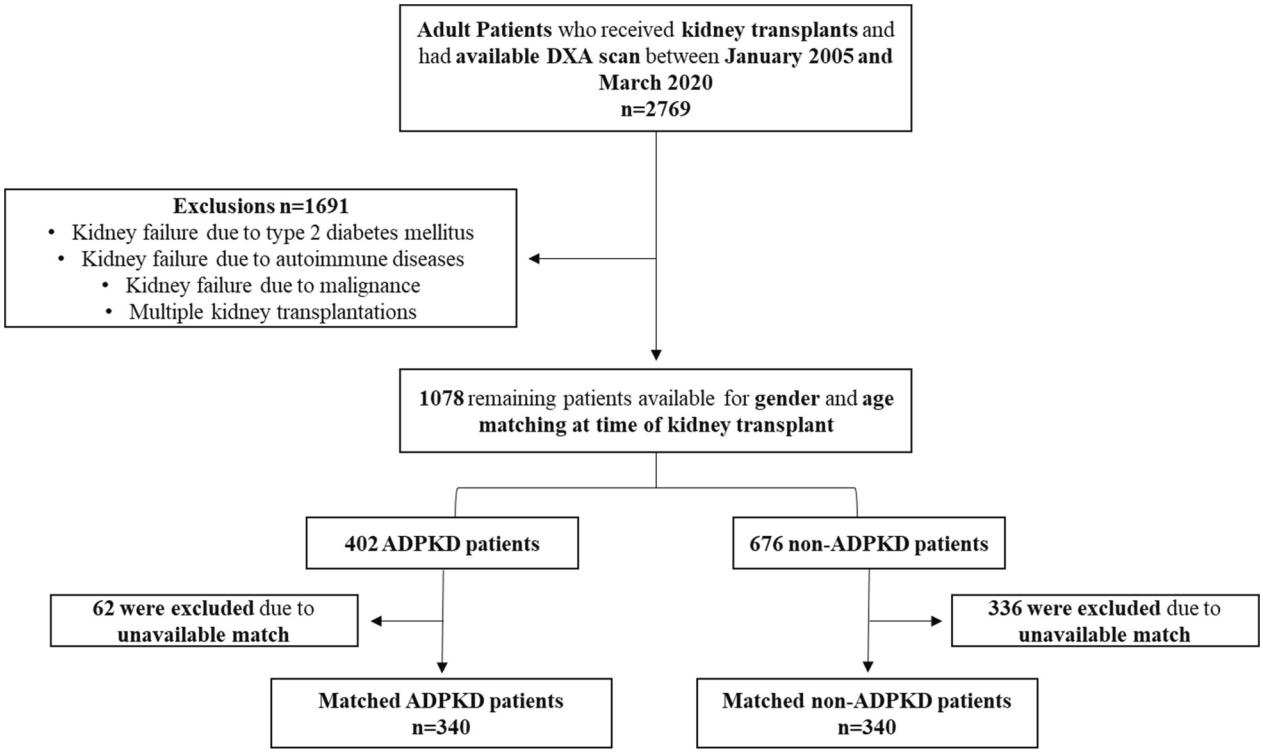

Fig. 1. Study flow chart and cohort selection illustrating patient exclusions and group allocation based on kidney transplantation and DXA scan availability. ADPKD, autosomal dominant polycystic kidney disease; DXA, dual-energy X-ray absorptiometry.

(maintenance steroids, bisphosphonate and denosumab within two years from DXA, and calcitriol within three months from DXA), height-adjusted total kidney volume (Ht-TKV), and dialysis history were obtained from Mayo Clinic PKD Database. *PKD1* and *PKD2* genotyping data were performed as previously described (Hopp et al., 2020; Cornec-Le Gall et al., 2018).

The first available DXA scan post-kidney transplantation was obtained. The DXA scan date was chosen as a baseline for laboratory parameter collection. The following labs were collected: total alkaline phosphatase [normal reference range: male 30–100 U/L; female 45–115 U/L; low: male <30 U/L; female <45 U/L], parathyroid hormone levels [normal reference range: 10–65 pg/mL], serum calcium [normal reference range: 8.8–10.2 mg/dL], 25-hydroxy (OH) vitamin D [normal reference range: 20–50 ng/mL], serum phosphorus [normal reference range: 2.5–4.5 mg/dL].

2.3. Bone mineral density

BMD measurements were performed using dual-energy X-ray absorptiometry (DXA) (GE Healthcare Lunar Prodigy System) at the total hip (TH), femoral neck (FN), and lumbar spine (LS). At least one site was available for measurement for each patient. All scans were interpreted following the International Society of Clinical Densitometry guidelines (Jankowski et al., 2019; Krohn et al., 2019). T-scores generated were stratified following the World Health Organization (WHO) criteria into normal (T-score ≥ -1.0), osteopenia ($-1.0 >$ T-score > -2.5), or osteoporosis (T-score ≤ -2.5). All available LS DXA images underwent trabecular bone score (TBS) measurement [iNsight software version 3.0.2 (Medimaps, Merignac, France)]. TBS was categorized as low (TBS ≤ 1.230), intermediate ($1.230 <$ TBS ≤ 1.310), or normal (TBS > 1.310) based on published studies (McCloskey et al., 2016; Hans et al., 2011). BMD values and T-scores were compared between ADPKD and non-ADPKD patients. ADPKD group was subcategorized into PKD1 and PKD2 groups for investigating the effect of genotype on the bone phenotype. In addition, the Mayo Imaging Classification (MIC) was used to detect possible differences exerted on BMD, T-score, and TBS among ADPKD patients.

2.4. Height-adjusted total kidney volume (Ht-TKV)

Height-adjusted total kidney volume (Ht-TKV) was measured by utilizing available computed tomography (CT) and magnetic resonance imaging (MRI) extracted from the Mayo Clinic Radiology Database (either the last imaging performed before the kidney transplant or the one obtained within 3 months post-transplant). The images with adequate quality were segmented using a fully automated kidney segmentation algorithm (van Gastel et al., 2019; Kline et al., 2017), and manually reviewed by a trained reader using the ITK-SNAP software. Furthermore, ITK-SNAP was used to calculate the total kidney volume (TKV): a prognostic biomarker of kidney function decline and progression to kidney failure in patients with ADPKD (Perrone et al., 2017). The ellipsoid formula was applied to estimate the TKVs of poor-quality filtered images (Shi, 2019). Age and height closest to the imaging data were collected to stratify the ADPKD patients according to the MIC using age-adjusted height-TKV (Ht-TKV) (Research, 2013).

2.5. Statistical analysis

The data were analyzed using JMP Pro software (SAS Institute, Inc., Cary, North Carolina, USA), R v4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism version 9.2.0 (GraphPad Software, San Diego, CA). Continuous variables without large outliers or skew were presented as mean with standard deviation (SD) and were summarized with the median and interquartile range. Categorical variables were presented as frequency (%). The between-groups comparison for categorical variables was performed using McNemar's test for paired data. For comparison of continuous variables between groups, the paired Wilcoxon signed-rank test was used for highly skewed variables while a paired *t*-test was used otherwise. These methods account for the matching that was performed prior to analysis. Additionally, multivariable analysis using generalized estimating equations to account for matching was performed to study the effect of PKD genotype, MIC, and preemptive kidney transplant on the bone phenotype after adjusting for gender and age at DXA the scan. A p-value <0.05 was considered statistically significant in all tests.

3. Results

3.1. Baseline characteristics

Our study cohort's baseline demographics, clinical, and genotype characteristics are summarized in Table 1. As patients were matched by sex and age at kidney transplant, both ADPKD and the control group were 57.1 % male with a mean age (SD) at kidney transplant of 54.78 (±9.98) years. The mean time (SD) from a kidney transplant to a DXA scan was [6.7 (±4.80) vs. 5.9 (±5.06) years, $p = 0.02$] in ADPKD and non-ADPKD groups, respectively. In addition, ADPKD and non-ADPKD groups had similar eGFR at their last follow-up [50.21 (±17.67) vs. 49.36 (±21.10), $p = 0.51$]. Both groups had comparable maintenance steroid therapy (77.4 % vs. 80.3 %, $p = 0.39$), bisphosphonates (17.9 % vs. 18.8 %, $p = 0.84$), denosumab (1.8 % vs. 2.6 %, $p = 0.57$) and calcitriol (10.6 % vs. 11.8 %, $p = 0.71$). The ADPKD group had significantly more preemptive kidney transplants (63.8 % vs. 44.4 %, $p < 0.001$) and a shorter mean (SD) time from dialysis initiation to kidney transplant [0.68 (±2.03) vs. 2.01 (±2.25) years, $p < 0.001$] than the non-ADPKD groups, respectively. Among the ADPKD group, 167 (49.11 %) patients had available PKD genotypes. A total of 155 (45.58 %) patients had *PKD1* pathogenic variants, 12 (3.52 %) *PKD2*, 3 (0.88 %) with no detected variants, and 173 (50.8 %) had unavailable genetic testing results. ADPKD patients were classified into 1B (12.8 %); 1C (33.9 %); 1D (25.0 %); 1E (28.3 %), according to the MIC.

Biochemical parameters were compared between the ADPKD and non-ADPKD groups (Table 2 and Supplemental Fig. 1). ADPKD patients had significantly lower median (Q1, Q3) total alkaline phosphatase (ALP) in comparison with non-ADPKD patients [65.0 (52.0, 83.0) vs. 79.0 U/L (62.2, 105.0), $p < 0.001$]. No significant differences were found in other biochemical markers such as intact PTH, serum calcium, 25-OH vitamin D, and phosphorus.

3.2. Bone density

DXA was obtained at a mean of 6 years following the transplant. Patients with ADPKD had a slightly higher mean (SD) BMD and T-scores at the right total hip (TH) compared to non-ADPKD patients (Fig. 2 and Supplemental Table 2) [BMD: 0.951 (±0.174) vs. 0.897 (±0.165), $p < 0.001$; T-score: −0.62 (±1.30) vs. -0.99 (±1.31), $p < 0.001$] and at left TH [BMD: 0.960 (±0.168) vs. 0.893 (±0.168), $p < 0.001$; T-score: −0.60 (±1.58) vs. -1.08 (±1.59), $p < 0.001$], respectively. Similar results were found at the right femoral neck (FN) between ADPKD and non-ADPKD [BMD: 0.887 (±0.162) vs. 0.848 (±0.143), $p = 0.001$; T-score: −1.20 (±1.26) vs. -1.41 (±1.05), $p = 0.01$] and at left FN [BMD: 0.885 (±0.162) vs. 0.840 (±0.153), $p < 0.001$; T-score: −1.16 (±1.15) vs. -1.46 (±1.11), $p = 0.001$]. At the LS level, ADPKD had similar BMD and lower T-score when compared to non-ADPKD [BMD: 1.120 (±0.193) vs. 1.126 (±0.384), $p = 0.93$; T-score: −0.66 (±1.50) vs. -0.23 (±1.79), $p = 0.008$].

Mean (SD) TBS did not differ between ADPKD and non-ADPKD groups [1.345 (±0.142) vs. 1.354 (±0.125); $p = 0.99$, respectively]. Although the differences in BMD were noted at the hips, there was no difference between the groups when stratified using the lowest T-scores: 160 (47.1 %) patients from the ADPKD group had osteopenia, 85 (25.0 %) had osteoporosis, and 95 (27.89 %) had normal bone density. In the

Table 1
Baseline demographic and clinical characteristics at kidney transplantation.

		ADPKD (n = 340)	non-ADPKD (n = 340)	p value
Male, n (%)		194 (57.1 %)	194 (57.1 %)	1.000
Caucasian, n (%)		323 (95.0 %)	287 (84.4 %)	**<0.001**
Age at kidney transplant (years), mean (±SD)		54.8 (±9.9)	54.8 (±10.0)	0.89
Age at DXA scan (years), mean (±SD)		61 (±10.8)	60.9 (±10.4)	0.34
Duration of dialysis before kidney transplant (years), mean (±SD)		0.68 (±2.0)	2.0 (±2.3)	**<0.001**
Preemptive kidney transplant, n (%)		217 (63.8 %)	151 (44.4 %)	**<0.001**
eGFR (mL/min/1.73 m^2), mean (±SD)		50 (±17.7)	49 (±21.1)	0.51
Time from kidney transplant to DXA scan (years), mean (±SD)		6.74 (±4.8)	5.9 (±5.1)	**0.02**
Body mass index (BMI) kg/m^2 at the time of DXA, mean (±SD)		28.9 (±5.9)	29.8 (±6.8)	0.06
Causes of kidney failure, n (%)				
ADPKD		340 (100 %)	–	
Pre-renal/renovascular		–	120 (35.4 %)	
Obstructive uropathy		–	101 (29.8 %)	
CKD of unknown etiology		–	38 (11.2 %)	
Hepatorenal syndrome		–	24 (7.1 %)	
Glomerular disease		–	22 (6.5 %)	
Inherited diseases, other than ADPKD		–	15 (4.4 %)	
Kidney tumors		–	11 (3.2 %)	
Miscellaneous		–	9 (2.6 %)	
Medication use, n (%)				
Maintenance steroids post-transplantation		263 (77.4 %)	273 (80.3 %)	0.39
Bisphosphonate (within 2 years of DXA)		61 (17.9 %)	64 (18.8 %)	0.84
Denosumab (within 2 years of DXA)		6 (1.8 %)	9 (2.6 %)	0.57
Active vitamin D (within 3 months of DXA)		36 (10.6 %)	40 (11.8 %)	0.71
PKD variants type, n (%)				
PKD1		155 (45.6 %)	–	–
PKD2		12 (3.5 %)	–	–
No mutation detected		3 (0.9 %)	–	–
Unavailable genetic analysis		173 (50.8 %)		
Mayo Imaging Classification, n (%)				
Rapidly progressive	1E	51 (28.3 %)	–	–
	1D	45 (25.0 %)	–	
	1C	61 (33.9 %)	–	–
Slowly progressive	1B	23 (12.8 %)	–	–

ADPKD, autosomal-dominant polycystic kidney disease; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; PKD, polycystic kidney disease. P values in bold indicate statistical significane ($p < 0.05$).

non-ADPKD group, 160 (47.1 %) patients had osteopenia, 94 (27.6 %) had osteoporosis, and 86 (25.3 %) had a normal bone density, p = 0.67.

Patients with ADPKD were more likely to receive a preemptive kidney transplant. Thus, we performed a sensitivity analysis to assess the effect of this factor on the bone phenotype (Table 3). The mean age for a preemptive kidney transplant was lower in the ADPKD group than in the non-ADPKD (53.8 ± 9.9 vs. 56.2 ± 10.1; p = 0.01). Compared to non-ADPKD, patients with ADPKD had overall better BMD and T-scores. When adjusting for gender, age at DXA and preemptive kidney transplants, patients with ADPKD had higher T-scores in the femoral neck and hip but lower in the lumbar spine (Table 4).

When studying the effect of PKD genotype on the bone phenotype,

Table 2
Biochemical parameters in ADPKD and non-ADPKD patients post kidney transplant.

	ADPKD (n = 340)	non-ADPKD (n = 340)	p value
ALP (U/L), median (Q1, Q3)	65.0 (52.0, 83.0)	79.0 (62.3, 105.0)	**<0.001**
PTH (pg/mL), median (Q1, Q3)	80 (58.0, 112.0)	79.0 (57.0, 129.0)	0.43
Serum calcium (mg/dL), median (Q1, Q3)	9.4 (9.1, 9.8)	9.5 (9.2, 9.8)	0.96
25-OH vitamin D (ng/mL), median (Q1, Q3)	41.0 (33.0, 48.0)	39.0 (30.0, 48.0)	0.11
Phosphorus (mg/dL), median (Q1, Q3)	3.4 (2.9, 3.8)	3.4 (3.0, 3.8)	0.27

ADPKD, autosomal-dominant polycystic kidney disease; ALP, total alkaline phosphatase; PTH, parathyroid hormone. P values in bold indicate statistical significane ($p < 0.05$).

PKD1 patients had higher BMD [average right total hip: 0.95 (±0.17) vs. 0.82 (±0.12), p = 0.02] and T-scores [average right total hip: −0.55 (±1.28) vs. -1.44 (±1.03), p = 0.03] (Supplemental Table 3, Supplemental Fig. 2A & B) when compared to PKD2. PKD1 patients reached kidney failure earlier, so we adjusted for gender and age at DXA and found they were not associated with a better bone phenotype in such multivariate analysis compared to PKD2 (Supplemental Table 4). Furthermore, when stratifying patients with ADPKD based on their cystic disease burden using the MIC, the bone phenotype progressively worsened as the cystic burden was lower (Supplemental Table 5, Supplemental Fig. 2C & D). Patients with MIC-1B who had the mildest cystic burden and subsequently reached kidney failure at an older age had a worse bone phenotype than MIC-1E, who had the most severe cystic burden and reached kidney failure earlier.

Among the subgroup of patients who received bisphosphonate, ADPKD (n = 61) patients had higher BMD as well as higher T-score at the right TH when compared to non-ADPKD (n = 64) [mean (SD) BMD: 0.820 (±0.122) vs. 0.763 (±0.124), p = 0.02; T-score: −1.63 (0.92) vs. -2.06 (0.94), p = 0.01]. Furthermore, the left TH showed similar results [BMD: 0.826 (±0.111) vs. 0.766 (±0.117), p = 0.007; T-score: −1.56 (±0.86) vs. -2.11 (±0.93), p = 0.002]. The right FN BMD was comparable between ADPKD and non-ADPKD with higher T-score in the ADPKD group [BMD: 0.771 (±0.116) vs. 0.735 (±0.101), p = 0.09; T-score: −1.98 (±0.75) vs. -2.30 (±0.73), p = 0.02]. Similar results were found at the left FN as well [BMD: 0.775 (±0.110) vs. 0.736 (±0.107), p = 0.06; T-score: −1.96 (±0.73) vs. -2.26 (±0.78), p = 0.03]. The results of the LS showed lower BMD and T-score in ADPKD compared to non-ADPKD [BMD: 0.983 (0.150) vs. 1.064 (0.203), p = 0.03; T-score: −1.66 (1.13) vs. -1.07 (1.62), p = 0.04] (Supplemental Table 6).

4. Discussion

In this large cohort of age and sex-matched patients, BMD identified by DXA was higher in patients with ADPKD following kidney transplantation compared to non-ADPKD. ADPKD patients had higher BMD and T-scores at the femoral neck and total hip but lower T-scores in the lumbar spine. Additionally, after adjusting for gender, age at DXA, and preemptive kidney transplants, patients with ADPKD still displayed higher BMD in the femoral neck and total hip. The predominance of cortical bone at the femoral neck compared to the predominance of trabecular bone at the lumbar spine may explain increased BMD exclusively at the femoral neck. The findings of our study are consistent with previously reported distinct bone phenotype of preserved cortical BMD in patients with advanced stages of ADPKD (Evenepoel et al., 2019).

Assessing mineral bone in ADPKD has been the subject of extensive research over the last few decades. Experimental models have shown that *Pkd1* and *Pkd2* are expressed in osteoblasts, osteocytes, and

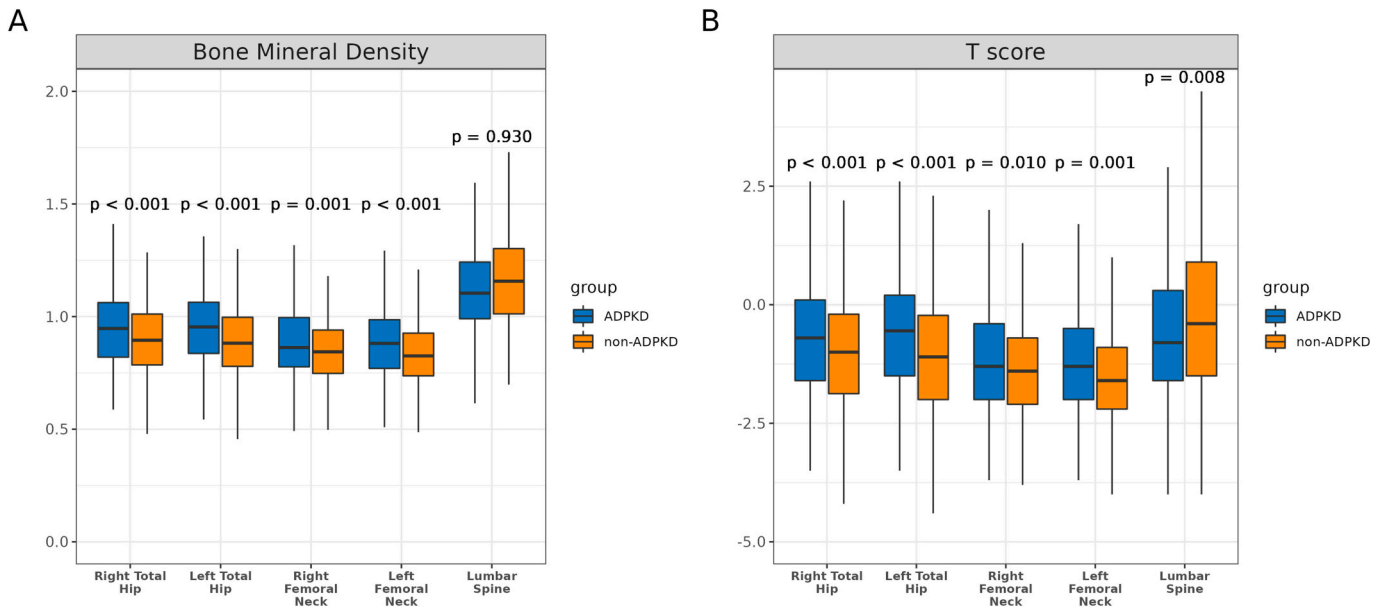

Fig. 2. A. Bone mineral density (BMD) in post-transplanted ADPKD and non-ADPKD patients. BMD measures were higher in ADPKD when compared to non-ADPKD in the femoral neck and hip w, with lower BMD in ADPKD at the lumbar spine region. B. A comparison between ADPKD and non-ADPKD T-score. The letter n represents the number of the available DXA results per group and region.

Table 3
DXA (dual-energy X-ray absorptiometry) scan results in ADPKD and non-ADPKD patients who underwent preemptive kidney transplantation.[a]

	ADPKD (n = 217)	Non-ADPKD (n = 151)	p value
Mean age at preemptive kidney transplant (years)	53.9 (±10.0)	56.8 (±9.8)	**0.007**
Right total hip			
BMD (g/cm^2)	0.965 (0.169)	0.910 (0.161)	**0.004**
T-score	−0.51 (1.27)	−0.87 (1.26)	**0.012**
Left total hip			
BMD (g/cm^2)	0.972 (0.164)	0.909 (0.170)	**<0.001**
T-score	−0.46 (1.24)	−0.94 (1.49)	**0.001**
Right femoral neck			
BMD (g/cm^2)	0.898 (0.160)	0.853 (0.141)	**0.008**
T-score	−1.14 (1.32)	−1.39 (1.05)	**0.06**
Left femoral neck			
BMD (g/cm^2)	0.898 (0.156)	0.844 (0.153)	**0.002**
T-score	−1.09 (1.13)	−1.42 (1.13)	**0.008**
Lumbar spine			
BMD (g/cm^2)	1.128 (0.187)	1.166 (0.187)	0.10
T-score	−0.62 (1.45)	−0.20 (1.57)	**0.02**
TBS	1.344 (±0.141)	1.369 (±0.110)	0.15

[a] Data are shown as mean (SD); DXA, dual-energy X-ray absorptiometry; ADPKD, autosomal-dominant polycystic kidney disease; BMD, bone mineral density; TBS, trabecular bone score. P values in bold indicate statistical significance ($p < 0.05$).

Table 4
Multivariate analysis using generalized estimating equations to assess the effect of ADPKD on BMD after adjusting for gender, age at DXA scan, and receiving a preemptive kidney transplant.

	Estimate	C.I.	p-Value
Hip BMD			
Intercept	1.18	1.11, 1.25	<0.001
Female (male as ref.)	−0.11	−0.14, −0.09	<0.001
Age at DXA scan (years)	−0.004	−0.005, −0.003	<0.001
Preemptive Tx (non-preemptive as ref)	0.04	0.01, 0.06	<0.001
ADPKD (non-ADPKD as ref.)	0.04	0.02, 0.07	**<0.001**
Femoral neck BMD			
Intercept	1.15	1.08, 1.21	<0.001
Female (male as ref.)	−0.08	−0.11, −0.06	<0.001
Age at DXA scan (years)	−0.004	−0.005, −0.003	<0.001
Preemptive Tx (non-preemptive as ref)	0.03	0.01, 0.05	0.004
ADPKD (non-ADPKD as ref.)	0.03	0.01, 0.05	**0.001**
Lumbar spine BMD			
Intercept	1.26	1.11, 1.41	<0.001
Female (male as ref.)	−0.12	−0.17, −0.06	<0.001
Age at DXA scan (years)	−0.001	−0.004, 0.000	0.14
Preemptive Tx (non-preemptive as ref)	0.04	−0.00, 0.10	0.06
ADPKD (non-ADPKD as ref.)	−0.02	−0.07, 0.03	**0.42**

P values in bold indicate statistical significane ($p < 0.05$).

chondrocytes, playing a crucial role in bone development and formation (Li et al., 2017; Xiao et al., 2010; Xiao et al., 2008). Mice with conditional *Pkd1* or *Pkd2* loss exhibited intramembranous and endochondral bone defects, decreased trabecular volume, bone mineral density, cortical thickness, and the presence of craniofacial anomalies (Li et al., 2017; Xiao et al., 2010; Xiao et al., 2008; Khonsari et al., 2013; Xiao et al., 2014). Children with ADPKD and preserved kidney function were found to have low serum phosphate and low bone-specific alkaline phosphatase, indicating a suppressed bone formation in this group compared to healthy controls (De Rechter et al., 2017). A recent study reported a unique bone phenotype, including suppressed turnover and preserved cortical bone mineral density in adults with ADPKD and kidney failure (Evenepoel et al., 2019). In a different study of bone phenotype in ADPKD patients with early CKD stages, ADPKD group did not demonstrate a higher risk of fracture, despite having lower ALP, higher circulating FGF23, and decreased bone formation rate when compared to a control cohort with early CKD (Gitomer et al., 2021). Additionally, a few case reports regarding ADPKD-associated bone disorders have described pronounced skeletal defects in an ADPKD newborn (Turco et al., 1993), and another ADPKD patient with pelvic insufficiency fracture who was reported to have histological findings of cortical bone abnormalities and resorption (Ubara et al., 2005).

Our findings suggest improved cortical but not trabecular BMD in ADPKD patients compared to non-ADPKD patients after 6 years of transplantation on average. The clinical significance of the improved

bone health in ADPKD patients is unclear yet. However, one might argue that the improved bone health post transplantation might be of critical relevance given the survival benefit across all modalities of renal replacement therapies for patients with ADPKD.

The discrepancy between the experimental and the present study findings might be explained by the differences in disease onset in human ADPKD and animal models. Biallelic fully pathogenic *PKD1* variants are lethal in human and animal models; therefore, it is challenging to mimic the natural history and protracted sequelae of the disease in animal models (Li et al., 2017). The changes observed in mice models may be confounded by complete loss rather than polycystin reduction in bone, the onset of gene expression at an early stage of development (e.g., PKD mutations at early stages of embryogenesis/skeletogenesis) in mice models, resulting in the observed skeletal anomalies. The discrepancy between humans' and mice's bone phenotypes could be explained by the level of functional polycystins. A complete loss of function in the pre-clinical models is likely associated with a severe phenotype, whereas a reduction in functional polycystins in humans might explain a milder or absent bone phenotype. Mice with $Pkd1^{RC/del2}$ had osteopenia and a decrease in trabecular and cortical mass, whereas $Pkd1^{RC/RC}$ animals with higher PC1 levels had no bone phenotype (Hopp et al., 2012). An alternate explanation might be related to other unknown compensatory mechanisms in patients with ADPKD that rescue the bone makeup. It is also possible that the difference in turnover is very subtle and does not translate into radiographic or clinical contrast within short time frames and may need decades to reflect in BMD changes and fractures. The onset of CKD in animal models also occurs during early development. In contrast, human ADPKD kidney dysfunction and CKD sequelae on bone metabolism are typically seen in adolescents or adulthood when skeletogenesis has already taken place (Rosenbloom, 2007). This may raise the question of whether PKD gene expression in osteoblasts is essential only at the early stages of human bone development.

Because of the adulthood onset of the kidney function decline in ADPKD and the second-hit hypothesis, skeletal changes such as those found in experimental models may be negligible in an adult with a fully formed skeleton. Furthermore, the levels of functional polycystin are associated with disease progression and cystic burden resulting in overt clinical presentation (Hopp et al., 2012). This phenomenon may play a similar role in other cell types, such as osteoblasts. We can speculate that bone disease manifestations are clinically silent in ADPKD, as osteoblast functional polycystin levels may not drop beneath the possible threshold needed for bone disease.

CKD patients exhibit high bone turnover and lower BMD due to a higher rate of bone resorption than formation (Hughes-Austin et al., 2020). CKD-associated metabolic bone disease (CKD-MBD) is a highly complex phenomenon that varies from adynamic bone disease to a high turnover state, with significant alteration in bone microarchitecture and an increased risk of fractures. Following a kidney transplant, the maximal decline in BMD occurs in the first year post-transplant, with subsequent stabilization; it remains, however, significantly lower than healthy counterparts (Akaberi et al., 2008). Indeed, a decrease in bone mineral density following a kidney transplant is a significant cause of morbidity and mortality, including a higher risk of fractures, hospitalization, and cost of healthcare in kidney transplant recipients (Forsén et al., 1999). Within the first five years after transplant, 22.5 % of kidney transplant recipients experience a fracture with an incidence as high as four times higher than the general population (Akaberi et al., 2008). Recent studies indicate that with newer immunosuppression protocols, BMD declines by 0.1–5.7 % at the lumbar spine level (Akaberi et al., 2008; Weisinger et al., 2006). Hence, a DXA scan close to the transplant may reveal the nadir of BMD and is less likely to reflect the bone stabilization post-kidney transplantation (Jørgensen et al., 2022). Prior studies have included ADPKD patients at different stages of disease progression, while we have enrolled patients post-kidney transplantation allowing us to match two comparable cohorts who were exposed to similar factors that could affect their bone metabolism, with the main difference being the cause of their kidney failure.

Our study has several strengths and limitations. The major strengths of our study are the large number of kidney-transplanted patients and the matching by age and sex with the control groups. Even though more patients were on dialysis prior to transplant in the control group, we performed a sensitivity analysis accounting for preemptive transplant as it is well known that these patients would have higher BMD at baseline at the time of transplant. Furthermore, our study is the first to report on TBS in patients with ADPKD, going beyond the limitations of BMD as measured by DXA. In our cohort of patients of non-ADPKD kidney transplantation, we excluded patients with diabetes mellitus (DM), given the established correlation between DM and alteration in fracture risk and bone microarchitecture (Forsén et al., 1999; Schwartz et al., 2001; Nicodemus and Folsom, 2001; Ottenbacher et al., 2002). We excluded other disease processes that might have been treated with systemic corticosteroids, including glomerular diseases and multiple prior kidney transplants, and patients with extra-renal malignancies that independently produce vitamin D or PTH-related peptide. An inherent limitation of retrospective analysis is the availability or comprehensiveness of clinical data of interest such as incidence and prevalence of fracture before and after transplantation. Nevertheless, the Mayo Clinic electronic system and Mayo Clinic PKD Database have been comprehensive in their available data for >2 decades. Our cohort had variable length between transplantation and DXA scan due to evolution of the protocol and variability of adherence. While this study design included the first available DXA scan, the average time was about 6 years which limits the availability to establish longitudinal evolution of bone health particularly in the early phase after transplantation when the risk of fracture is highest in setting of using high dose corticosteroids. Future studies studying the evolution of bone health within the first 2 years after kidney transplantation would be informative. Although BMD measurements by DXA are major predictors of bone strength and fracture risk, advancements in skeletal research have highlighted the limitations of this technology, such as the 2-dimensional areal, rather than true volumetric, measurements and the lack of ability to distinguish between the trabecular and cortical compartments of bone (Adams, 2013; Glüer, 2017). TBS, a texture index derived from the standard lumbar spine (LS) DXA imaging, can provide information about the underlying trabecular bone microarchitecture. Importantly, TBS has been shown to predict the risk of osteoporotic fractures independent of areal BMD by DXA (Hans et al., 2011). The results from our cohort indicate the lack of trabecular bone degradation, as measured by TBS, in patients with ADPKD compared to the non-ADPKD group.

In conclusion, our retrospective study indicates that BMD by DXA is higher in patients with ADPKD compared to non-ADPKD following kidney transplantation in sites where cortical and not trabecular bone is predominant. The clinical significance of the preserved cortical bone BMD in patients with ADPKD needs to be explored in future studies.

CRediT authorship contribution statement

Research idea and study design: DZ, AKR, CH, BHS, NSI, JGS, FTC; data acquisition: DZ, AKR, MC, DK, LN, YGM, RMN, AVG, CH, FTC; genetic analysis: CDM, SRS, PCH; data analysis and interpretation: DZ, MC, CH, BHS, NSI, JGS, FTC; statistical analysis: BHS, DZ, CH, FTC; writing, review and editing: DZ, CH, BHS, JGS, FTC; supervision and mentorship: TLK, ZMZ, SMB, NSI, PCH, VET, JGS, FTC. DZ and CH contributed equally to this work. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Declaration of competing interest

PCH reports receiving grants and/or research reagents from Amgen,

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Data sharing statement

The data that support the findings of this study are not publicly available because they contain information that could potentially compromise the privacy of the research participants and are however available from the corresponding author FTC on reasonable request.

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Appendix A. Supplementary data

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References

Adams, J.E., 2013. Advances in bone imaging for osteoporosis. Nat Rev Endocrinol 9 (1), 28–42.
Akaberi, S., et al., 2008. Can DXA predict fractures in renal transplant Patients? Am. J. Transplant. 8 (12), 2647–2651.
Boulter, C., et al., 2001. Cardiovascular, skeletal, and renal defects in mice with a targeted disruption of the Pkd1 gene. Proc. Natl. Acad. Sci. U. S. A. 98 (21), 12174–12179.
Chebib, F.T., Torres, V.E., 2016. Autosomal dominant polycystic kidney disease: core curriculum 2016. Am. J. Kidney Dis. 67 (5), 792–810.
Chebib, F.T., et al., 2016. Effect of genotype on the severity and volume progression of polycystic liver disease in autosomal dominant polycystic kidney disease. Nephrol. Dial. Transplant. 31 (6), 952–960.
Research, M.F.A.M.E.A, 2013. Available from: https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754.
Cornec-Le Gall, E., et al., 2018. Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. Am. J. Hum. Genet. 102 (5), 832–844.
Cornec-Le Gall, E., Alam, A., Perrone, R.D., 2019. Autosomal dominant polycystic kidney disease. Lancet 393 (10174), 919–935.
De Rechter, S., et al., 2017. Evidence for bone and mineral metabolism alterations in children with autosomal dominant polycystic kidney disease. J. Clin. Endocrinol. Metab. 102 (11), 4210–4217.
Ecder, T., Schrier, R.W., 2009. Cardiovascular abnormalities in autosomal-dominant polycystic kidney disease. Nat Rev Nephrol 5 (4), 221–228.
Evenepoel, P., et al., 2019. A distinct bone phenotype in ADPKD patients with end-stage renal disease. Kidney Int. 95 (2), 412–419.
Forsén, L., et al., 1999. Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trøndelag health survey. Diabetologia 42 (8), 920–925.
van Gastel, M.D.A., et al., 2019. Automatic measurement of kidney and liver volumes from MR images of patients affected by autosomal dominant polycystic kidney disease. J Am Soc Nephrol 30 (8), 1514–1522.
Gitomer, B., et al., 2021. Mineral bone disease in autosomal dominant polycystic kidney disease. Kidney Int. 99 (4), 977–985.
Glüer, C.C., 2017. 30years of DXA technology innovations. Bone 104, 7–12.
Hans, D., et al., 2011. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J. Bone Miner. Res. 26 (11), 2762–2769.
Hopp, K., et al., 2012. Functional polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity. J. Clin. Invest. 122 (11), 4257–4273.
Hopp, K., et al., 2020. Detection and characterization of mosaicism in autosomal dominant polycystic kidney disease. Kidney Int. 97 (2), 370–382.
Hou, B., et al., 2009. The polycystic kidney disease 1 (Pkd1) gene is required for the responses of osteochondroprogenitor cells to midpalatal suture expansion in mice. Bone 44 (6), 1121–1133.
Hughes, J., et al., 1995. The polycystic kidney disease 1 (PKD1) gene encodes a novel protein with multiple cell recognition domains. Nat. Genet. 10 (2), 151–160.
Hughes-Austin, J.M., et al., 2020. Biomarkers of bone turnover identify subsets of chronic kidney disease patients at higher risk for fracture. J. Clin. Endocrinol. Metab. 105 (8), e2903–e2911.
Jankowski, L.G., et al., 2019. Cross-calibration, least significant change and quality Assurance in Multiple Dual-Energy X-ray absorptiometry scanner environments: 2019 ISCD official position. J. Clin. Densitom. 22 (4), 472–483.
Jørgensen, H., et al., 2022 Mar. Natural history of bone disease following kidney transplantation. J Am Soc Nephrol 33 (3), 638–652.
Khonsari, R.H., et al., 2013. Multiple postnatal craniofacial anomalies are characterized by conditional loss of polycystic kidney disease 2 (Pkd2). Hum. Mol. Genet. 22 (9), 1873–1885.
Kline, T.L., et al., 2017. Performance of an artificial multi-observer deep neural network for fully automated segmentation of polycystic kidneys. J. Digit. Imaging 30 (4), 442–448.
Krohn, K., et al., 2019. Dual-energy X-ray absorptiometry monitoring with trabecular bone score: 2019 ISCD official position. J. Clin. Densitom. 22 (4), 501–505.
Lavu, S., et al., 2020. The value of genotypic and imaging information to predict functional and structural outcomes in ADPKD. JCIInsight 5 (15).
Levey, A.S., et al., 2009. A new equation to estimate glomerular filtration rate. Ann. Intern. Med. 150 (9), 604–612.
Li, S., et al., 2017. A conditional knockout mouse model reveals a critical role of PKD1 in osteoblast differentiation and bone development. Sci. Rep. 7, 40505.
Lu, W., et al., 2001. Comparison of Pkd1-targeted mutants reveals that loss of polycystin-1 causes cystogenesis and bone defects. Hum. Mol. Genet. 10 (21), 2385–2396.
Markowitz, G.S., et al., 1999. Polycystin-2 expression is developmentally regulated. Am. J. Phys. 277 (1), F17–F25.
McCloskey, E.V., et al., 2016. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J. Bone Miner. Res. 31 (5), 940–948.
Mochizuki, T., et al., 1996. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science 272 (5266), 1339–1342.
Nicodemus, K.K., Folsom, A.R., 2001. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. Diabetes Care 24 (7), 1192–1197.
Ottenbacher, K.J., et al., 2002. Diabetes mellitus as a risk factor for hip fracture in mexican american older adults. J. Gerontol. A Biol. Sci. Med. Sci. 57 (10), M648–M653.
Perrone, R.D., Ruthazer, R., Terrin, N.C., 2001. Survival after end-stage renal disease in autosomal dominant polycystic kidney disease: contribution of extrarenal complications to mortality. Am. J. Kidney Dis. 38 (4), 777–784.
Perrone, R.D., et al., 2017. Total kidney volume is a prognostic biomarker of renal function decline and progression to end-stage renal disease in patients with autosomal dominant polycystic kidney disease. Kidney Int. Rep. 2 (3), 442–450.
Peters, D.J., et al., 1999. Cellular localization and tissue distribution of polycystin-1. J. Pathol. 188 (4), 439–446.
Qiu, N., et al., 2012. Conditional mesenchymal disruption of pkd1 results in osteopenia and polycystic kidney disease. PLoS One 7 (9), e46038.
Rosenbloom, A.L., 2007. Physiology of growth. Ann. Nestle Eng. 65 (3), 97–108.
Schwartz, A.V., et al., 2001. Older women with diabetes have an increased risk of fracture: a prospective study. J. Clin. Endocrinol. Metab. 86 (1), 32–38.
Shi, B., 2019. Prognostic performance of kidney volume measurement for polycystic kidney disease: a comparative study of ellipsoid vs. manual segmentation. Sci. Rep. 9 (1), 10996.
Torres, V.E., Harris, P.C., Pirson, Y., 2007. Autosomal dominant polycystic kidney disease. Lancet 369 (9569), 1287–1301.
Tsiokas, L., et al., 1997. Homo- and heterodimeric interactions between the gene products of PKD1 and PKD2. Proc. Natl. Acad. Sci. U. S. A. 94 (13), 6965–6970.
Turco, A.E., et al., 1993. Molecular genetic diagnosis of autosomal dominant polycystic kidney disease in a newborn with bilateral cystic kidneys detected prenatally and multiple skeletal malformations. J. Med. Genet. 30 (5), 419–422.
Ubara, Y., et al., 2005. Pelvic insufficiency fracture related to autosomal dominant polycystic kidney disease. Am. J. Kidney Dis. 46 (6), e103–e111.
Weisinger, J.R., et al., 2006. Bone disease after renal transplantation. Clin. J. Am. Soc. Nephrol. 1 (6), 1300–1313.
Xiao, Z., et al., 2006. Cilia-like structures and polycystin-1 in osteoblasts/osteocytes and associated abnormalities in skeletogenesis and Runx2 expression. J. Biol. Chem. 281 (41), 30884–30895.
Xiao, Z., et al., 2008. Polycystin-1 regulates skeletogenesis through stimulation of the osteoblast-specific transcription factor RUNX2-II. J. Biol. Chem. 283 (18), 12624–12634.
Xiao, Z., et al., 2010. Conditional disruption of Pkd1 in osteoblasts results in osteopenia due to direct impairment of bone formation. J. Biol. Chem. 285 (2), 1177–1187.
Xiao, Z., et al., 2014. Osteoblast-specific deletion of Pkd2 leads to low-turnover osteopenia and reduced bone marrow adiposity. PLoS One 9 (12), e114198.
Yoder, B.K., Hou, X., Guay-Woodford, L.M., 2002. The polycystic kidney disease proteins, polycystin-1, polycystin-2, polaris, and cystin, are co-localized in renal cilia. J Am Soc Nephrol 13 (10), 2508–2516.