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Research Article

Hip geometry and strength remain stable the first year after kidney transplantation—an ibandronate/placebo *post hoc* analysis

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Abstract

The sensitivity of bone mineral density (BMD) to identify patients with high fracture risk after kidney transplantation is low, therefore alternative tools are needed. Hip Structure Analysis (HSA) provides an estimation of hip structural geometry and strength based on conventional DXA scans for hip analyses. We aimed to investigate the effect of antiresorptive therapy on hip geometrical and strength parameters by HSA. In a *post hoc* analysis of a 12-month randomized, double-blind, placebo-controlled trial evaluating the effect of ibandronate in addition to active vitamin D and calcium in kidney transplant recipients (KTR), we re-analyzed dual total hip and femoral neck DXA scans to measure cortical bone thickness (CBT) in the femoral neck (CBT_{NECK}), calcar (CBT_{CALCAR}), and shaft (CBT_{SHAFT}), along with femur neck width, hip axis length, and to estimate buckling ratio and strength index. DXA measurements were performed within 5 weeks after transplantation and repeated at 10 weeks and 1-year post-transplant. The study included a total of 127 *de novo* KTR with estimated glomerular filtration rate >30 mL/min at baseline. The 5 geometrical and the strength and stability hip parameters remained stable over the first post-transplant year irrespective of antiresorptive therapy. We detected no statistically significant between-group differences in any of the HSA measures. Change in geometrical hip parameters and buckling ratio over the study duration was not correlated with change in plasma parathyroid hormone or change in dual total hip BMD. In this study, the so far largest of HSA in KTR, antiresorptive therapy with ibandronate for 12 months did not affect measures of hip geometry or strength.
Clinical Trial Registration: www.clinicaltrials.gov as NCT00423384, EudraCT number 2006-003884-30.

Keywords: DXA, hip structure analysis, cortical bone, kidney transplantation, bisphosphonate

Lay Summary

Bone loss occurs both before and after kidney transplantation. Kidney transplant recipients have a high fracture risk, but how do we identify those most at risk? DXA scans measure bone mass, but we can also use DXA images of the hip to assess hip structural geometry and strength using a special software called Hip Structure Analysis. We studied the effect of a bone preserving and strengthening medication called bisphosphonate, in 127 patients during the first year after kidney transplantation. We found that hip geometry and strength parameters remain stable during the first year after transplantation irrespective of bisphosphonate use.

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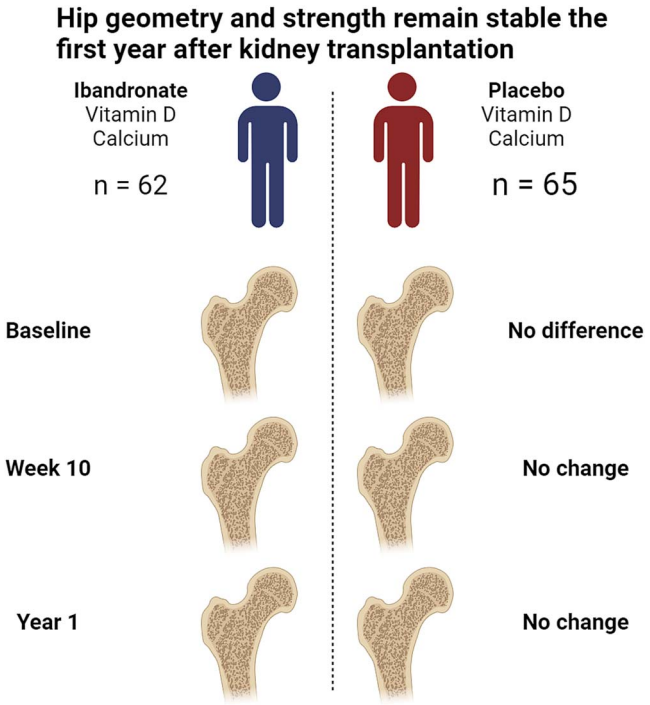
Graphical Abstract



Introduction

Hip fractures are associated with significant morbidity and mortality in the general population, but even more so in patients with chronic kidney disease (CKD), be it with or without a functioning kidney transplant.[1-4] The sensitivity of bone mineral density (BMD) to identify patients with high fracture risk after kidney transplantation is low, therefore supplementary tools are needed.[5]

Cortical bone is an important determinant of bone strength and fragility.[6,7] There has been considerable research focus on trabecular bone in patients with CKD and kidney transplant recipient (KTR);[8] however, these patients also have cortical bone loss with reduced cortical bone thickness (CBT), higher buckling ratios and increased cortical porosity compared with age- and sex-matched background population.[9-13] Hip Structure Analysis (HSA) can easily be performed with a novel computer software (Advanced Hip Assessment) and provides an estimation of hip structural geometry and strength based on analyses of cross-sections of conventional DXA scans for dual total hip BMD.[14] HSA measures CBT in the proximal femur: at the neck (CBT_{NECK}), intertrochanteric calcar (CBT_{CALCAR}), and shaft (CBT_{SHAFT}). Furthermore, the program determines the femur neck width (FNW) and hip axis length (HAL) and provides estimates of strength index (an estimate of hip strength) and buckling ratio (an index of femoral neck instability). To date, most data have been focused on estrogen deprivation, ie, postmenopausal osteoporosis, where a reduced CBT, longer HAL, and increased buckling ratio have been associated with hip fracture.[15-18] HSA has yet to be used in clinical diagnosis of disease in the general population. PTH excess and shifts in calcium homeostasis is common in the first year after kidney transplantation and may be a major cause of cortical bone loss.[13] It could be anticipated that hip structure parameters in *de novo* KTR would deteriorate during this early period. The general population does not have the same PTH drive as those with CKD, and for them it may be that BMD is still a satisfactory predictor of fracture risk. HSA could prove useful in fracture prediction for KTR and monitoring of antiresorptive therapy.[19] However, studies on the effect of common anti-fracture therapies on HSA in KTR are scarce.[20]

In this *post hoc* analysis of a 12-month randomized, double-blind, placebo-controlled trial we investigated early ibandronate treatment in addition to active vitamin D and calcium in KTR.[21] Our aim was to use HSA to investigate the effect of antiresorptive therapy on CBT in the femoral region, on buckling ratio, and on strength index. Our hypothesis was that antiresorptive therapy with ibandronate in the first post-transplant year would positively affect CBT and biomechanical properties in the femoral region.

Materials and methods

Study population

A 12-month randomized, placebo-controlled trial evaluating the effect of ibandronate in addition to active vitamin D and calcium was conducted on 129 patients transplanted between January 2007 and December 2009 at our center, Oslo University Hospital, Rikshospitalet.[21] The sample size of the original randomized controlled trial (RCT) was based on an expected difference of 4% in lumbar spine BMD, from baseline to 12 months, between the ibandronate and placebo groups (latter expected to lose 7%); 49 participants per group would provide 90% power at a 5% 2-sided α level. The patient flow diagram is presented in Supplementary Figure 1. Patients of either sex over 18 years old and with an adequate graft function (estimated glomerular filtration rate

of at least 30 mL/min), who were clinically stable over 7 consecutive days, had baseline study investigations performed within 5 weeks after transplantation. Eligible patients were randomized according to a computer-generated list of random numbers to allocate patients in a 1:1 ratio using a block size of 8 to treatment with either intravenous ibandronate 3 mg or placebo (intravenous isotonic saline) every 3 months for 1 year. Patients were given a randomization number and treatment was administered from vials labeled with their number. The participants and study staff were blinded to treatment allocation for the duration of the study. Ibandronate was chosen as it could be administered intravenously once every 3 months and was in 2007 one of few bisphosphonates on the market available for parenteral administration. All patients received supplementation with calcium (1 g/day) and active vitamin D3 (calcitriol 0.25 mcg/day). When the RCT was conducted, many transplant centers recommended vitamin D and calcium for all *de novo* KTR. Therefore, when the RCT was planned, it was decided to provide all patients with vitamin D and calcium as a basic preventive therapy to assure external validity. Active vitamin D was chosen over for example cholecalciferol to ensure availability of 1,25-dihydroxyvitamin D in target tissue throughout the study, irrespective of potential fluctuations in graft function. Main exclusion criteria were hypercalcemia, treatment for bone disease within the last 12 months, and previous parathyroidectomy. Because of this RCT, 2 DXA scans were performed within a short time interval, both at baseline (within 5 weeks and before study drug administration) and at 10 weeks, before discharge to local hospital (transplant center protocol). Of the 129 trial participants, 127 patients had valid DXA-scans at baseline available for HSA assessment; one patient was excluded due to age under 20 years (no femur analysis available in the software), another due to bilateral hip prosthesis.

Biochemical analysis

Fasting blood samples were collected on the days of DXA measurements: baseline (<5 weeks), 10 weeks, and 1-year post-transplant. Plasma creatinine, calcium, and phosphate were analyzed consecutively by accredited methods at the Department of Medical Biochemistry, Oslo University Hospital, according to standard protocols. Intra- and interassay coefficients of variation were <5% for all assays.

Samples collected for 25-hydroxyvitamin D [25-OH-vitD] and PTH analysis were centrifuged at the time of collection time and stored at -80 °C until analysis. Serum 25-OH-vitD were assessed by competitive RIA using a kit from DiaSorin Inc., Stillwater, MN, United States and plasma PTH were analyzed in one run, in a research lab, by whole PTH kit (Scantibodies Laboratory Inc, Santee, CA, United States).[21] All samples from a given patient were analyzed at the same time to minimize the run-to-run variability. The intra- and interassay coefficients of variation for 25-OH-vitD was <10%; for PTH the intra- and interassay coefficients of variation were 5.2% and <9.2%, respectively.

DXA measurements

For the DXA measurements, we used a narrow fan-beam GE Lunar Prodigy densitometer (GE Medical Systems, Lunar Corp., Madison, WI, United States). DXA scans were measured at baseline (on average 16 days after transplantation), 10 weeks and 12 months after transplantation. No hardware changes were made during the study period, but there were several upgrades of the software during the study time. All the scans were reanalyzed in February 2023 by the same software version 18 (SP3) (GE Medical Systems, Lunar Corp., Madison, WI, United States).[22] Daily calibration was performed.[23] The short- and long-term coefficients of variation for our densitometer were 0.8% and 1.4%, respectively.[24]

BMD analyses

We analyzed the mean value of the right and left total hip and femoral necks for absolute BMD values (g/cm^2). T- and Z-scores were estimated by comparison with the reference population present in the software, suitable for clinical use in a Norwegian population.[25]

The scan mode for all femur scans was determined by the machine according to the patient's body mass index (BMI), which for our study was either standard or thin scan mode. Manual corrections of the femur analyses were performed in case of obvious errors. The scanning protocol ensured that the femoral shaft was straight, and the femoral head and greater trochanter were within the scan region with soft tissue above the greater trochanter and below the ischium.

Hip Structure Analysis

HSA gives a DXA-based estimation of structural geometry and strength in the total femur region.[26-29] HSA is based on BMD and dimensional data.[14,30] In the software, images of cortical bone are created when lines of pixel value cross over the bone axis in a bone mass image.[31] The femur scans were retrospectively analyzed with the Advanced Hip Assessment software (AHA Version 18 [SP3]; EnCore, GE Medical Systems, WI). An International Society for Clinical Densitometry (ISCD) certified densitometry technologist (KG) performed all the analyses based on the original scans.

CBT was measured at the femoral neck (CBT_{NECK}), calcar (CBT_{CALCAR}), and proximal shaft (CBT_{SHAFT}). Femur neck width was assessed at the narrowest point. Hip axis length is defined as the distance from the greater trochanter to the inner pelvic rim.[17] Figure 1 provides a visualization of these 5 geometrical parameters.

Buckling ratio and strength index were calculated as measures of hip stability and strength. Buckling ratio is an index of bending strength; it is an estimation that is derived from the maximum distance from the center of mass to the outer cortex/superior neck margin in relation to CBT_{NECK}.[29] The strength index combines the measurement of age, height, weight, BMD, and femoral geometry with subject demographics.[32] An explanation is provided in Figure 2.

HSA was performed on both hips and the mean values calculated for each patient. Due to insufficient area for measurement in one of the hips or positioning errors, artifacts, or prosthesis in 5 patients, values included in the analyses for these patients were doubled 1-sided readings. HSA was not available for the youngest participants ($n = 1$), as pediatric scan protocols without femur measurements are standard at our center for patients less than 20 years old. To assess the reproducibility of our HSA measures, we performed a brief validation study in a different, but representable, cohort of our patients ($n = 30$) during 2023. These patients were subject to 2 repeated measurements within a 3-month period, and these measurements were used to calculate the intraclass correlation coefficient (ICC). The ICC was overall excellent and is shown

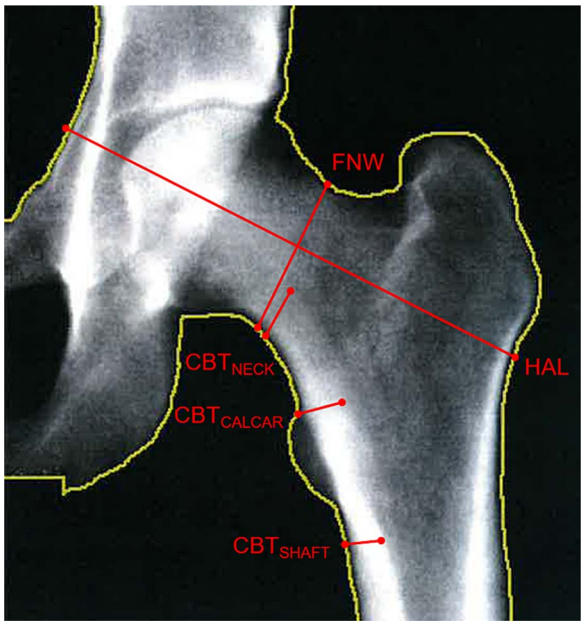


Figure 1. The 5 geometrical hip parameters. Hip structural analysis measures cortical thickness at the femoral neck (CBT_{NECK}), calcar (CBT_{CALCAR}), and proximal shaft (CBT_{SHAFT}). Femur neck width (FNW) was assessed at the narrowest point. Hip axis length (HAL) is defined as the distance from the greater trochanter to the inner pelvic rim. All cursors are manually drawn.

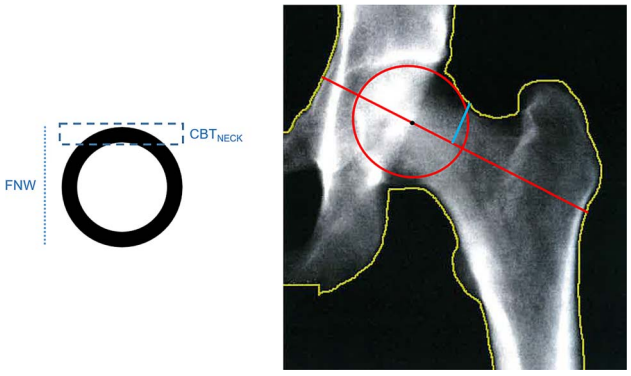


Figure 2. Buckling ratio is represented by the blue line; it is an estimation of the distance from the center of mass to the superior neck margin in relation to CBT_{NECK}. CBT_{NECK}: cortical bone thickness in the femoral neck. FNW: femur neck width. All cursors are manually drawn.

in Supplementary Table 1 for each HSA parameter included in this study.

Immunosuppressive therapy

The standard immunosuppressive protocol consisted of induction with basiliximab and methylprednisolone followed by maintenance therapy including a low-dose calcineurin inhibitor (cyclosporine, target trough levels <6 months 200-300 μg/L, >6 months 75-125 μg/L or tacrolimus, 3-7 μg/L from the day of engraftment), prednisolone (initiated at 80 mg, then gradually reduced to 10 mg/day at 10 weeks and 5 mg from 6 months),[33] and mycophenolate, as described previously.[21]

Statistical analysis

Longitudinal changes were evaluated using linear mixed effects models, treating intervention group (ibandronate or placebo), visit, and their interaction as fixed effects, while individual intercepts were treated as random effects. Model assumption of normally distributed residuals was assessed visually. When this assumption was violated, the dependent variable was transformed using the natural logarithm and the models were adjusted for the theoretically introduced bias. All statistical analyses were performed using R 4.3.2. Pearson's correlation coefficient was used to investigate associations between change in 1-year geometrical hip parameters, buckling ratio, BMD, and plasma PTH. *p*-values below 0.05 were considered statistically significant.

Ethics

The study was approved by the Regional Ethics Committee for Medical Research in Southern Norway, the Norwegian Data Inspectorate as well as the Norwegian Medicines Control Agency. The trial was registered at www.clinicaltrials.gov as NCT00423384, and with EudraCT number 2006-003884-30. The current study was conducted in compliance with the Helsinki II Declaration. All patients provided written informed consent prior to trial participation.

Results

Baseline

Baseline demographics and patient characteristics are presented in Table 1. The characteristics were similar between the 2 groups, except for a larger proportion of patients with diabetes in the placebo group. There were 10 patients with type 1 diabetes mellitus and 12 patients with type 2 diabetes mellitus. Patients with type 2 diabetes mellitus had higher BMI and somewhat poorer graft function (data now shown), but otherwise patients with diabetes had comparable values with the rest of our cohort. Baseline plasma creatinine and mineral metabolism markers did not differ between study groups. At the time of the first DXA, a total of 9 patients (7%) had T-scores $\leq$ -2.5 at the total hip. Baseline values for HSA parameters are shown in Table 2.

The study cohort and the cohort of the overall population of KTR during this time period were numerically similar with regards to age, gender, BMI, and creatinine 10 weeks post-transplantation; this is shown in Supplementary Table 2.

Parathyroid hormone

Figure 3 shows the change in plasma PTH over the first post-transplant year. Both groups showed a swift decline in levels until 10 weeks after transplantation and stabilization thereafter. 52% had PTH above normal values at 10 weeks, while 49% had PTH above upper reference limit at 1 year.

HSA and BMD

Figure 4 shows parameters of bone geometry and strength at baseline (<5 weeks), 10 weeks and 1 year. Due to software limitations, lost to follow-up or death, 4 patients were missing HSA parameters at 10 weeks and 6 patients at 1 year. Absolute change in hip strength parameters and PTH (Year 1—baseline) is shown in Figure 5.

A longitudinal decrease was found in strength index for the placebo group ($p = .049$) only, but there was otherwise no systematic change in the 5 geometrical hip parameters or buckling ratio over the study duration. No statistically significant between-group differences were found in any of the HSA

Table 1. Demographic characteristics at baseline.

Variable	Ibandronate/VitD/Ca ($n = 62$)	Placebo/VitD/Ca ($n = 65$)
Age, years, mean (SD)	49.7 (14.8)	52.5 (12.2)
Sex, male, n (%)	47 (76)	50 (77)
Ethnicity, Caucasian, n (%)	60 (97)	65 (100)
BMI, kg/m^2, mean (SD)	25.8 (3.6)	25.5 (3.7)
Time since start of KRT, months, median (IQR)	10 (25)	9 (19)
Pre-emptive Tx, n (%)	21 (34)	24 (34)
Pre-Tx diabetes mellitus type 1, n (%)	2 (3)	8 (12)
Pre-Tx diabetes mellitus type 2, n (%)	4 (7)	8 (12)
Pre-Tx active vitamin D, n (%)	44 (71)	47 (72)
Pre-Tx calcium, n (%)	3 (5)	5 (8)
Pre-Tx bisphosphonate, n (%)	0	1 (1.5)
Pre-Tx cinacalcet, n (%)	9 (14.5)	4 (6.2)
Immunological cause of kidney failure, n (%)	29 (46.8)	24 (36.9)
CNI, tacrolimus, n (%)	31 (50)	26 (40)
P-Creatinine, μmol/L, mean (SD)	109 (24.2)	115 (26.7)
P-Calcium, mmol/L, median (IQR)	2.3 (0.2)	2.3 (0.1)
P-Phosphate, mmol/L, mean (SD)	0.7 (0.2)	0.7 (0.2)
P-PTH, pg/mL, median (IQR)	58.7 (70)*	59.6 (52)*
S-25-OH-vitD, nmol/L, median (IQR)	54 (42)	53 (28)

Abbreviations: BMI = body mass index; CNI = calcineurin inhibitor; IQR = interquartile range; KRT = kidney replacement therapy; P = Plasma; SD = standard deviation; S = Serum. Data expressed as mean (SD) for normally distributed data and median (IQR) for non-normal distributions. Categorical data expressed as absolute numbers with frequencies. *n = 61 for Ibandronate/VitD/Ca and n = 64 for Placebo/VitD/Ca

Table 2. Baseline values for HSA parameters.

Variable	Combined ($n = 127$)	Ibandronate/VitD/Ca ($n = 62$)	Placebo/VitD/Ca ($n = 65$)
CBT_{NECK} (mm)	5.2 (1.8)	5.2 (1.8)	5.2 (1.8)
CBT_{CALCAR} (mm)	4.0 (1.0)	3.9 (1.0)	4.1 (1.0)
CBT_{SHAFT} (mm)	5.2 (1.3)	5.1 (1.3)	5.3 (1.3)
Femur neck width (mm)	34.3 (3.7)	34.3 (3.6)	34.2 (3.8)
Hip axis length (mm)	118 (10.7)	119 (10.8)	118 (10.6)
Buckling Ratio	4.2 (1.6)	4.3 (1.6)	4.1 (1.5)
Strength Index	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)

Data expressed as mean (SD) for normally distributed data

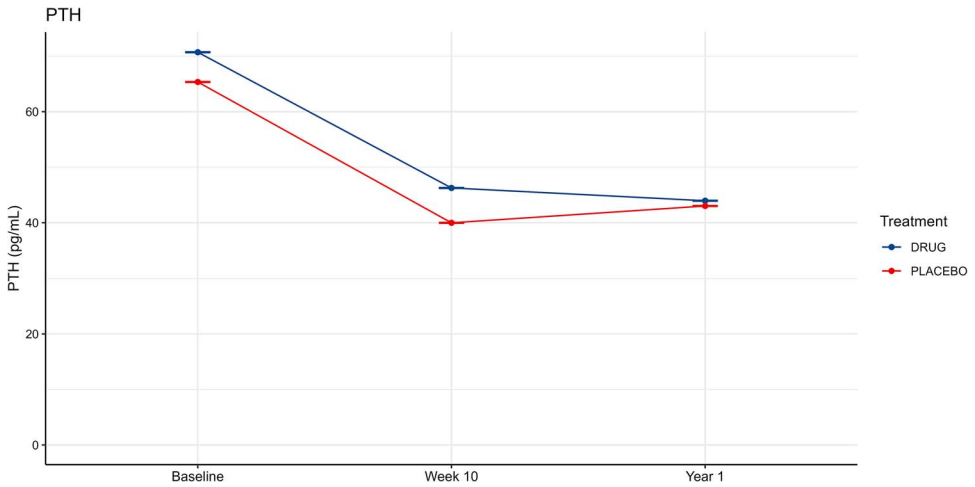


Figure 3. Changes in PTH over the first transplant year for patients receiving ibandronate vs placebo, presented as estimated marginal means ± standard error.

measures. We also investigated if the effect of ibandronate differed between patients in the lowest and highest quartile of each HSA parameter at baseline. This revealed a difference for HAL only, where the change over the study duration was greater for the lowest (-2.2 [95% CI: -3.9, -0.46]) when compared with the highest (0.78 [95% CI: -1.1, 2.6]).

Change in 1-year geometrical hip parameters and buckling ratio was not correlated with 1-year change in plasma PTH or

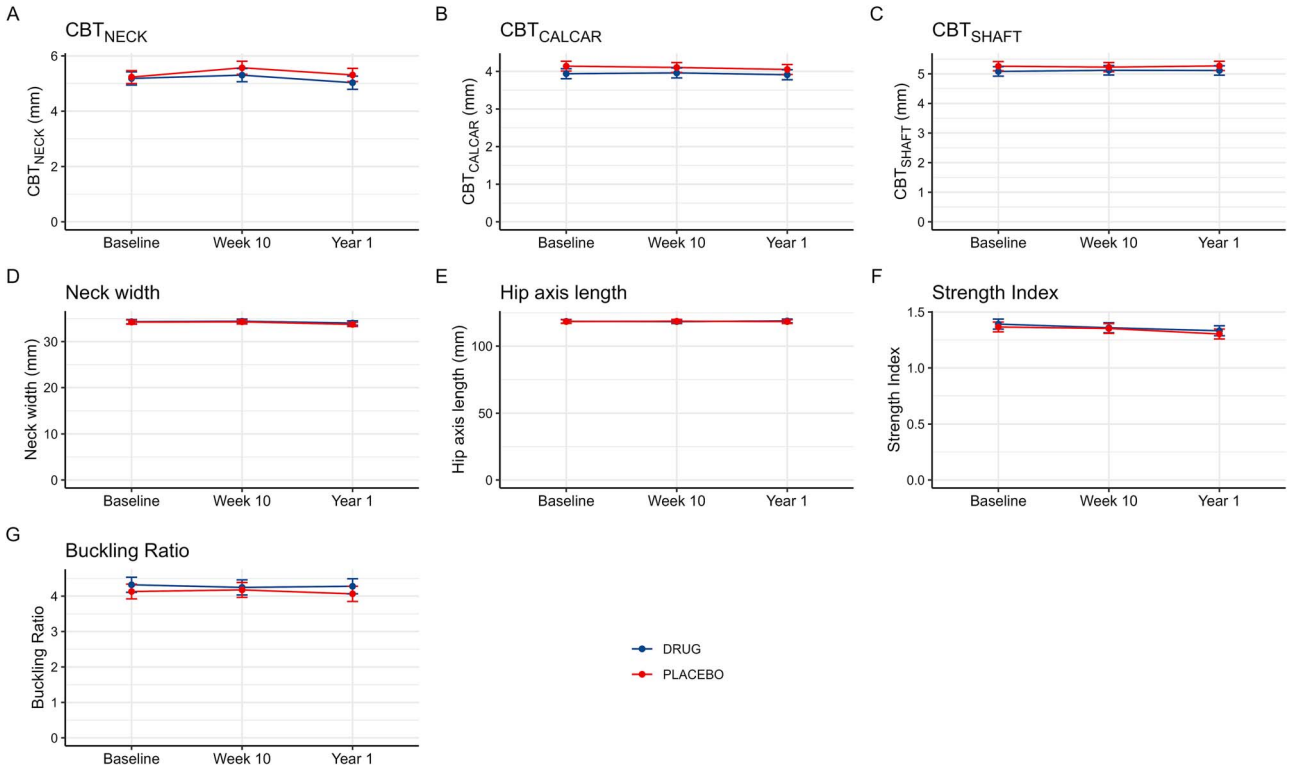


Figure 4. Parameters of bone geometry and strength in patients receiving ibandronate vs placebo, measured at baseline (<5 weeks), 10 weeks and 1-year post-transplant, presented as estimated marginal means ± standard error.

change in dual total hip BMD when compared with baseline, except for a weak correlation CBT_{SHAFT} and change in PTH ($r = 0.19$, $p = .04$).

Discussion

In this study of *de novo* KTR, treatment with ibandronate in addition to active vitamin D and calcium supplement in the first year after transplantation did not show any benefit for the hip geometric and strength parameters compared with active vitamin D and calcium alone. Changes in HSA parameter values over the first post-transplant year were not convincingly correlated with change in dual total hip BMD or plasma PTH.

In a cross-sectional study of 226 KTR who were compared with age- and sex-matched community dwellers, KTR had lower CBT_{NECK}, CBT_{CALCAR}, and CBT_{SHAFT}, and had higher buckling ratios, even when adjusted for dual total hip BMD Z-scores.[9] Furthermore, for KTR, BMD at dual total hip and femoral necks correlated with CBT_{NECK}, CBT_{CALCAR}, and CBT_{SHAFT}, negatively to buckling ratio, and CBT_{NECK} was positively correlated to levels of PTH in this study.[9] Interestingly, reduced CBT_{NECK} and higher buckling ratio were associated with prevalent vertebral fractures.[9] From an HSA perspective, our population appeared "healthier" at baseline than the above mentioned cohort, with higher CBT_{NECK} values and lower buckling ratios.[9] Indeed, almost half of our patients had not been in dialysis before transplantation, in contrast to only 3 percent (6/226 patients) in the cross-sectional study, a fact that is also reflected in our relatively low PTH at baseline. The proportion of our patients with total hip BMD in the osteoporotic range at baseline was also low (7%). The above mentioned large study sought to present normative data for HSA; however, it is not directly comparable to ours as this cohort was of a different ethnicity, not all the same parameters have been measured or estimated and an older software was used.

Possible reasons for the lack of correlations between HSA measures and BMD/PTH in the present study may be that our first DXA scans were performed as early as 2 to 5 weeks after transplantation. This is a time of rapid changes in bone metabolism and graft function, but HSA values may still be more representative of bone in patients with CKD stage 5. We saw marked inter-individual variation in changes in HSA parameters over the study duration, especially in buckling ratio and CBT variables, leading us to conclude that a kidney transplant with its rapid changes in hormone and blood mineral levels, as well as drug regimens, does not lead to any uniform change in measures of hip geometry. In the quartile analysis of change in HSA parameters between the groups, change in HAL was greater for the lowest quartile receiving ibandronate. While the underlying mechanism is unclear, it is curious that this was the case only for HAL; it suggests that ibandronate was more effective for patients with lower baseline HAL.

When analyzing HSA values in patients undergoing simultaneous pancreas kidney transplantation (SPK) due to CKD from Type 1 diabetes mellitus, even lower CBT was measured at all hip sites and higher buckling ratios than compared with those patients with CKD from other causes.[34] In our study, baseline HSA parameters in patients with pre-transplant diabetes mellitus ($n = 22$) were comparable with the rest of the cohort (data not shown), indicating that dysregulation of bone metabolism related to hyperglycemia was less pronounced than what is seen in diabetic patients considered candidates for SPK.

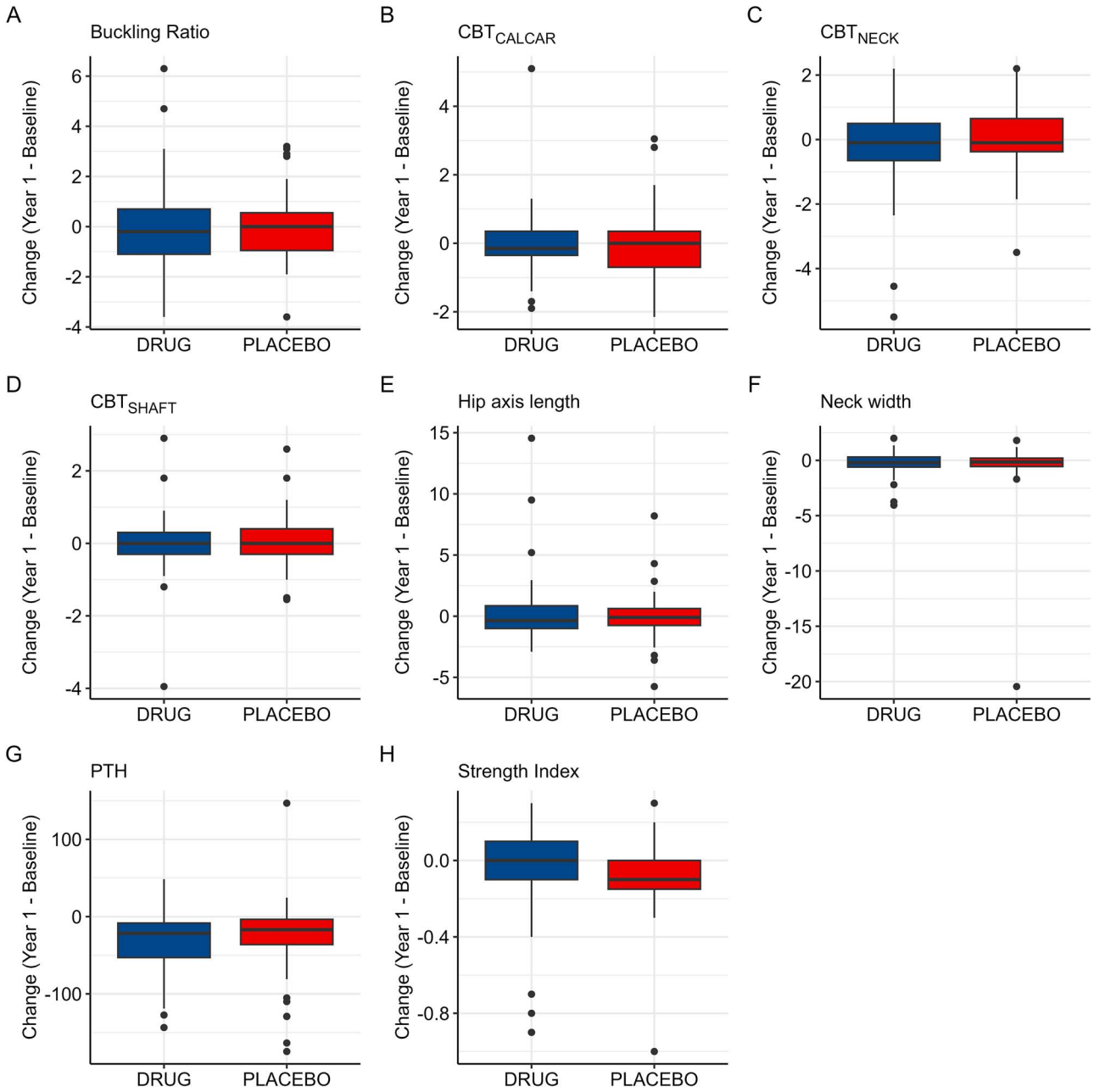


Figure 5. Change in geometrical and strength hip parameters and PTH (Year 1—baseline).

The effect of persistent CKD-MBD and immunosuppressive medications on bone tissue in KTR is highly variable between individuals; however, KTR tend to present with low BMD,[35,36] and high bone turnover due to secondary/tertiary hyperparathyroidism.[13] In a study over 1.5 years where CKD patients were assessed by HRpQCT there was significant cortical bone loss at the radius and this was associated with higher PTH; however, trabecular bone was preserved.[12] This was supported by a cohort study of KTR over the first post-transplant year, where HRpQCT of the distal radius and tibia showed reduced cortical area, density, and thickness, with the cortical reduction directly related to PTH levels.[37] As graft function improves, PTH gradually decreases potentially slowing down the high bone turnover state.[13,38] However, with the addition of immunosuppression, including initial high doses of glucocorticoids that inhibit bone formation, we may see a secondary increase in bone resorption.[13,39] Furthermore, calcineurin inhibitors have been shown to increase PTH.[13] Raised PTH has also been shown to be preferentially catabolic toward cortical bone over a longer period of 5 years in KTR.[40] This may explain why KTR tend to fracture more in the peripheral skeleton than the central skeleton.[41,42]

In light of the above, it is interesting that HSA parameters remained stable during the first post-transplant year in our cohort. This is also in accordance with a recent longitudinal study showing trabecular thickness, cortical porosity, and thickness, assessed by bone histomorphometry and μCT, to be unchanged 1 year after kidney transplantation.[43] PTH has repeatedly been shown to decrease during the first post-transplant year in the majority of KTR.[43,44] Our cohort may represent a low-risk population among KTR, as their PTH levels were generally well controlled at the time of

transplantation. Interestingly, nearly all our patients received PTH lowering medication before transplantation. We hypothesize that improved management of CKD-MBD both pre- and post-transplant results in resolution of hyperparathyroidism to a larger extent than in previous eras, resulting in stable HSA parameters.

There are several benefits to measuring HSA in addition to BMD. BMD from DXA is limited to a 2-dimensional measurement of bone density. HSA provides cortical geometry and microarchitectural deterioration not detected by BMD. HSA is noninvasive, readily available, and inexpensive. Thus, HSA is complementary to the classical BMD assessment for KTR as we know these patients are at increased risk of fracture, especially in the early post-transplant period.[4,45] We have previously shown our study cohort to maintain stable BMD in different body compartments over the first post-transplant year.[21,46] While the median BMD T-scores remained in the normal range, median trabecular bone score started out below the cut-off value that has been used to identify KTR at high fracture risk.[47]

For middle-aged and elderly (50-89 years) Norwegian women the use of bisphosphonate and denosumab has been found to lower first-time hip fracture risk.[48] Further, hip geometry and strength parameters have been shown to predict incident hip fracture independent of clinical risk factors and BMD.[49] Moreover, in a cohort of Japanese postmenopausal women, treatment with bisphosphonates seemed to influence HSA parameters positively.[50] However, CKD-MBD both before and after kidney transplant involves complex bone metabolic disturbances, hence we may not extrapolate results from studies in postmenopausal osteoporosis to populations with CKD. The literature lacks long-term studies in CKD and KTR on the predictive value of HSA on future hip fractures, but our study sheds light on the possible protective effect of ibandronate on proximal femur geometry and strength.

While we were not able to detect a positive effect of ibandronate on HSA parameters, an RCT investigating the effect of zoledronic acid on 33 *de novo* KTR found a positive treatment effect: an improvement in the subperiosteal parameter, endocortical diameter, and cross-sectional moment of inertia at the narrow neck was demonstrated in the intervention group compared with placebo.[20] As in our study, both groups received the same dosages of calcium and active vitamin D supplements.[20] The baseline measures and hence results are not directly comparable with ours as they used a different DXA machine, Hologic Horizon, with a different HSA software (APEX), giving parameters that are not available in our Lunar DXA. Moreover, this RCT had shorter follow-up (6 months vs 12 months), fewer patients (33 vs 127), and a cohort of different ethnicity (Middle Eastern vs Caucasian).[20] Larger interventional studies of longer duration are needed to clarify the role of modern bone-protective agents in preserving cortical bone after kidney transplantation.

There are several strengths of the present study being the so far largest study to assess the effect of bisphosphonate on HSA in *de novo* KTR, with the longest observational time. The data are based on our previously published RCT with a well-characterized population. These longitudinal DXA data were analyzed *post hoc* in "one run" with the same software version and by a single certified investigator (KG). Some limitations are worth mentioning. HSA is based on 2-dimensional DXA imaging and we are therefore dependent on good images and satisfactory femur rotation. The software assumes that cortical bone is homogenous and evenly distributed in the cross-sections taken, which is not true, as this is dependent on wear and strain. There are no normative reference values for HSA; these values are highly desired and vital, but not available in the software and though studies have sought to present such reference data, they are not directly comparable. The follow-up duration of 12 months is quite short and we do not yet possess data on fracture rates. Our study population was predominantly Caucasian, and as such our results may not be otherwise generalizable.

Conclusion

In this so far largest study assessing the effect of bisphosphonate on HSA in KTR, antiresorptive therapy with ibandronate for 12 months did not affect measures of hip geometry or strength. The utility of HSA should be further investigated in the CKD and transplant setting, to investigate if hip structural geometry and strength parameters can be used to evaluate fracture risk and therapeutic monitoring of antiresorptive care.

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Author contributions

Ruth Strømmen (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing—original draft, Writing—review & editing), Kristin Godang (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), Markus Hovd (Data curation, Formal analysis, Resources, Writing—original draft, Writing—review & editing), Trine E. Finnes (Writing—review & editing), Knut Smerud (Conceptualization, Funding acquisition, Investigation, Methodology, Writing—review & editing), Anders Hartmann (Conceptualization, Funding acquisition, Investigation, Methodology, Writing—review & editing), Anders Åsberg (Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing), Jens Bollerslev (Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing—original draft, Writing—review & editing), and Hege K. Pihlstrøm (Investigation, Methodology, Project administration, Supervision, Writing—original draft, Writing—review & editing)

Supplementary material

Supplementary material is available at *JBMR Plus* online.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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