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Bone Mineral Density in Relation to Chronic Kidney Disease After Heart Transplantation: A Retrospective Single-center Study at Skåne University Hospital in Lund 1988–2016

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Background. Our aim was to investigate the bone mineral density (BMD) evolution and incidence of osteoporosis in relation to chronic kidney disease (CKD) up to 10 years after heart transplantation (HT). **Methods.** A retrospective analysis was performed on 159 HT patients at Skåne University Hospital in Lund 1988–2016. **Results.** The median follow-up time was 6.1 years (interquartile range = 7.5 y). HT patients with CKD stage <3 or normal kidney function before HT exhibited a greater mean BMD loss in the lumbar spine, compared to patients with CKD stage ≥3 before HT, at the first (–6.6% versus –2.5%, $P = 0.029$), second (–3.7% versus 2.1%, $P = 0.018$), and third (–2.0% versus 4.1%, $P = 0.047$) postoperative years, respectively. All included HT patients exhibited a BMD loss in the femoral neck at the first postoperative year (–8.8% [–10.3 to –7.3] in patients with CKD stage <3 or normal kidney function and –9.3% [–13.2 to –5.5] in patients with CKD stage ≥3 before HT), which was not fully reversed up to 10 years after HT. In adjusted models, CKD stage <3 before HT did not predict osteopenia and osteoporosis in the lumbar spine or femoral neck. **Conclusions.** CKD before HT did not predict BMD loss or osteoporosis development after HT. The study is, however, limited by a lack of data on fractures, and further studies on the relationship between CKD and postoperative bone strength are encouraged.

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Heart transplantation (HT) recipients require immunosuppression to prevent organ rejection.[1] One well-documented adverse effect of the immunosuppression is osteoporosis, defined as a skeletal disorder with reduced bone strength, measured as bone mineral density (BMD), which increases the risk of bone fractures.[2] Not only do fractures increase morbidity but also mortality rates.[3,4] It has previously been reported that the mortality rate increases 1.5-fold for each SD decrease in BMD in patients with osteoporosis.[5] Hence, the need for early identification and treatment of osteoporosis is of great value.

Out of the currently used immunosuppressants, corticosteroids are the most common cause of drug-induced osteoporosis.[6] Calcineurin inhibitors have also been reported to negatively influence bone homeostasis.[7-10] Furthermore, the period before HT also attributes to impairment of skeletal health.[11-18] Thus, the pathophysiology behind osteoporosis after HT is multifaceted, involving more attributors than the immunosuppressive therapy.[19] Furthermore, chronic kidney disease (CKD) is, like osteoporosis, frequently found in the HT patient population and may arise as a side effect of the immunosuppressive therapy. The most nephrotoxic immunosuppressants after HT are the calcineurin inhibitors, particularly cyclosporine.[20,21]

Kidney dysfunction is, furthermore, known to be associated with impaired bone strength and increased risk of fractures.[22,23] The combination of CKD and bone disorders is termed CKD-mineral and bone disorders, defined by the Kidney Disease: Improving Global Outcomes committee as a systemic disorder of mineral and bone metabolism as a result of CKD.[24] Hence, HT patients with CKD might have increased mortality rates on multiple bases, which emphasizes

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the importance of early detection and reduction of the risk factors. The aim of the present study was, therefore, to investigate the BMD evolution and incidence of osteoporosis in relation to CKD up to 10 years after HT.

MATERIALS AND METHODS

Study Design and Patient Selection

The present study was part of the establishment of Lund Heart Transplantation Research Register. A description of the patient cohort and study design is available in a previous report on BMD loss and osteoporosis in relation to immunosuppressive therapy, which included 169 patients who underwent HT at an age of at least 20 years between January 1988 and June 2016 at Skåne University Hospital in Lund (31). The present study was approved by the local ethics board in Lund (approval nos. 2010/114, 2011/777, 2014/92).

Data Collection

Data were collected from the clinical records of the preoperative transplantation assessment (TA) and from postoperative annual check-ups up to 10 years after HT. Measurement of BMD was obtained using Dual-energy X-ray absorptiometry from the lumbar spine and femoral neck, and osteoporosis was defined as a BMD of at least 2.5 SD below the mean BMD of young, healthy adults, in accordance with the World Health Organization.[25] Other data collected included the glomerular filtration rate (GFR [mL/min/1.73 m^2]), immunosuppressive induction and maintenance therapy, body mass index (BMI [kg/m^2]), age (recipient and donor), gender, time on waiting list, survival, ischemic time, and cause of death, as well as biochemical data such as albumin-to-creatinine ratio and serum levels of creatinine, urea, calcium, alkaline phosphatase (ALP), and parathyroid hormone (PTH).

CKD Stage

Classification of CKD was primarily based on plasma clearance of iohexol because it is considered to accurately reflect GFR.[26] The estimated GFR (eGFR) was calculated through the CKD epidemiology collaboration (CKD-EPI) equation using serum creatinine levels and was used for the classification of CKD when iohexol clearance measurements were missing. Classification of CKD stage was based on definitions described in a report by the Kidney Disease: Improving Global Outcomes.[27] Normal kidney function was defined as GFR ≥90 mL/min/1.73 m^2.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows (version 22.0, Armonk, NY: IBM Corp). All tests were 2-tailed with a 5% level of significance. The mean and 95% confidence interval or median and interquartile range was calculated for continuous variables. In the main analyses, patients were pooled into groups based on the presence or absence of CKD stage ≥3 before HT to increase statistical power.

Continuous baseline variables were compared using independent *t* test and Mann-Whitney U test for parametric and nonparametric data, respectively. Categorical variables were compared through χ^2 test. Comparisons of the change in BMD and the GFR evolution between the groups were performed using independent *t* test. A χ^2 test was performed to compare the preoperative prevalence of osteopenia and osteoporosis between the groups. Survival free from osteopenia and osteoporosis was calculated using Kaplan-Meier estimates, and comparisons between groups were performed as previously described.[28]

Univariate and multivariate Cox regressions were performed to analyze the incidence of osteopenia and osteoporosis in relation to CKD stage ≥3, including previously well-documented factors with impact on BMD such as age, gender, and BMI. Several additional analyses included era of HT (1988–1999 versus 2000–2016), hemodialysis, and osteoporosis preventive treatment, as well as serum urea, creatinine, and albumin-to-creatinine ratio at TA. Univariate and multivariate Cox regressions were also performed to analyze the incidence of osteopenia and osteoporosis in relation to the mean change (%) in GFR, stratified into 3 percentiles (>6.5%, –28.5 to 6.5%, and <–28.5%), from TA to 1 year after HT. Adjustments were made for age, gender, BMI, and era of HT.

To analyze the accuracy of preoperative eGFR compared with the measured GFR based on plasma iohexol clearance, an independent *t* test was used, including HT patients with both eGFR and iohexol clearance data.

RESULTS

Study Population

Of the included 159 HT patients, 23 (14%) had normal kidney function, whereas 58 (34%), 69 (41%), 8 (5%), and 1 (0.6%) had CKD stage 2, 3, 4, and 5, respectively, before HT. Five of the included patients were kidney transplanted after HT. The median follow-up time for the included patients was 6.1 years (interquartile range = 7.5 y). Baseline characteristics, with stratification based on CKD stage or normal kidney function, are displayed in Table 1.

Immunosuppression

At hospital discharge after HT, 32% received a combination of corticosteroids + cyclosporine + azathioprine, 34% corticosteroids + cyclosporine + mycophenolate mofetil, and 28% corticosteroids + tacrolimus + mycophenolate mofetil, whereof the latter combinations being favored during the past couple of decades.[28] At initiation of the maintenance immunosuppressive therapy, doses were standardized and thereafter down-titrated on a regular basis, as previously described.[28] Cyclosporine and tacrolimus doses were down-titrated based on calcineurin inhibitor trough (C0) levels, whereas adjustment of corticosteroids and antimetabolite doses was based on center-specific protocols.[28]

Preoperative CKD Stage as an Indicator of Postoperative BMD Loss

HT patients with CKD stage <3 or normal kidney function before HT exhibited a mean BMD loss in the lumbar spine more than twice as great during the first year compared with their counterparts (–6.6% [–8.8 to –4.5] versus –2.5% [–5.6 to 0.6], $P = 0.029$). Furthermore, HT patients with CKD stage ≥3 before HT gained a mean lumbar BMD of +2.1% (–2.1 to 6.3) and +4.1% (–1.2 to 9.4) at second and third postoperative year, respectively, whereas patients with CKD stage <3 or normal kidney function before HT lost a mean lumbar BMD of –3.7% (–5.8 to –1.6) and –2.0% (–4.6 to 0.5) at second ($P = 0.018$) and third ($P = 0.047$) postoperative year, compared with preoperative measurements. No differences between the groups were thereafter detected in the lumbar spine ($P > 0.05$) (Figure 1A).

In the femoral neck, all included HT patients exhibited a mean BMD loss at the first postoperative year (–8.8% [–10.3 to –7.3] in patients with CKD stage <3 or normal kidney

TABLE 1.

Baseline characteristics

	Normal kidney function	CKD stage			CKD stage <3 or normal kidney function	CKD stage ≥3	
		2	3	4+5			
Baseline characteristics	**N = 23**	**N = 58**	**N = 69**	**N = 9**	**N = 81**	**N = 78**	***P***
Age[a] (y), median (IQR)	47 (15)	54 (37)	56 (41)	56 (30)	52 (14)	56 (11)	0.065
Female, n (%)	6 (26.1)	12 (20.7)	18 (26.1)	1 (11.1)	18 (22.2)	19 (24.4)	0.852
BMI[a] (kg/m^2), mean (95% CI)	24.2 (23.2 to 26.9)	25.4 (24.1 to 26.2)	26.1 (25.1 to 27.1)	26.9 (24.3 to 29.8)	25.1 (24.2 to 26.0)	26.2 (25.3 to 27.1)	0.097
Follow-up (y), median (IQR)	5.4 (7.4)	6.5 (7.0)	6.2 (7.7)	3.4 (8.1)	6.5 (7.0)	6.2 (7.8)	0.304
Biopsies per patient within the first y after HT (N), median (IQR)	14 (0)	14 (1)	14 (1)	14 (1)	14 (0)	14 (1)	0.324
ACR ≥ grade 2R (%), median (IQR)	0 (6.6)	0 (6.4)	5.6 (10.4)	7.9 (9.4)	0 (6.3)	5.7 (10.4)	0.013
Waiting time (d), median (IQR)	56 (135)	103 (167)	91 (179)	150 (680)	80 (147)	106 (179)	0.241
Ischemic time (min), mean (95% CI)	175 (139 to 212)	178 (160 to 197)	190 (171 to 208)	217 (126 to 307)	178 (162 to 193)	192 (175 to 210)	0.208
Serum creatinine[a] (µmol/L), median (IQR)	73 (21)	92 (35)	110 (36)	171 (135)	82 (32)	113 (50)	<0.001
Serum urea[a] (mmol/L), median (IQR)	5.7 (3.1)	7.4 (3.0)	10.2 (4.9)	22 (7.3)	6.6 (3.5)	10.6 (8.6)	<0.001
Iohexol-GFR[a] (mL/min/1.73 m2), median (IQR)	94 (4)	71 (14)	50 (13)	23 (5)	73 (14)	48 (16)	
eGFR[a] (mL/min/1.73 m2), median (IQR)	104 (21)	79 (31)	61 (27)	35 (29)	91 (32)	59 (30)	
Iohexol-GFR or eGFR[a] (mL/min/1.73 m2), median (IQR)[b]	97 (15)	71 (13)	50 (13)	23 (5)	81 (24)	45 (17)	
Urine albumin/creatinine ratio[a] (g/mol), median (IQR)	2.5 (5.8)	2.4 (2.9)	1.4 (5.9)	0.8 (2.2)	2.4 (3.3)	1.3 (3.5)	0.231
Maintenance immunosuppressive therapy, n (%)							0.833
CS + AZA + CSA	5 (21.7)	20 (35.1)	21 (33.3)	2 (25.0)	25 (31.3)	23 (32.4)	
CS + MMF + CSA	11 (47.8)	15 (26.3)	25 (39.7)	2 (25.0)	26 (32.5)	27 (38.0)	
CS + MMF + TAC	6 (26.1)	17 (29.8)	15 (23.8)	2 (25.0)	23 (28.8)	17 (23.9)	
Other	1 (4.3)	5 (8.8)	2 (3.2)	2 (25.0)	6 (7.5)	4 (5.6)	
Cumulative CS dose (g), median (IQR)	17.6 (13.2)	17.6 (11.0)	15.3 (15.7)	9.8 (13.5)	17.6 (12.3)	14.8 (15.5)	0.270
Time with CS (y), median (IQR)	6 (9)	7 (8)	4 (9)	2 (6)	6 (8)	4 (9)	0.118
Daily CS dose at 1 y after HT (mg), mean (95% CI)	7.5 (5.9 to 9.1)	7.6 (6.9 to 8.3)	7.6 (6.9 to 8.4)	8.2 (6.5 to 10.0)	7.6 (6.9 to 8.3)	7.7 (7.0 to 8.4)	0.665
BMD[a] (g/m^2), mean (95% CI)							
Lumbar spine	1.12 (1.41 to 1.20)	1.10 (1.04 to 1.15)	1.12 (1.07 to 1.17)	1.14 (0.99 to 1.28)	1.10 (1.05 to 1.15)	1.12 (1.08 to 1.17)	0.499
Femoral neck	1.00 (0.93 to 1.07)	0.96 (0.91 to 1.00)	0.96 (0.92 to 1.00)	0.92 (0.79 to 1.05)	0.97 (0.93 to 1.01)	0.95 (0.92 to 0.99)	0.506
T score[a] (SD), mean (95% CI)							
Lumbar spine	−0.76 (−1.40 to −0.13)	−1.00 (−1.47 to −0.54)	−0.75 (−1.17 to −0.32)	−0.73 (−1.97 to 0.50)	−0.94 (−1.31 to −0.57)	−0.75 (−1.14 to −0.36)	0.474
Femoral neck	−0.51 (−1.00 to −0.01)	−0.85 (−1.16 to −0.54)	−0.82 (−1.11 to −0.53)	−1.26 (−2.21 to −0.31)	−0.76 (−1.02 to −0.50)	−0.88 (−1.16 to −0.61)	0.510

[a]At TA.
[b]Calculated eGFR was added if iohexol clearance GFR was missing.
Maintenance immunosuppression at discharge from hospital after HT.
ACR, acute cellular rejection; AZA, azathioprine; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CS, corticosteroids (Prednisolone); CSA, cyclosporine A; (e)GFR, (estimated) glomerular filtration rate; HT, heart transplantation; IQR, interquartile range; MMF, mycophenolate mofetil/mycophenolic acid; SD, standard deviation; TA, transplant assessment; TAC, tacrolimus.

function and −9.3% [−13.2 to −5.5] in patients with CKD stage ≥ 3 before HT), which was not fully reversed up to 10 years after HT. There was, however, no evidence for a difference between the groups (Figure 1B).

Osteopenia and Osteoporosis Before HT

Fifty percent of the HT patients had osteopenia or osteoporosis in the lumbar spine before HT, and the corresponding number for the femoral neck was 45% (Figure 2). No association between preoperative osteopenia or osteoporosis and CKD stage ≥ or <3 and normal kidney function was detected.

Incidence of Osteopenia and Osteoporosis by CKD

The cumulative incidence of osteopenia in the lumbar spine was higher in HT patients with CKD stage <3 or normal kidney function than CKD stage ≥3 at TA (P = 0.042) up to 10 years after HT (Figure 3A). There were, however, no statistically significant differences in the cumulative incidence of osteopenia in the femoral neck between the groups (P = 0.280) (Figure 3B).

No evidence of a predictive effect of CKD stage ≥3 at TA on osteopenia and osteoporosis in the lumbar spine and femoral neck was detected in the crude and adjusted models (Tables 2 and 3).

Incidence of Osteopenia and Osteoporosis by Change in GFR

No differences in survival without osteopenia or osteoporosis up to 10 years after HT were found between HT patients stratified into 3 percentiles by the mean change (%) in GFR

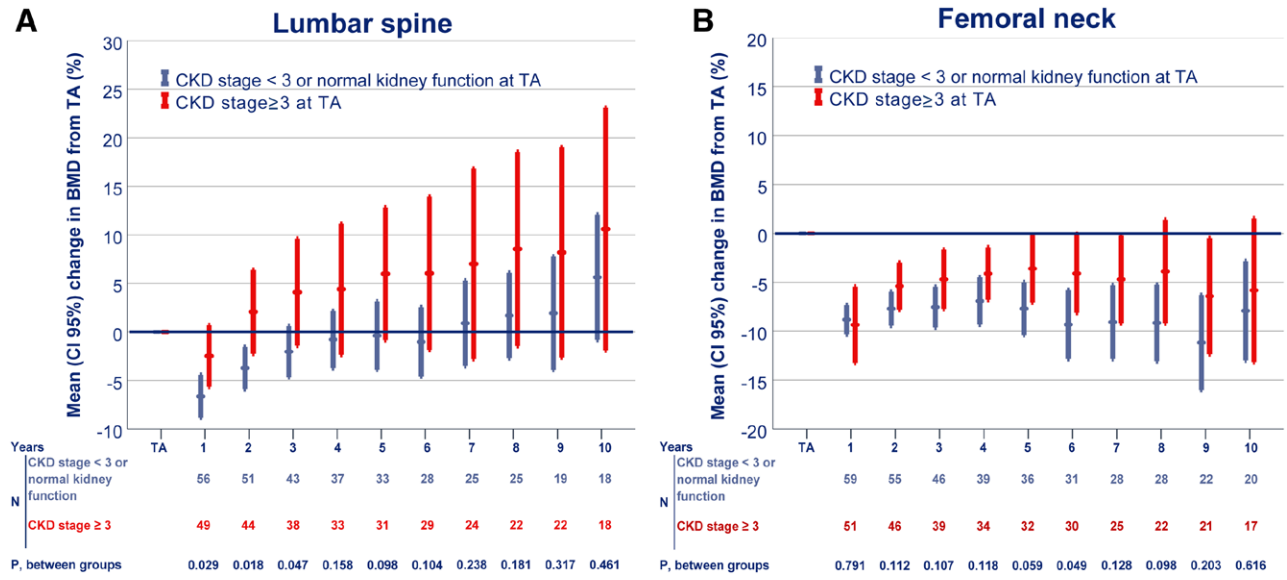

FIGURE 1. BMD change by CKD. The change (%) in BMD in relation to CKD stage <3 and CKD stage ≥3 in (A) the lumbar spine and (B) femoral neck, from TA up to 10 y after HT. BMD, bone mineral density; CI, confidence interval; CKD, chronic kidney disease; HT, heart transplantation; TA, transplantation assessment.

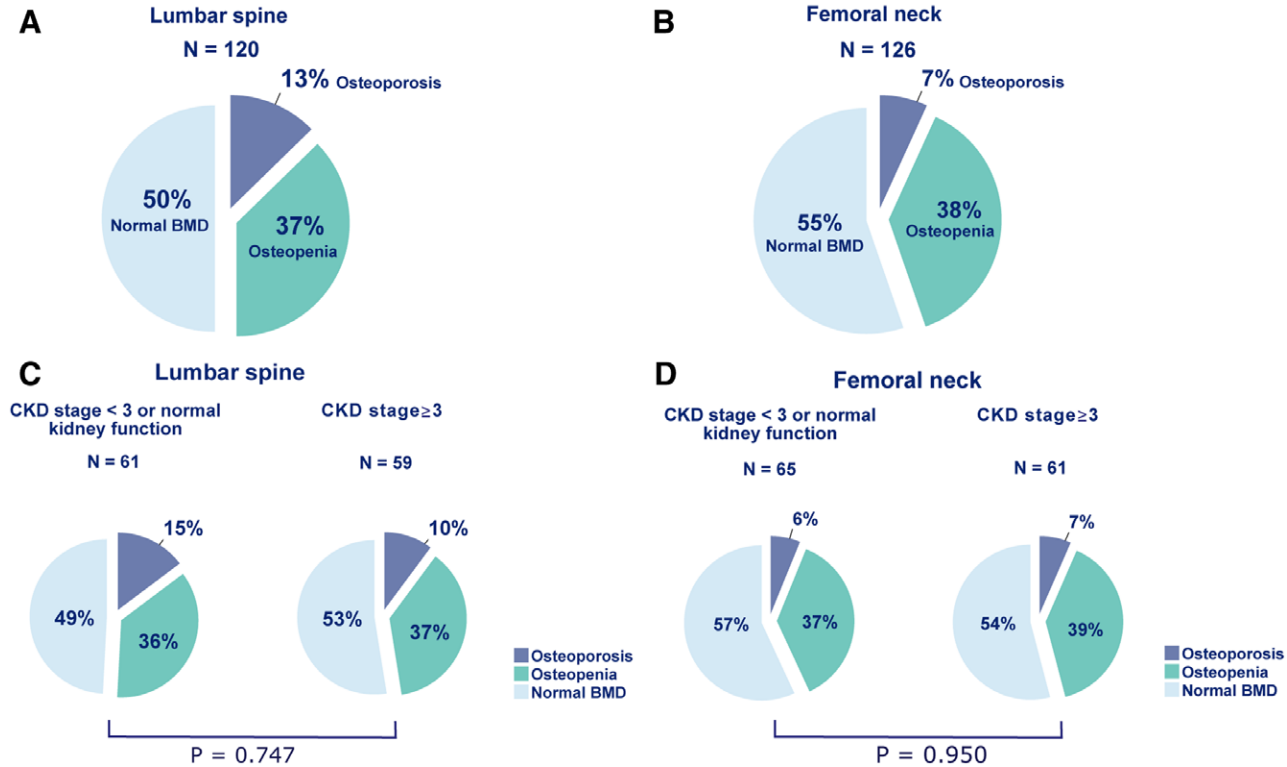

FIGURE 2. Prevalence of osteopenia and osteoporosis at baseline. Prevalence of osteopenia and osteoporosis in the total cohort in (A) the lumbar spine and (B) femoral neck, as well as in relation to CKD stage <3 or normal kidney function and CKD stage ≥3 at the TA before HT in (C) the lumbar spine and (D) femoral neck. BMD, bone mineral density; CKD, chronic kidney disease; HT, heart transplantation; TA, transplant assessment.

from before HT to the first postoperative year (Figure 4). Likewise, when adjusted for age, gender, BMI, and era, no differences in the incidence of osteopenia or osteoporosis were found in the lumbar spine or femoral neck (Tables 4 and 5).

Serum Calcium, PTH, and ALP

Serum concentrations of calcium, PTH, and ALP in relation to CKD stage <3 or normal kidney function and CKD stage ≥3 at TA, from TA and up to 10 years after HT, are displayed in Figure 5.

Accuracy of eGFR at Baseline

In total, 72% of the HT patients had preoperative data on both eGFR and iohexol clearance and were included in the analysis. The CKD-EPI formula overestimated GFR at baseline with a mean of 14.5 mL/min/1.73^2 (11.1–17.8) or 29.1%

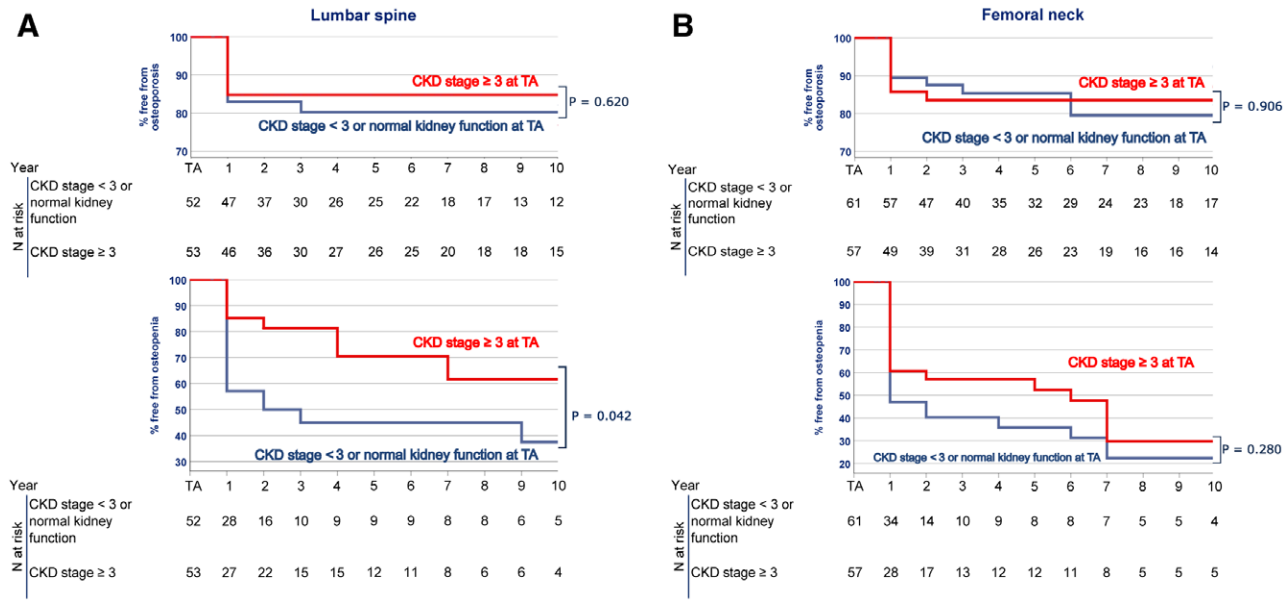

FIGURE 3. Survival without osteopenia or osteoporosis by CKD. Survival without osteopenia or osteoporosis stratified by CKD stage <3 or normal kidney function and CKD stage ≥3 from before HT (TA) up to 10 y after HT in (A) the lumbar spine and (B) femoral neck. CKD, chronic kidney disease; HT, heart transplantation; TA, transplant assessment.

TABLE 2.

Cox regression analyses of the incidence of osteopenia in the lumbar spine and femoral neck, in relation to presence of CKD stage ≥3 at TA

Osteopenia within 10 y after HT			CKD stage ≥3 at TA			
			Lumbar spine		Femoral neck	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Crude model			0.46 (0.20-1.08)	0.075	0.76 (0.41-1.42)	0.391
Adjusted for						
Model 1	Age[a], gender (male), BMI[a]		0.62 (0.24-1.58)	0.316	0.80 (0.41-1.59)	0.527
Model 2	Model 1 + era of HT (1988–1999 vs 2000–2016)		0.62 (0.24-1.58)	0.312	0.86 (0.43-1.74)	0.674
Model 3	Model 1 + hemodialysis[b]		1.14 (0.36-3.63)	0.824	0.66 (0.27-1.58)	0.346
Model 4	Model 1 + serum urea[a] (mmol/L)		0.71 (0.26-1.96)	0.511	0.94 (0.45-1.95)	0.870
Model 5	Model 1 + Serum creatinine[a] (μmol/l)		0.69 (0.24-2.02)	0.495	1.07 (0.50-2.29)	0.870
Model 6	Model 1 + albumin-to-creatinine ratio[a] (mg/g)		0.39 (0.10-1.49)	0.167	0.43 (0.13-1.44)	0.171
Model 7	Model 1 + osteoporosis preventive treatment[a]	Calcium carbonate	0.56 (0.20-1.54)	0.258	0.83 (0.41-1.69)	0.609
Model 8	Model 1 + osteoporosis preventive treatment[a]	Vitamin D	0.55 (0.20-1.50)	0.246	0.83 (0.41-1.67)	0.595
Model 9	Model 1 + osteoporosis preventive treatment[a]	Bisphosphonates	0.65 (0.25-1.71)	0.384	0.82 (0.40-1.68)	0.592
Model 10	Model 1 + osteoporosis preventive treatment[a]	Calcium carbonate, vitamin D, and/or bisphosphonates	0.59 (0.21-1.62)	0.305	0.85 (0.41-1.72)	0.644

[a]At TA.
[b]At any time after HT.
BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; HT, heart transplantation; TA, transplant assessment.

(21.8–36.5) compared with the GFR measured through iohexol clearance ($P < 0.001$). The CKD-EPI formula misclassified 37.3% of the HT patients into better CKD stage than the CKD stage assessed with iohexol clearance. Only 6.5% were misclassified into worse CKD stage with the CKD-EPI formula than iohexol clearance.

GFR Evolution

GFR in patients with CKD stage ≥3 at TA remained lower than GFR in their counterparts throughout the follow-up period, as seen in Figure 6.

DISCUSSION

Osteoporosis is a common condition in HT patients with significant impact on morbidity and mortality, but early risk factors for postoperative development of osteoporosis remain to be discovered.[3,4] There is evidence of associated pathogeneses between osteoporosis and CKD. Hence, kidney function before HT might constitute a significant factor of early detection and management of postoperative BMD loss and osteoporosis.[29]

This was a single-center retrospective cohort study that aimed to investigate the BMD evolution and incidence of osteoporosis in relation to CKD up to 10 years after HT. Patients with CKD stage <3 or normal kidney function before HT lost significantly more lumbar BMD within the first postoperative year. They also continued to lose BMD after the first year, whereas patients with CKD stage ≥3 before HT started gaining BMD from the second postoperative year. Similarly, the cumulative incidence of osteoporosis in the lumbar spine after HT was higher in the group with CKD stage <3 or normal

TABLE 3.

Cox regression analyses of the incidence of osteoporosis in the lumbar spine and femoral neck, in relation to presence of CKD stage ≥ 3 at TA

Osteopenia within 10 y after HT		CKD stage ≥3 at TA			
		Lumbar spine		Femoral neck	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Crude model		0.79 (0.30-2.13)	0.646	0.95 (0.37-2.40)	0.910
Adjusted for					
Model 1	Age[a], gender (male), BMI[a]	1.00 (0.36-2.80)	0.994	0.91 (0.34-2.42)	0.850
Model 2	Model 1 + era of HT (1988–1999 vs 2000–2016)	1.01 (0.35-2.85)	0.992	0.94 (0.35-2.53)	0.899
Model 3	Model 1 + hemodialysis[b]	1.20 (0.25-5.82)	0.817	0.93 (0.28-3.11)	0.906
Model 4	Model 1 + serum urea[a] (mmol/L)	1.04 (0.31-3.51)	0.953	1.23 (0.38-3.93)	0.733
Model 5	Model 1 + Serum creatinine[a] (μmol/l)	1.40 (0.44-4.50)	0.571	1.04 (0.35-3.12)	0.939
Model 6	Model 1 + albumin-to-creatinine ratio[a] (mg/g)	0.30 (0.07-1.38)	0.122	0.58 (0.12-2.73)	0.486
Model 7	Model 1 + osteoporosis preventive treatment[a] Calcium carbonate	1.06 (0.37-3.09)	0.912	0.84 (0.31-0.31)	0.733
Model 8	Model 1 + osteoporosis preventive treatment[a] Vitamin D	1.06 (0.37-3.08)	0.915	0.82 (0.30-2.20)	0.690
Model 9	Model 1 + osteoporosis preventive treatment[a] Bisphosphonates	1.10 (0.38-3.17)	0.864	0.85 (0.32-2.26)	0.738
Model 10	Model 1 + osteoporosis preventive treatment[a] Calcium carbonate, vitamin D, and/or bisphosphonates	1.18 (0.39-3.55)	0.773	0.84 (0.30-2.34)	0.738

[a]At TA.
[b]At any time after HT.
BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; HT, heart transplantation; TA, transplant assessment.

kidney function. This is surprising and in conflict with the suggested relationship between CKD and BMD loss. A possible explanation would be that HT candidates with a more advanced CKD are more closely monitored and might receive prophylactic osteoporosis therapy to a greater extent than other HT candidates, although, in a multiple Cox regression analysis, adjustments were made for pharmacological osteoporosis preventive treatment. However, wide confidence interval of the effect indicates insufficient power and the analysis needs to be repeated in a larger cohort to properly estimate the effect. Also, a trend toward a shorter duration and lower cumulative dose of corticosteroids was observed with increasing CKD stage (Table 1). It is also possible that the results reflect an overestimation of the lumbar BMD because of vascular calcification, which is associated with renal disease.[30,31] Another possible explanation would be a relationship between worse renal function, more severe heart failure, and administration of more diuretics, resulting in worse BMD at baseline, and, thus, leading to a larger clinical benefit after HT, also in terms of BMD improvement. However, the renal function remained lower in these patients than their counterparts throughout the follow-up period (Figure 6).

The impact of CKD stage as a predictor of BMD loss is not well studied in patients after organ transplantations, but there are, however, several reports that have shown that CKD have a significant impact on the risk of fragility fractures, the main consequence of osteoporosis. In a cross-sectional analysis of the Third National Health and Nutrition Examination Survey, including 39 695 subjects, it was concluded that patients with CKD stage 3–4, assessed through calculation of eGFR using serum creatinine through the Modification of Diet in Renal Disease (MDRD) formula, had a >2-fold increase in the probability of hip fracture history.[32] In accordance with these results, a prospective cohort study of older adults showed that CKD stage 2–3, also based on eGFR using the MDRD formula, was associated with increased risk of hip fracture.[33] A recently published study on HT patients from our hospital concluded that the MDRD formula significantly overestimated the true GFR with a mean (SD) of 12.0 mL/min/1.73 m^2 (15.4 mL/min/1.73 m^2).[21] These results were consistent with the findings in nontransplanted patients where the same formula also tends to overestimate kidney function.[34] Consequently, there is reason to believe that the true GFR in HT patients is lower and, thus, significant BMD loss, incidence of osteoporosis, and fragility fractures might be associated with less advanced stages of eGFR-based CKD than previously thought.

During the last couple of decades, the value of Dual-energy x-ray absorptiometry measurement in diagnosis of osteoporosis has been intensely discussed, while evidence of alternative indicators have emerged. Among them are several advanced imaging techniques, such as high-resolution peripheral quantitative computed tomography which measures a volumetric BMD rather than an areal, as well as provides 3-dimensional images and, thus, assesses the microarchitecture of the skeleton in vivo.[35] In spite of its accuracy and important informational contribution in patients without evident CKD, it was shown to be insufficient as a diagnostic tool for prevalent fractures in patients with CKD.[36] Also, high-resolution peripheral quantitative computed tomography still has a limited use universally due to its relatively high cost. Other emerging indicators of bone disease are bone turnover markers which have shown to be of significant importance in estimating risk of fragility

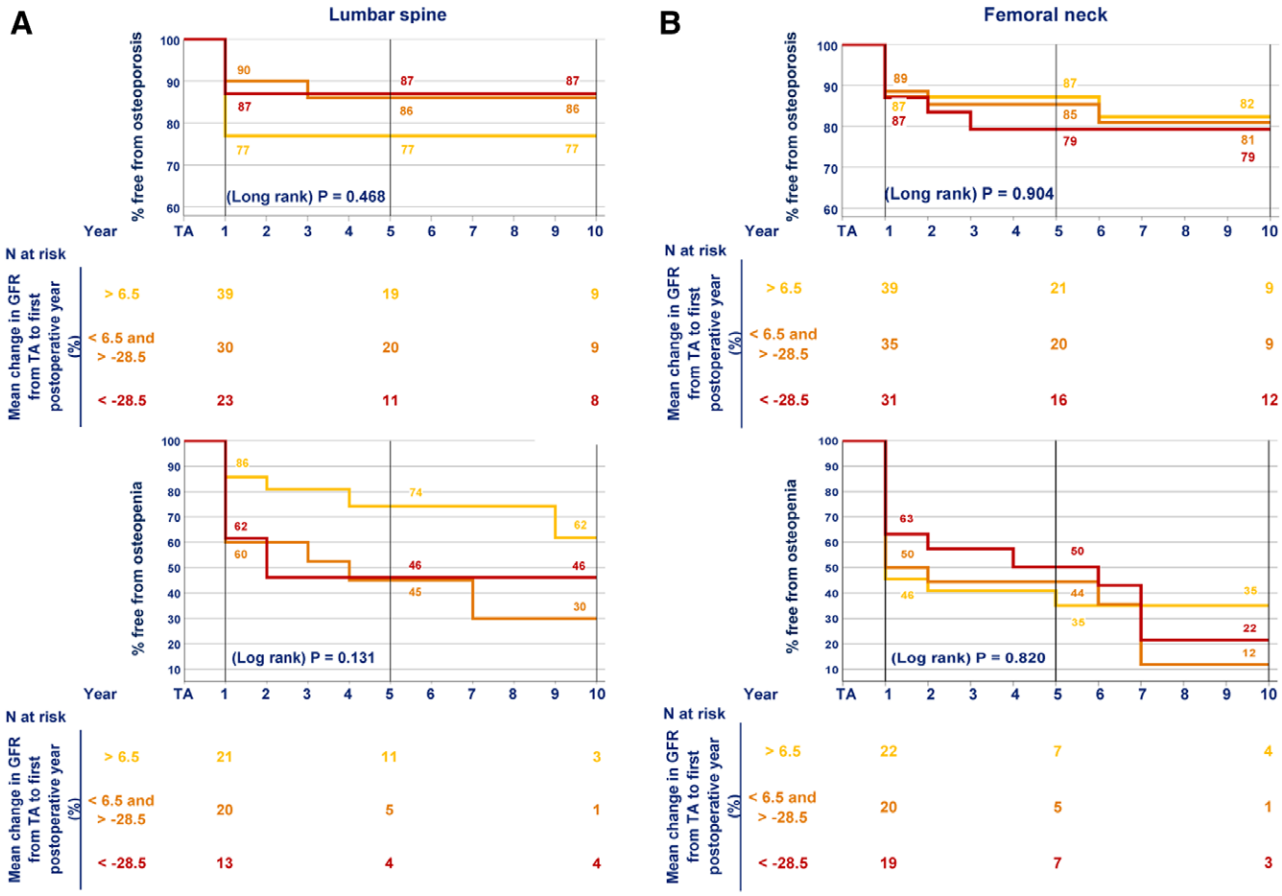

FIGURE 4. Survival without osteoporosis or osteopenia by change in GFR. The survival without osteoporosis up to 10 y after HT in relation to the mean change (%) in GFR from before HT (TA) to the first postoperative year stratified by 3 percentiles in (A) the lumbar spine and (B) the femoral neck. The figure also displays the corresponding data on survival without osteopenia in (C) the lumbar spine and (D) femoral neck. GFR, glomerular filtration rate; HT, heart transplantation; TA, transplant assessment.

TABLE 4.

Cox regression analyses of the incidence of osteopenia in the lumbar spine and femoral neck

Osteopenia within 10 y after HT	Mean change (%) in GFR from TA to 1 y after HT			
	Lumbar spine		Femoral neck	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Crude model				
First percentile[a]		0.214		0.885
Second percentile[a]	2.38 (0.87-6.50)	0.090	1.17 (0.56-2.45)	0.683
Third percentile[a]	2.14 (0.72-6.40)	0.172	0.98 (0.46-2.09)	0.962
Adjusted for age,[b] gender (male), BMI,[b] era of HT (1988–1999 vs 2000–2016)				
First percentile[a]		0.402		0.878
Second percentile[a]	2.03 (0.67-6.15)	0.209	1.22 (0.55-2.71)	0.630
Third percentile[a]	1.95 (0.62-6.07)	0.252	1.04 (0.45-2.37)	0.931

[a]First (>6.5), second (-28 - 6.5), and third (<-28.5) percentile by the mean change (%) in GFR from TA to 1 y after HT.
[b]At TA.
BMI, body mass index; CI, confidence interval; GFR; glomerular filtration rate; HR, hazard ratio; HT, heart transplantation; TA, transplant assessment.

fractures in patients with CKD.[37] In a cross-sectional study, it was concluded that the bone turnover markers osteocalcin, procollagen type-1 N-terminal propeptide, and tartrate-resistant acid phosphatase-5b were independently associated with the risk of a history of fractures.[37] In the same study, it was also suggested that bone turnover markers may increase the accuracy of imaging techniques (both volumetric and areal) regarding the history of fractures. Whether these results are applicable on an HT patient population is, however, yet unclear. Therefore, further investigations on the exact role of bone turnover markers in this particular patient population are highly encouraged.

The major strength of the present study was the close and long-term follow-up of the included patients. The study was conducted at a single center which facilitated data collection. The long-term follow-up of the patients after HT

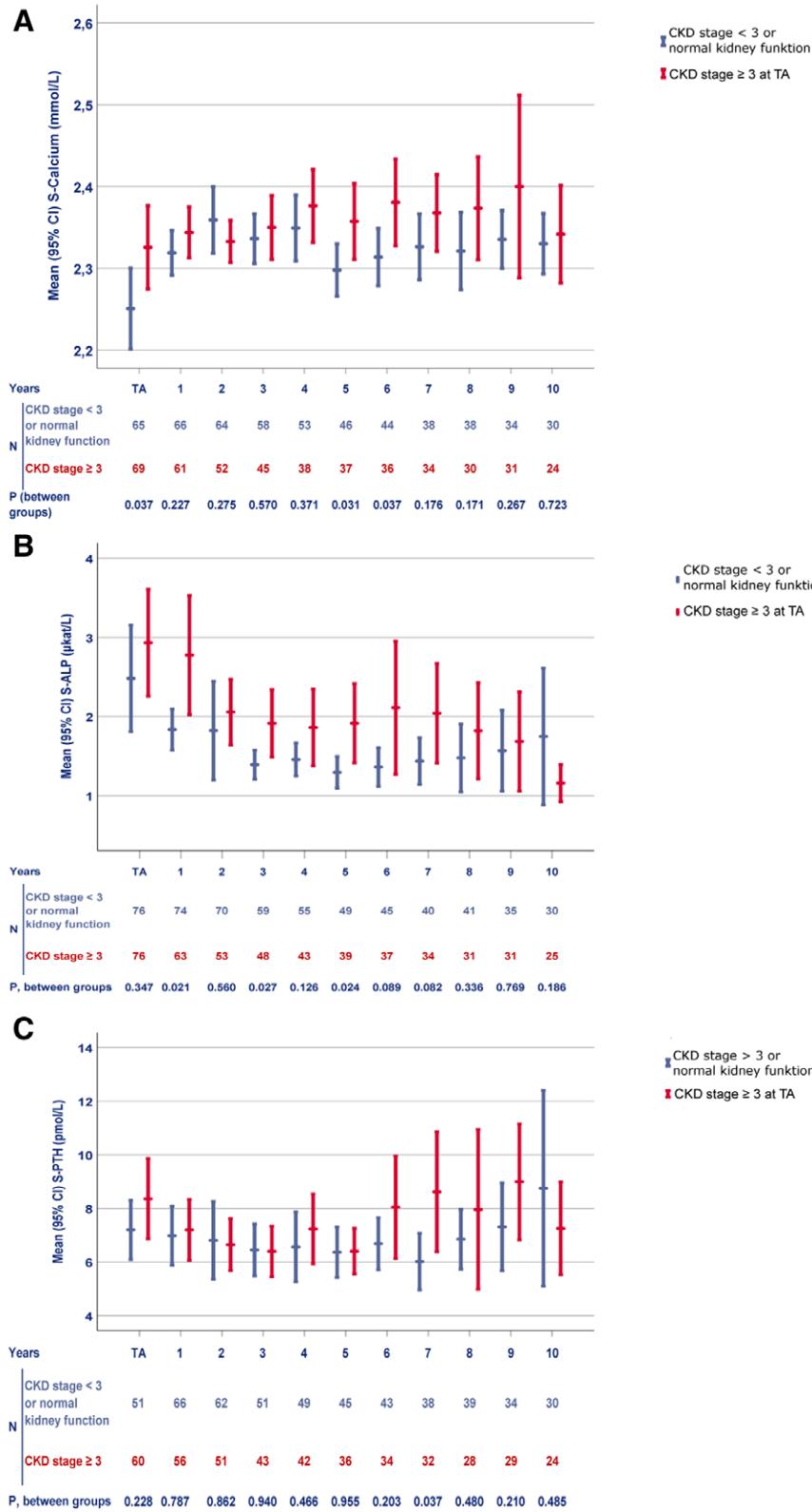

FIGURE 5. Calcium, ALP, and PTH serum levels. Serum levels of (A) calcium, (B) ALP, and (C) PTH up to 10 y after HT in relation to presence or absence of CKD stage ≥3 at TA. ALP, alkaline phosphatase; CI, confidence interval; CKD, chronic kidney disease; HT, heart transplantation; PTH, parathyroid hormone; TA, transplant assessment.

made it possible to observe chronic conditions and their impact on long-term survival. Regarding limitations of this study fracture data had not been registered systematically and were therefore not included in this retrospective study, consequently constituting a main limitation of the study, as did missing values and the limited amount of included patients. Also, the retrospective design limited the possibility of influencing the data obtainment. Those limitations should

TABLE 5.

Cox regression analyses of the incidence of osteoporosis in the lumbar spine and femoral neck

	Mean change (%) in GFR from TA to 1 y after HT			
	Lumbar spine		Femoral neck	
Osteoporosis within 10 y after HT	HR (95% CI)	*P*	HR (95% CI)	*P*
Crude model				
First percentile[a]		0.531		0.912
Second percentile[a]	0.57 (0.18-1.84)	0.346	1.10 (0.36-3.42)	0.864
Third percentile[a]	0.57 (0.15-2.09)	0.394	1.28 (0.41-3.96)	0.670
Adjusted for age,[b] gender (male), BMI,[b] era of HT (1988–1999 vs 2000–2016)				
First percentile[a]		0.472		0.836
Second percentile[a]	0.46 (0.12-1.80)	0.265	0.92 (0.28-3.08)	0.893
Third percentile[a]	0.59 (0.16-2.20)	0.435	1.30 (0.41-4.14)	0.658

[a]First (>6.5), second (-28 - 6.5), and third (<-28.5) percentile by the mean change (%) in GFR from TA to 1 y after HT.
[b]At TA.
BMI, body mass index; CI, confidence interval; GFR; glomerular filtration rate; HR, hazard ratio; HT, heart transplantation; TA, transplant assessment.

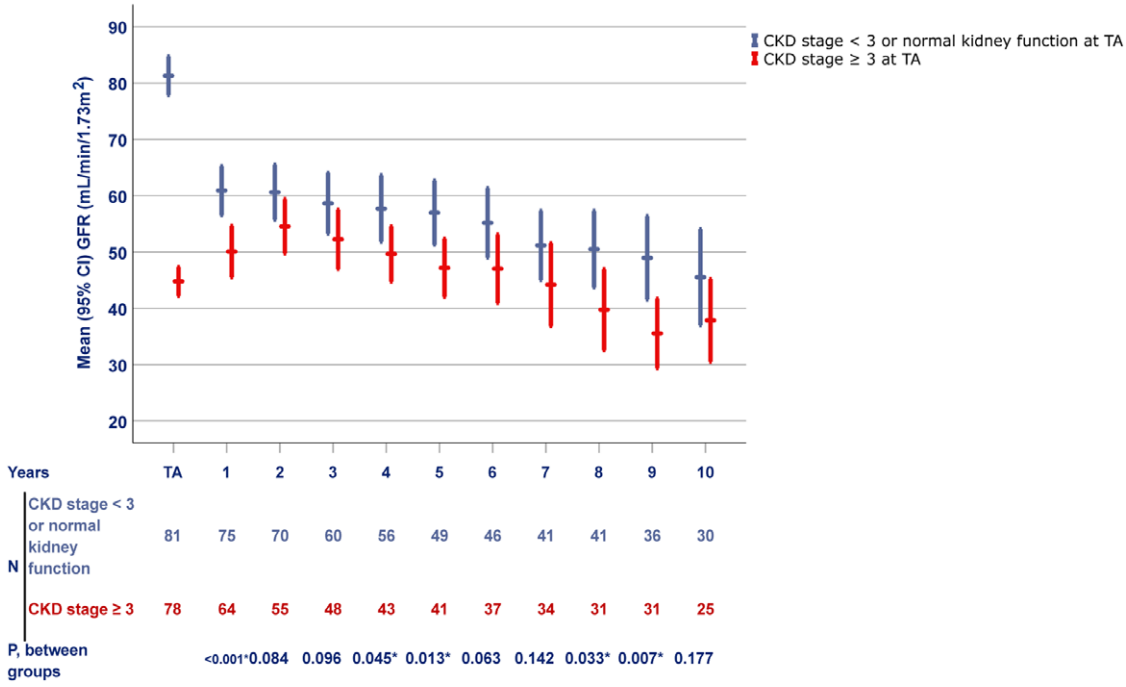

FIGURE 6. GFR evolution. The GFR evolution up to 10 y after HT in relation to the presence or absence of CKD stage ≥3 at TA. CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; HT, heart transplantation; TA, transplant assessment.

be kept in mind before clinical implementation of the present results. For the future, it would be desirable to investigate the impact of CKD stages on BMD loss after HT, using a prospective multicenter study design.

CONCLUSION

CKD stage ≥3 before HT was associated with higher lumbar BMD after HT and was not a predictor of osteoporosis. Moreover, HT patients with CKD stage <3 or normal kidney function before HT exhibited a greater BMD loss in the lumbar spine. Furthermore, a change in GFR during the first postoperative year did not predict BMD loss or osteoporosis, up to 10 years after HT. However, evidence is limited because fracture data were not available. Further studies on the relationship between CKD and postoperative bone strength, including fracture data, in larger patient cohorts and prospective study designs, are highly encouraged.

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