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Stro-1-positive BMSCs predict postoperative periprosthetic bone mineral density outcomes in uncemented total hip arthroplasty patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Bone marrow cell profiles are variable after total hip arthroplasty (THA), including variable levels of Stro-1$^+$ and bone morphogenetic protein receptor (BMPRs)$^+$ cells. We investigated the impact of bone marrow cell profiles on changes in periprosthetic bone mineral density (BMD) in uncemented THA patients.

Material/Methods: Bone marrow aspirates were collected from the metaphyseal region of discarded femoral heads from 24 consecutive THA patients (12 men and 12 women; mean age 66.7±11.0 years; range 52–87 years) treated from March 2009 to March 2011 at a single facility. Perioperative proportions of Stro-1$^+$ and BMPR$^+$ cells in femoral heads were assessed by flow cytometry. Follow-up examined the proximal femur Gruen zones R1 and R7 at 1 week and at 3, 6, and 12 months after THA, using dual-energy X-ray absorptiometry. Associations between BMD loss and age, gender, BMPRs$^+$, and Stro-1$^+$ were analyzed.

Results: At 3 months, R1 and R7 BMD decreased by 4.4% and 6.4%, respectively (P<0.05). At 12 months, the overall BMD decreases in R1 and R7 were 10.2% and 1%, respectively (P<0.05). Higher Stro-1$^+$ cells proportion predicted R7 BMD increases at all time points (P<0.05) and R1 BMD increases at 6 and 12 months (P<0.05). BMPR1a$^+$ proportion was associated with BMD increases at 6 months in the R1 region. BMPR2$^+$ was not significantly associated with BMD (P>0.05).

Conclusions: Elevated Stro-1$^+$ bone marrow cell profile may be a useful prognostic indicator for uncemented THA patients.

MeSH Keywords: Absorptiometry, Photon • Osteogenesis • Chemokine CXCL12 • Mesenchymal Stromal Cells • Arthroplasty, Replacement, Hip • Bone Morphogenetic Proteins

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Background

Total hip arthroplasty (THA) is a worldwide-accepted treatment for end-stage hip osteoarthritis. However, bone remodeling in regions adjacent to the proximal stems of long bones may affect the long-term success of THA [1]. To achieve good outcomes in THA, early and rapid osseointegration is required, which requires the recruitment of bone marrow stromal cells (BMSC) to the periprosthetic site [2], and careful monitoring of bone mineral density (BMD) in and around the proximal femur [3,4]. Periprosthetic loss of BMD and subsequent loss of bone tissue in the proximal femur are common in the first year following THA [5–8]. The lost bone tissue is usually not recovered [9,10]. Furthermore, severe periprosthetic bone loss may contribute to complications such as aseptic loosening of the prosthesis [11,12] and an increased risk of periprosthetic fracture [13].

To monitor and assess BMD after THA, dual-energy X-ray absorptiometry (DEXA) is commonly used to examine the overall bone remodeling status [14]. However, there is a need for improved strategies for assessing BMD following THA, to ensure consistent and good patient outcomes, and to minimize patient risks. Identifying patients at high risk of complications would allow the use of personalized medical strategies to improve BMD, such as the use of alendronate [15] or stem cells [16].

Indeed, successful bone remodeling requires a favorable bone marrow microenvironment with sufficient osteoprogenitor cells to preserve BMD [17,18]. These osteoprogenitor cells possess the ability to differentiate into the necessary functional osteoblasts in response to specialized growth factors known as bone morphogenetic proteins (BMPs) [19,20]. BMPs play a critical role in controlling new bone formation around implant osseointegration [21–24]. BMP signaling through type I and II subtype serine/threonine kinase receptors has been involved in bone marrow cell profile diversification [24,25]. BMP receptor type Ia (BMPR1a [ALK3]) is required for extracellular matrix deposition by osteoblasts [24,25]. Activation of BMPR2 is required for the activation of the Smad protein signaling pathway [24,25]. In addition, Stro-1 is a cell surface antigen that is variably expressed in human BMSCs [26–29]. Stro-1$^+$ cells are able to differentiate into multiple mesenchymal lineages, including adipocytes, osteoblasts, and chondrocytes [27–30]. Recently, Stro-1$^+$ and BMP receptor-positive (BMPRs$^+$) cell profiles have been examined in THA patients [28]; however, the effects of patients' demographics and characteristics on postoperative BMD changes have not been well studied.

It is still unclear if the profile of Stro-1$^+$ and BMPRs$^+$ bone marrow cells have an impact on postoperative periprosthetic BMD. We hypothesized that an increased proportion of these cells is associated with reduced loss of BMD after THA. The objective of the present study was to assess the relationship between perioperative bone marrow cell profiles and periprosthetic BMD change after uncemented THA over 1 year after surgery, and the relation with demographic factors. Determination of such a relationship may allow more accurate determination of prognosis, and may be useful to determine the surgical strategy, thereby minimizing patient risks.

Material and Methods

Study design

A total of 24 consecutive osteoarthritis patients undergoing primary THA (12 men and 12 women; mean age 66.7±11.0 years, range 52–87 years) in the posterolateral Moore approach (lateral position) performed by the same team of 2 experienced surgeons were treated from March 2009 to March 2011 in a study conducted by Shen et al. [28]. This previous study aimed to assess the diversity of bone marrow Stro-1$^+$ and BMPRs$^+$ cell profiles in THA patients. The same patients' data was used to retrospectively examine the relationship between perioperative bone marrow cell profiles and periprosthetic BMD changes during follow-up after uncemented THA.

Standardization was conducted as previously described by Lebherz et al. [31], wherein accuracy of DEXA was confirmed by controlling hip rotation. Both the initial and current studies were approved by the Institutional Ethics Committee of the Renji Hospital, Shanghai JiaoTong University School of Medicine, and written informed consent was obtained from all patients for their initial participation.

Patients

Inclusion criteria from the initial study were: 1) diagnosis of end-stage osteoarthritis; 2) age >18 years; 3) a surgical candidate for uncemented stems THA (Dorr ≥0.75); 4) underwent primary THA with the Smith & Nephew Synergy™ Hip System (Smith & Nephew Advanced Orthopedic Devices, Memphis, TN, USA); and 5) underwent surgery using uncemented stems (Porous Plus HA and a grit blasted) and Reflection™ cup press-fit acetabular components (Smith & Nephew Advanced Orthopedic Devices, Memphis, TN, USA). Exclusion criteria were: 1) symptoms or signs of inflammation and infection, rheumatoid arthritis, or other autoimmune disease; or 2) took non-steroidal anti-inflammatory drugs (NSAIDs) within 1 month prior to surgery. Preoperative pain management was done using other types of drugs. This study was approved by the institutional review board of the Ren Ji Hospital (Shanghai, China), and written informed consent was obtained from each participant.

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Preparation of bone marrow stromal cells (BMSC)

Bone marrow aspirates (5 mL) were obtained from the metaphyseal region of the femoral head removed during THA, as described previously [28]. Briefly, bone marrow aspirates were prepared immediately after bone removal, by dilution 1: 4 in phosphate-buffered saline (PBS), and layered on Histopaques density gradient (Sigma Aldrich, St Louis, MO, USA). Mononuclear cells were isolated by density gradient centrifugation at 600 g for 30 min and washed in PBS. The supernatant (bone marrow aspirate washout) was collected and stored at –70°C. BMSCs were collected and culture-expanded in alpha-modified Eagle's medium (α-MEM)/10% fetal bovine serum (FBS) medium. The medium was changed initially at day 4 and then every other day until the cultures reached confluence. At day 14, cells were digested with TrypLE Express (Gibco, Grand Island, NY, USA), collected by centrifugation at 200 g for 10 min, and fixed in 2% (w/v) paraformaldehyde in PBS for 15 min. Cell culture was successful in all patients.

Flow cytometry analysis

Quantitative measurement of cell surface markers Stro-1, BMPR1A, and BMPR2 was performed using the FACS Calibur Flow Cytometry System (Becton Dickinson, Beckman Coulter, Brea, CA, USA) equipped with Cell Quest software (Beckman Coulter, Brea, CA, USA). BMSCs suspensions were incubated with primary antibodies for 1 h at 4°C. Unbound antibodies were removed by washing with PBS. The following 1:100 dilutions of primary monoclonal antibodies conjugated with fluorescein isothiocyanate (FITC), phycoerythrin (PE), or allophycocyanin (APC) were used to detect BMPR-1a, BMPR-2, and Stro-1 using immunofluorescence (BD Pharmingen, San Diego, CA, USA). After incubation for 14 days, cells were washed and measured by flow cytometry to verify that the expression of surface molecular makers (Stro-1 and BMPRs) BMSCs were not altered by culture expansion *in vitro*. The average fluorescence intensity (AFI) of the cell population was calculated for each antigen, and the AFI of negative control samples (nonspecific mouse IgG1) was subtracted, as previously described [28].

DEXA analysis of bone mineral density

DEXA scans were performed using a HOLOGIC Discovery W (Hologic Inc., Waltham, MA, USA) scanner at 1 week and at 3, 6, and 12 months. Patients were placed in supine position with the affected leg at 10° internal rotation (patella up) with the foot secured in the Hologic foot positioning device to obtain reproducible rotation and thereby limiting measurement errors, as previously described [32]. The femoral stem component and cortical bone were excluded manually during DEXA analysis. Regions of interest (ROI) for each patient were saved using the Hologic image analysis software system (Hologic, Inc., USA) and used for all subsequent measurements. DEXA precision was assessed for all subjects. BMD (g/cm^2) was determined in the proximal femur regions R1 (greater trochanter region) and R7 zones (calcar region) for each patient using the Gruen zone partition method [33] (Figure 1). A single researcher blinded to flow cytometry results performed all examinations and analyzed all BMD data.

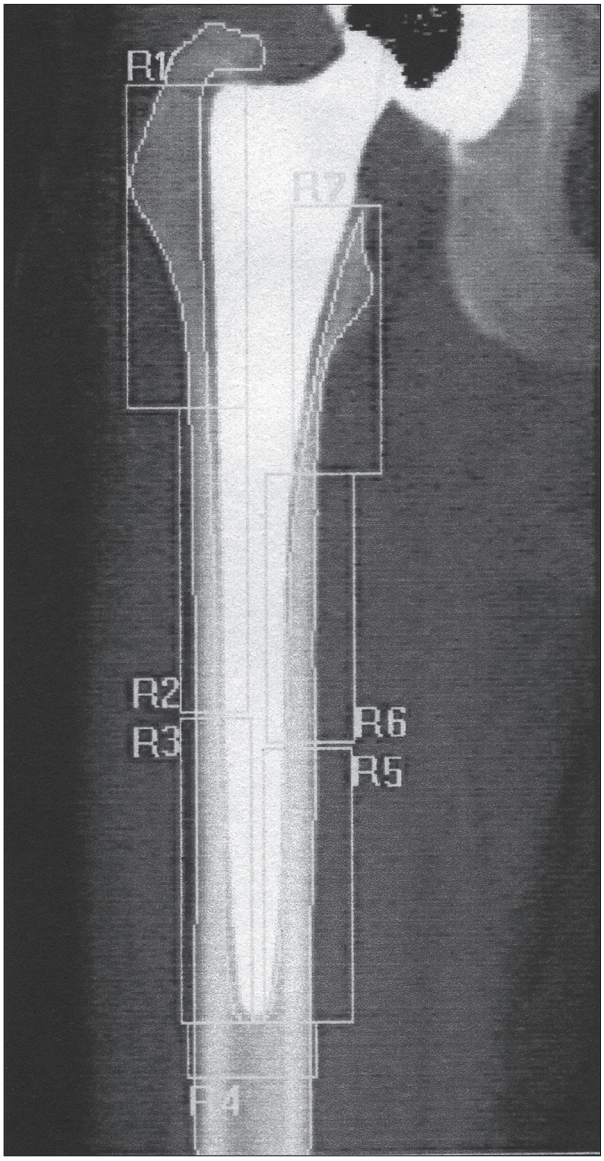

Figure 1. The seven regions of Gruen zones and standardized regions of interest (ROI) used during DEXA analysis.

Statistical analysis

Patients were stratified as younger (<70 years) or older (≥70 years), or according to gender. All data were analyzed using SPSS 18.0 (SPSS, Inc. Chicago, IL, USA) and expressed as mean ±SD. Variables were compared using one-way analysis of variance (ANOVA)

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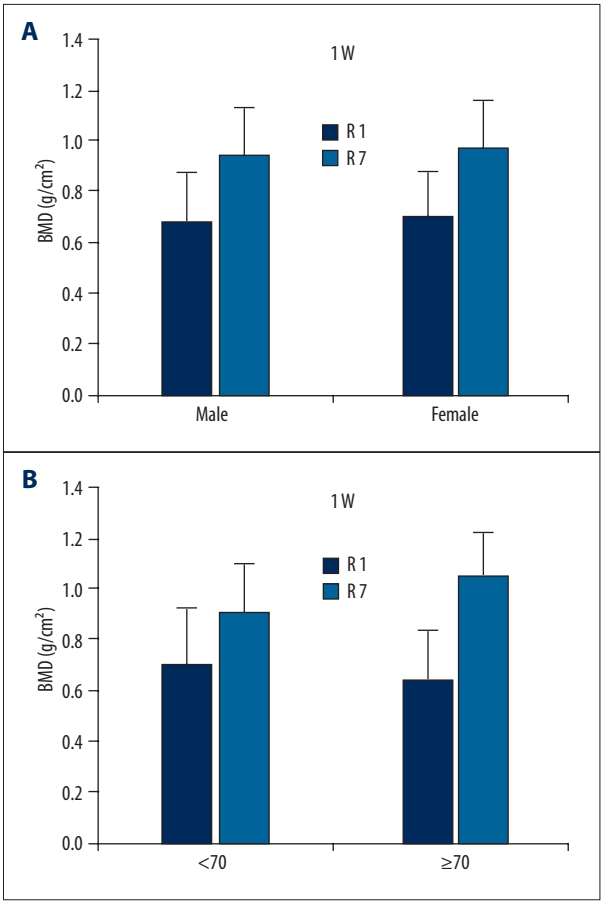

Figure 2. Age- and gender-related differences in BMD value (R1 and R7 region) one week after THA. (**A**) Female (*n*=12) *vs.* male (*n*=12) patients. (**B**) Younger (<70 years, *n*=13) *vs.* older (≥70 years, *n*=11).

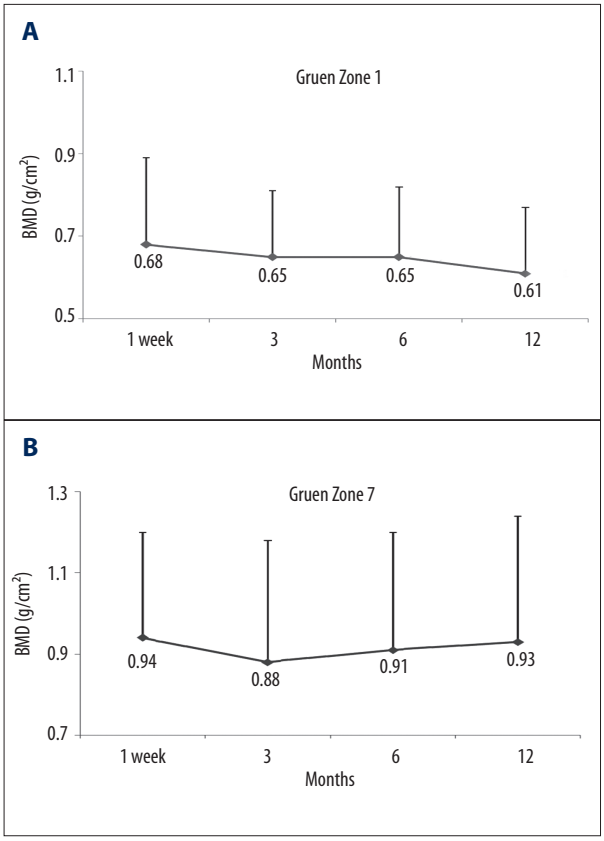

Figure 3. Postoperative BMD changes in the proximal femur region: (**A**) R1 and (**B**) R7. Showed as median and dispersion (*n*=24).

with Newman-Keuls post hoc test (normally distributed) or Mann-Whitney U test (non-normally distributed). Correlation between BMD and bone marrow cell profiles was assessed using Spearman's tests. *P* values <0.05 were considered significant.

Results

Patients' characteristics

All 24 original patients were included in the current study. Clinical, demographic, and other medical characteristics were previously reported in detail [28]. No patients experienced infection, loosening, or periprosthetic fracture during the 12-month follow-up period. The previously identified BMSC profiles according to proportions of Stro-1+, BMPR1a+, and BMPR2+ cells were used in the current analysis. Stro-1+, BMPR1a+, and BMPR2+ cells represented mean proportions of 17.77±13.88% (3.07–48.89%), 21.24±21.35% (1.79–91.36%), and 28.22±24.66% (0.95–95.99%) of all BMSCs, respectively. No significant relationship was observed between bone marrow profiles and either age or gender of THA patients [28].

Immediate postsurgical effects of age and gender on BMD

In the immediate postsurgical period (first week after surgery), gender had no effect on BMD at R1 (men: 0.68±0.19 g/cm² *vs.* women: 0.67±0.24g/cm²; *P*=0.88) or at R7 (men: 0.93±0.32 g/cm² *vs.* women: 0.96±0.21g/cm²; *P*=0.83), nor did age on R1 (<70: 0.68±0.19 g/cm², *n*=13 *vs.* ≥70: 0.63+0.20 g/cm², *n*=11; *P*=0.38), or on R7 BMD (<70: 0.89±0.22 g/cm² *vs.* ≥70: 0.96±0.21 g/cm²; *P*=0.30) (Figure 2).

Postoperative periprosthetic BMD changes after 1 year

BMD at both R1 and R7 were significantly decreased at 3 months by 4.4% and 6.4% (*P*<0.05), respectively. After that, continual BMD decreases were only observed in R1 (greater trochanter region), demonstrating an overall reduction of 10.2% during the initial 12-month period following surgery (Figure 3). A slight increase in R7 BMD was observed at 6 and 12 months, and demonstrated an overall reduction of 1.0%. As shown in Table 1, no significant differences were observed

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Table 1. Postoperative BMD changes (g/cm^2) in the R1 and R7 regions by gender.

Time points	Gender*		Age**	
	R1	R7	R1	R7
1 week	0.68±0.19/0.67±0.24 (*P*=0.88)	0.68±0.19/0.67±0.24 (*P*=0.88)	0.68±0.19/0.63±0.20 (*P*=0.38)	0.89±0.22/0.96±0.21 (*P*=0.30)
3 months	0.65±0.13/0.65±0.19 (*P*=0.97)	0.87±0.34/0.90±0.26 (*P*=0.77)	0.67±0.19/0.64±0.13 (*P*=0.65)	0.84±0.24/0.94±0.36 (*P*=0.4)
6 months	0.63±0.15/0.67±0.20 (*P*=0.54)	0.87±0.34/0.95±0.23 (*P*=0.51)	0.67±0.21/0.63±0.13 (*P*=0.67)	0.85±0.25/0.98±0.33 (*P*=0.27)
12 months	0.58±0.14/0.64±0.18 (*P*=0.40)	0.88±0.36/0.98±0.26 (*P*=0.48)	0.61±0.16/0.61±0.18 (*P*=0.97)	0.87±0.27/0.99±0.36 (*P*=0.35)

R1 and R7 indicate the proximal femur region according to Gruen zone. * Data are presented as male/female (between-group comparisons performed using Newman-Keuls or Mann-Whitney U-tests). ** Data are presented as patients <70 years (*n*=11)/patients ≥70 years (*n*=13) (between-group comparisons performed using Newman-Keuls or Mann-Whitney U-tests).

Table 2. Correlation analysis between the proportions of Stro-1+, BMPR1a+, BMPR2+ cells and periprosthetic BMD.

	R1 region			R7 region		
	Stro-1+	BMPR1a+	BMPR2+	Stro-1+	BMPR1a+	BMPR2+
1 week	0.0557	0.0452	0.0015	0.2621*	0.0017	0.0541
3 months	0.023	0.0776	0.0095	0.2476*	0.001	0.0582
6 months	0.2997**	0.2142*	0.1033	0.2719**	0.0034	0.0596
12 months	0.1661*	0.1533	0.1479	0.2406*	0.0027	0.0403

R1 and R7 indicate the proximal femur region according to Gruen zone. Values are presented as R^2 values from correlation coefficient (r) analysis by Pearson analysis. * $P<0.05$; ** $P<0.01$.

in age, gender, and postoperative periprosthetic BMD changes in R1 and R7 BMD at 3, 6, and 12 months.

Stro-1+, BMPR1a+, BMPR2+ BMSCs and postoperative BMD

BMSCs were assessed from the femoral heads collected during surgery, and the correlations between the proportions of Stro-1+, BMPR1a+ BMPR2+ cells and BMD during follow-up were assessed. An association was observed between higher Stro-1+ cell proportions and R7 BMD increase at all time points ($P<0.05$) and R1 BMD increases at 6 and 12 months ($P<0.05$). No significant association was observed between BMPR2+ cells and BMD, although a significant association between higher BMPR1a+ cell proportion and BMD increase was observed at 6 months in the R1 region only ($P<0.05$) (Table 2).

Discussion

The objective of the present study was to assess the relationship between preoperative bone marrow cell profiles and periprosthetic BMD changes over a 1-year period after uncemented THA, and to assess the relation with demographic factors. Progressive decreases in R1 and R7 BMD were observed, indicating that many THA patients may be at risk for complications due to BMD losses and resultant structural failure of bones and prosthetic devices. The proportions of Stro-1+ cells was shown to correlate with R1 and R7 BMD during follow-up, while BMPR1a+ cells proportions correlated only with R1 BMD, and proportions of BMPR2+ cells did not correlate with BMD during follow-up. Gender and age did not influence R1 or R7 BMD in THA patients immediately after surgery, suggesting that these demographic parameters are not likely to affect surgical outcomes.

The methods used for original selection and standardization of the data used in this study are well-documented. The selection of THA patients undergoing uncemented THA was based on observations that bone loss, recognizable by dramatic decreases in BMD and resulting in the structural failure of prosthetic devices, is extremely common in the proximal femurs of these patients [3,34]. Furthermore, the use of DEXA for BMD analysis has

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been demonstrated in many recent studies [35–37], generally using the Gruen zones approach to evaluate bone remodeling after implantation of conventional and short-stem prostheses [36,38,39]. Furthermore, it has been suggested that maximum bone remodeling takes place 6 months after surgery, reaching a plateau at 1 year, followed by a much slower and progressive biomechanical adaptation during years 2 and 3 [10,14,36–38]. Results from the present study suggest that BMD decreases in the greater trochanter region (R1) and calcar region (R7) after THA, and that the large proximal cross-section of the implant may lead to stress shielding in these proximal femur regions. These observations are consistent with previous findings showing that both R1 and R7 regions were most susceptible to BMD loss within the first year following THA [35,40]. Thus, bone loss during the first year may be critical to THA success and may be used as a prognostic marker for patients eligible for THA.

Poor bone marrow cell profiles may indicate an underlying condition, such as lack of osteogenic cells, which may be an assessable risk factor for extensive bone loss after THA. In contrast to the findings of the present study, the proportion of Stro-1$^+$ BMSC has been shown to vary with age and gender [26,27] and osteoarthritis background [41,42]. Even if BMD decreased in patients after THA, the time-dependent association between the proportion of Stro-1$^+$ cells and periprosthetic BMD changes in the proximal femur R1 and R7 regions observed in the present study indicates that Stro-1$^+$ cell levels may be a useful biomarker in THA patient prognosis prior to surgery. Indeed, Stro-1$^+$ cells has been shown to be involved in bone repair processes [41]. Furthermore, great variations in BMPR1a$^+$ and BMPR2$^+$ cell profiles between patients indicate that these cells may play a role in BMD loss, although no significant findings were apparent in the limited study population of the present study. Since the R1 and R7 regions of the proximal femur are composed of abundant trabecular bones, active bone remodeling is expected to occur after THA. The close relationship between the proportion of Stro-1$^+$ bone marrow cells and BMD changes in the proximal femur R1 and R7 regions suggest that the bone marrow microenvironment and bone marrow cell quantity and quality may be useful predictors of implant stability and implant-bone interface fusion (osseointegration) after THA. However, further studies are required to assess this point.

The present study is not without limitations. First, although no correlation was observed between BMD and age and gender in this cohort, associations that may be apparent in larger and more diverse patient cohorts cannot be neglected when considering these findings, as the study size was relatively small and diversity was limited. Secondly, potential effects of observer bias in DEXA analysis conducted in the current study cannot be ignored, as this assessment is somewhat subjective based on operator experience and training. Third, a longer follow-up period would also be useful in confirming these results and those of previous studies beyond the initial year after surgery, and comparison with overall BMD status using lumbar spine assessments would be necessary to indicate the exact type and quality of BMD loss required for prognostic assessment applications [43,44]. Fourth, in the present study, proportions of cells were assessed from the femoral head removed during surgery. Thus, the proportions of the harvested cells are thought to be representative of the cells before surgery and of the initial bone's condition. However, we cannot completely exclude a traumatic effect from the surgery *per se*. Finally, the BMSCs were obtained from the metaphyseal region of the femoral head, while we assessed BMD in the R1 and R7 regions. Nevertheless, these cells are thought to be able to mobilize were they are needed [2,41], and since it would be technically difficult to sample these cells from the R1 and R7 regions, we had to work on the samples from the metaphyseal region.

Conclusions

Bone mass loss can be recognized by decreasing BMD in the proximal femur regions R1 and R7 after uncemented THA surgery in patients of all ages and genders. While only slight BMD decreases were observed immediately after placement of uncemented stems, a progressive decrease in BMD was apparent during the first year following surgery in many patients. Furthermore, this decrease in BMD was found to be associated with increasing proportions of Stro-1$^+$ bone marrow cells, a measurable perioperative parameter. Thus, the proportion of Stro-1$^+$cell could be used as a prognosis marker for the quality and extent of periprosthetic BMD changes following THA.

Conflict of interest

All the authors have no conflicts of interest to declare.

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