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.
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. Other data collected included 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.

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. At initiation of the maintenance immunosuppressive therapy, doses were standardized and thereafter down-titrated on a regular basis, as previously described. 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.

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
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 Stage

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 = 0.208) (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.

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**TABLE 1.** Baseline characteristics

| Baseline characteristics | Normal kidney function | CKD stage | CKD stage <3 or normal kidney function | CKD stage ≥3 |
|--------------------------|------------------------|-----------|----------------------------------------|-------------|
|                          | N = 23 | N = 58 | N = 69 | N = 9 | N = 81 | N = 78 | P     |
| Age (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 |
| BMD (g/m2), 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 (7.3) | 6.2 (7.7) | 3.4 (8.1) | 6.5 (7.3) | 6.2 (7.8) | 0.304 |
| Biopsies per patient within the first y after HT (N) | 14 (0) | 14 (1) | 14 (1) | 14 (1) | 14 (0) | 14 (1) | 0.324 |

**Note:**

- *TA*
- Calculated eGFR was added if iohexol clearance GFR was missing.
- Maintenance immunosuppressive therapy, n (%) 0.833

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| Biopsies per patient within the first y after HT (N) | 14 (0) | 14 (1) | 14 (1) | 14 (1) | 14 (0) | 14 (1) | 0.324 |
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/1.73² (11.1–17.8) or 29.1%

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**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.
(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.\(^2\)\(^9\)

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 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)    | 0.76 (0.41–1.42)   | 0.391               |
| Adjusted for                   |                     |                    |                    |
| Model 1 Age\(^a\), gender (male), BMI\(^b\) | 0.62 (0.24–1.58) | 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) | 0.86 (0.43–1.74) | 0.674               |
| Model 3 Model 1 + hemodialysis\(^a\) | 1.14 (0.36–3.63) | 0.86 (0.27–1.58) | 0.346               |
| Model 4 Model 1 + serum urea (mmol/L) | 0.71 (0.26–1.96) | 0.94 (0.45–1.95) | 0.870               |
| Model 5 Model 1 + Serum creatinine (µmol/l) | 0.69 (0.24–2.02) | 1.07 (0.50–2.29) | 0.870               |
| Model 6 Model 1 + albumin-to-creatinine ratio (mg/g) | 0.39 (0.13–1.44) | 0.43 (0.13–1.44) | 0.171               |
| Model 7 Model 1 + osteoporosis preventive treatment\(^a\) - Calcium carbonate | 0.56 (0.20–1.54) | 0.83 (0.41–1.69) | 0.609               |
| Model 8 Model 1 + osteoporosis preventive treatment\(^a\) - Vitamin D | 0.55 (0.20–1.50) | 0.83 (0.41–1.67) | 0.595               |
| Model 9 Model 1 + osteoporosis preventive treatment\(^a\) - Bisphosphonates | 0.65 (0.25–1.71) | 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) | 0.85 (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.
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 transplanted.

| CKD stage ≥ 3 at TA | Lumbar spine | Femoral neck |
|--------------------|--------------|--------------|
| HR (95% CI)        | HR (95% CI)  | P            |
|                    | Crude model  | Adjusted for |                    | Crude model  | Adjusted for |
|                    | 0.79 (0.29-2.13) | 0.91 (0.36-2.80) | 0.646 | 0.79 (0.30-2.13) | 0.95 (0.37-2.40) | 0.646 |
|                    | 1.01 (0.36-2.85) | 1.23 (0.38-3.39) | 0.992 | 1.01 (0.36-2.85) | 0.94 (0.36-2.53) | 0.992 |
|                    | 1.30 (0.35-5.20) | 0.122 | 0.122 | 1.30 (0.35-5.20) | 0.58 (0.18-1.82) | 0.122 |
|                    | 1.10 (0.37-3.40) | 0.912 | 0.912 | 1.10 (0.37-3.40) | 0.84 (0.29-2.30) | 0.912 |
|                    | 1.18 (0.39-3.45) | 0.864 | 0.864 | 1.18 (0.39-3.45) | 0.84 (0.30-2.34) | 0.864 |

The impact of CKD stage as a predictor of BMD loss is not well studied in patients after organ transplantation, 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 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 m² (15.4 mL/min/1.73 m²).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.
fractures in patients with CKD. 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. 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 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

|                         | Lumbar spine | Femoral neck |
|-------------------------|--------------|--------------|
| **Osteopenia within 10 y after HT** | **Mean change (%) in GFR from TA to 1 y after HT** | **Mean change (%) in GFR from TA to 1 y after HT** |
|                         | Lumbar spine | Femoral neck |
| **Crude model**         | **HR (95% CI)** | **P** | **HR (95% CI)** | **P** |
| First percentile         | 0.214        | 0.885        | 0.172        | 0.963        |
| Second percentile        | 2.38 (0.87-6.50) | 0.090 | 1.17 (0.56-2.45) | 0.683 |
| Third percentile         | 2.14 (0.72-6.40) | 0.172 | 0.98 (0.46-2.09) | 0.962 |
| **Adjusted for age, gender (male), BMI, era of HT (1988–1999 vs 2000–2016)** | | | |
| First percentile         | 0.402        | 0.878        | 0.402        | 0.878        |
| Second percentile        | 2.03 (0.67-6.15) | 0.209 | 1.22 (0.55-2.71) | 0.630 |
| Third percentile         | 1.95 (0.62-6.07) | 0.252 | 1.04 (0.45-2.37) | 0.931 |

*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.

TA, TA.

BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; HT, heart transplantation; 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

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.
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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