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Use of High Resolution Dual-energy X-ray Absorptiometry-Region Free Analysis (DXA-RFA) To Detect Local Periprosthetic Bone Remodeling Events

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ABSTRACT

Dual energy x-ray absorptiometry (DXA) is the gold standard method for measuring periprosthetic bone remodeling, but relies on a region of interest (ROI) analysis approach. Whilst this addresses issues of anatomic variability it is insensitive to bone remodeling events at the sub-ROI level. We have validated a high-spatial resolution tool, termed DXA-Region-Free Analysis (DXA-RFA) that uses advanced image processing approaches to allow quantitation of bone mineral density (BMD) at the individual pixel (data-point) level. Here we compared the resolution of bone remodeling measurements made around a stemless femoral prosthesis in 18 subjects over 24 months using ROI-based analysis versus that made using DXA-RFA. Using the ROI approach the regional pattern of BMD change varied by region, with greatest loss in ROI5 (20%, $P<0.001$), and largest gain in ROI4 (6%, $P<0.05$). Analysis using DXA-RFA showed a focal zone of increased BMD localized to the prosthesis-bone interface (30-40%, $P<0.001$) that was not resolved using conventional DXA analysis. The 20% bone loss observed in ROI5 with conventional DXA was resolved to a focal area adjacent to the cut surface of the infero-medial femoral neck (up to -40%, $P<0.0001$). DXA-RFA enables high resolution analysis of DXA datasets without the limitations incurred using ROI-based approaches.

Keywords: bone mineral density, femur, total hip arthroplasty, dual energy x-ray absorptiometry region-free analysis.

INTRODUCTION

Dual energy x-ray absorptiometry (DXA) is the gold standard method for measuring bone remodeling events that occur following total hip arthroplasty (THA). However, current analysis approaches express BMD as an average value within a given region of interest (ROI).[1] . This value is calculated as the mean BMD value derived from large numbers of pixels contained within the defined ROI. However, bone remodeling events occurring after prosthesis insertion are spatially-complex and may not be uniform across a given ROI,[2] For example, within a large ROI the BMD change occurring over a given time at the bone-prosthesis interface may differ substantially to that occurring at the bone periosteal surface.[2] Such differences cannot be resolved using ROI-based DXA analysis technology, whilst the alternate computed tomography-based approach is accompanied with a higher radiation exposure dose.[3; 4] Further, different ROI models may also be required to measure BMD change around prostheses with differing geometries,[5-7] making quantitative comparisons of bone remodeling between prostheses challenging.

In order to solve these issues we recently developed and validated a high-spatial resolution tool for measuring femoral periprosthetic BMD change events, termed DXA-Region-Free Analysis (DXA-RFA).[8] This analysis approach uses the data contained within a standard DXA acquisition and applies contemporary image processing techniques to allow full statistical use of the spatial information contained within each DXA scan,[9; 10] shedding this limitation of ROI-based analysis approaches.

In this study we compared and contrasted the sensitivity of DXA-RFA versus ROI-based DXA analysis to detect BMD change over 24 months in the setting of a stemless, hydroxyapatite-coated femoral prosthesis (The Silent hip prosthesis, DePuy International Ltd, Leeds, UK). Specifically, we aimed to determine whether DXA-RFA provides greater analysis resolution of local bone remodeling events.

METHODS

Study design, recruitment, and randomization

The DXA scans were collected as part of a single-center, prospective cohort study of 18 patients undergoing primary THA using the Silent Hip. The study was approved by the South West National Health Service Research Ethics Committee, UK (05/WSE02/133), and all patients provided written, informed, consent prior to inclusion. The inclusion criteria were adult males and females with osteoarthritis of the hip requiring THA, and considered suitable for a cementless prosthesis. The exclusion criteria were pregnancy, known drug or alcohol abuse or psychological disorders that could affect care or treatment outcomes, participation in clinical trials of an investigational medical product within the last 6 months, osteonecrosis of the femoral neck, Paget's disease, significant bone loss or gross deformity in the region of the femoral neck identified on pre-operative radiographs, and patients with Charnley C functional classification. All operations were performed through a posterior approach with the patient in the lateral position. The femoral and acetabular components were inserted with a press-fit technique in accordance with the manufacturer's instructions. All patients were mobilized on the first or second post-operative day with unrestricted weight bearing.

Patient monitoring and assessments

A Harris Hip Score and an Oxford hip score were assessed pre-operatively, and 3, 6, 12, and 24 months post-operatively.[11; 12] Patients underwent DXA of the operated hip at post-operative baseline within 10 days of surgery, and at months 3, 6, 12, and 24 thereafter. All acquisitions were made using the same Hologic Discovery fan beam densitometer (Hologic Inc, Bedford, MA, USA) using the "metal-removal hip" scanning mode.

DXA scan analysis using conventional ROI approach

A 5 ROI analysis model similar to that described by Albanese et al was applied,[13] but adapted for the shorter length of the Silent Hip (Figure 1). The inter-observer repeatability of this ROI model was evaluated by comparison of 54 scan acquisitions by 2 independent, experienced DXA analysis technicians, and precision expressed as the coefficient of variation (CV%) using a formula described previously.[14] The inter-observer CV% was 0.3, 1.0, 0.5, 1.6, and 4.3 for ROIs 1 to 5, respectively, and similar to that described by Albanese et al (1.9 to 3.4%).[13]

DXA scan analysis using DXA-RFA

DXA scan analysis using DXA-RFA was implemented in Matlab v6.11.0.584r2010b (Mathworks Inc, Cambridge, MA), and performed as previously described.[8] The DXA-RFA bone map data extraction algorithm was written using proprietary Hologic technical information provided under a non-disclosure agreement between the University of Sheffield and Hologic Inc, and is based on the Hologic Inc algorithm APEX 3.2. A BMD image of each proximal femur was extracted from each archived Hologic scan file using DXA-RFA. The raw x-ray attenuation images were read from the scan files then segmented into prosthesis, bone, and soft tissue compartments using automated edge-detection, intensity thresholding, and morphological operations. The BMD at each pixel within the bone compartment was then calculated using the DXA-RFA algorithm. A single scan template was generated from the full population of acquired scans using the Generalized Procrustes Alignment method from a set of anatomical landmarks located automatically around the femur.[10] The individual scans were then registered to the template using thin plate splines.[15] The accuracy of the method was quantitated in an independent study using a hip phantom and was within 2% of that measured using the Hologic APEX 3.2 proprietary algorithm.[8] The NET clinical repeatability of the method (CV%), assessed previously in 29 independent patients undergoing repeated scan acquisitions on the same day after repositioning, was 1.7%.

The median CV% of the method at the individual datapoint level was 13.6% (interquartile range 11.9 to 15.6).

Statistical analysis

Categorical data were analyzed using the chi-squared test. Continuous data were analyzed within-group by paired t-test or by Wilcoxon test, as appropriate, comparing each follow-up time-point with the baseline data. All analyses were made 2-tailed with a critical P-value of 0.05. For DXA-RFA measurements change versus baseline for each BMD datapoint was analyzed using the paired t-test and presented as heatmaps of BMD change (%) together with its statistical significance.

RESULTS

Patient characteristics, clinical and patient reported outcomes

Eighteen patients (13 male, 5 female) with a mean age of 54.4 years (standard deviation 6.4) and body mass index of 28.1Kg/m^2 (standard deviation 3.5) participated in the study. All patients received the Silent Hip prosthesis (median length 55mm, range 45 to 70). All patients completed baseline post-operative, 3 month and 6 month clinical assessments and DXA measurements. Sixteen patients had assessments at 12 months. Two patients failed to attend the 12 month follow up appointments and were excluded from this analysis. Fifteen patients underwent assessments at 24 months. Three patients failed to attend at 24 months, and were excluded from the analyses of this time-point.

Clinical and patient reported outcomes, measured by Harris hip score and Oxford hip score, respectively, were consistent with expected improved physical function over 24 months after THA (Table 1, P<0.001, both scores). These improvements were most rapid over the first 3 months following surgery, with a slower rate of improvement continuing to 24 months.

DXA scan results for conventional ROI approach

The regional distribution of periprosthetic BMD at baseline varied from 0.70 to 1.34g/cm^2 (Figure 1). Higher BMD was observed in diaphyseal versus metaphyseal ROIs consistent with the overall average of the relative amount of cortical and cancellous bone within each ROI.

Post-operatively, the NET ROI showed a transient fall in BMD of 4% ($P<0.001$) at 3 months, which recovered to approximately baseline levels by 24 months. ROI3 showed no change in BMD at any time-point. An increase in BMD of 6% ($P<0.05$) in ROI4 was identified at 24 months. Falls in BMD were measured in ROIs 1, 2, and 5 ($P<0.05$). In ROI1 and ROI2 these falls had nadirs of 8 and 7%, respectively ($P<0.01$), and were followed by partial recovery in BMD. In ROI5 BMD loss commenced early after surgery and continued throughout follow-up, with a 20% decrease in BMD by 24 months ($P<0.001$).

DXA scan results using DXA-RFA

In contrast to the ROI-based analyses, quantitation using DXA-RFA resolved a baseline BMD distribution consistent with the anatomic macro-architecture of the proximal femur, with high bone mass recorded in anatomic cortical areas, and lower mass in the cancellous bone areas of the metaphysis and trochanters (Figures 2A and B). This baseline post-operative analysis also showed a focal area of high BMD at the superolateral border of the prosthesis tip (>4.0±2.5g/cm^2) that may represent bone compaction during prosthesis insertion.

Post-operative BMD change measured by DXA-RFA was observed in discrete, focal areas of the proximal femur over the duration of the study (Figures 3A to 3D). The majority of BMD change events occurred over the first 6 months following surgery. The reduction in

bone mass observed in ROI5 using the conventional approach was visualized as a highly discrete area at the most supero-medial aspect of the inferior femoral neck (>30% over 24 months, P<0.0001). Site-specific increases in bone mass were visualized at the prosthesis-bone interface over 24 months (up to 40%, P<0.001). The pattern of BMD change at the greater trochanter was heterogeneous over the first 3 months. The dominant remodeling pattern following this timepoint was one of increased BMD, initially in the most proximal trochanter, and moving distally over time, with a general trend towards increased BMD throughout the region by 24 months. The dominant remodeling pattern at the femoral diaphysis was one of a small reduction in bone mass over the 24 month period, but the discrete, focal nature of the changes remained a characteristic feature.

DISCUSSION

We compared bone remodeling events using conventional ROI-based analysis versus that made using an ROI-free computational approach (DXA-RFA) over 24 months after hip replacement using a stemless femoral prosthesis. Analysis using DXA-RFA demonstrated baseline post-operative spatial distribution of bone mass and subsequent BMD change at higher resolution than that observed using ROI-based analysis. BMD change that was observed as -20% BMD loss at 24 months in ROI5 using the conventional approach was resolved using DXA-RFA as a highly focal area adjacent to the neck resection site, and clearly defined within the first 6 months post-operatively. The DXA-RFA method was also able to resolve bone remodeling events at the prosthesis-bone interface that were not visualized using ROI-based DXA analysis.

These data confirm previous observations that BMD distribution at the proximal femur is spatially-complex,[16] and that the quantitation of remodeling events after prosthesis insertion is best made using high resolution approaches.[2] DXA-RFA provides a low-radiation

dose alternative to computed tomography for such imaging. This approach may provide a novel opportunity to study non-invasively in clinical trials the effect of investigational drugs or implant surface modifications suggested in animal studies to modulate prosthesis osseointegration.[17-20] This interface is less easily visualized using CT or MRI because of beam hardening, metal susceptibility and magnetic field artifacts, despite recent advances in data analysis using these modalities.[21]

DXA-RFA also has limitations. The generation of a common template and elastic registration of all images to this template causes some image distortion, resulting in poorer precision at the individual datapoint level than that observed at ROI level with conventional DXA. However, the precision error incurred is outweighed by the additional resolution achieved. The method also requires that all the scans analyzed in a series are included in the template generation. Thus far we have only applied the method to Hologic densitometer datasets. However, the DXA acquisition algorithms used in other manufacturer's densitometers also utilize a pixel bone map that may be extracted in a similar fashion. Finally, DXA is a 2-dimensional method used to resolve events that occur in 3 dimensions. However, this is a limitation of the acquisition technology, rather than the analytical approach, which may also be applied to cross-sectional imaging datasets.[9]

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	Harris Hip Score	Oxford Hip Score
Pre-operative baseline	48 (40 to 51)	21 (17 to 27)
3 months (n=18)	**96 (90 to 100)	**47 (38 to 48)
6 months (n=18)	***100 (93 to 100)	***48 (44 to 48)
12 months (n=16)	***100 (100 to 100)	***48 (48 to 48)
24 months (n=15)	***100 (99 to 100)	***48 (48 to 48)

Table 1. Harris hip score and Oxford hip score measured over 24 months. Data are median (interquartile range). Data in parentheses adjacent to follow up date are number of complete respondents at each timepoint. Analysis is within-group by Wilcoxon test, comparing completers at each follow-up time-point with their baseline data, *P<0.05, **P<0.01, ***P<0.001.

FIGURE LEGEND

Figure 1. Baseline and mean percentage change in BMD in each region versus baseline analyzed using a conventional analysis approach. Inset image shows the distribution of the 5 analysis regions of interest**.** Baseline value is mean±standard deviation. Analysis is by absolute change at each timepoint versus absolute baseline value by paired t-test. *P<0.05, **P<0.01, ***P<0.001.

Figure 2. Baseline BMD measurements made using DXA-RFA. A) Mean BMD (g/cm^2) at each pixel, and B) standard deviation (std BMD) of the BMD at each pixel. Colorbars indicate values for each parameter.

Figure 3. Average post-operative BMD change (%) and its statistical significance analyzed using DXA-RFA. BMD change is shown at 3A) 3 months, 3B) 6 months, 3C) 12 months, and 3D) 24 months post operatively. Analysis is in completers versus baseline at each timepoint by paired t-test. Colorbars indicate values for each parameter.

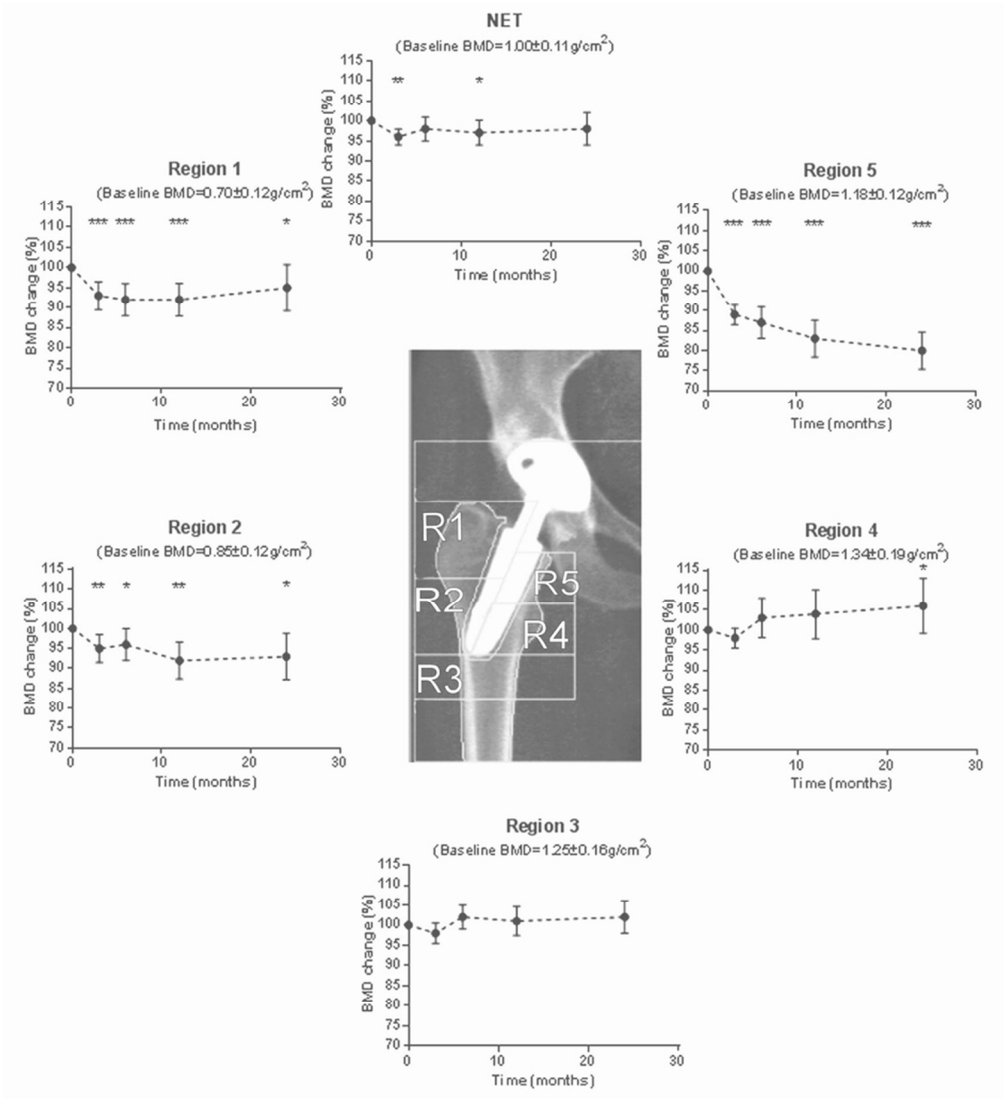

Figure 1
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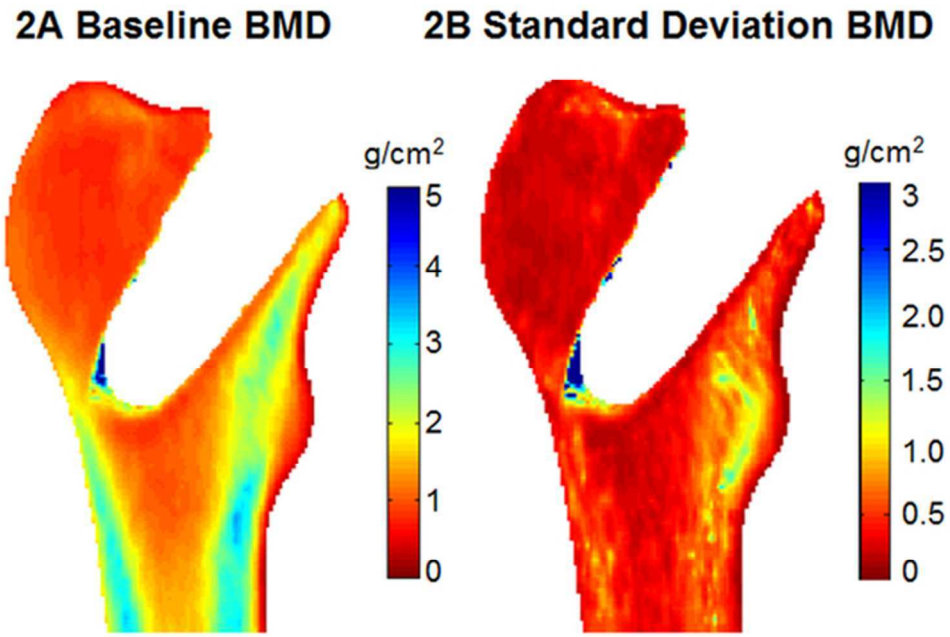

Figure 2
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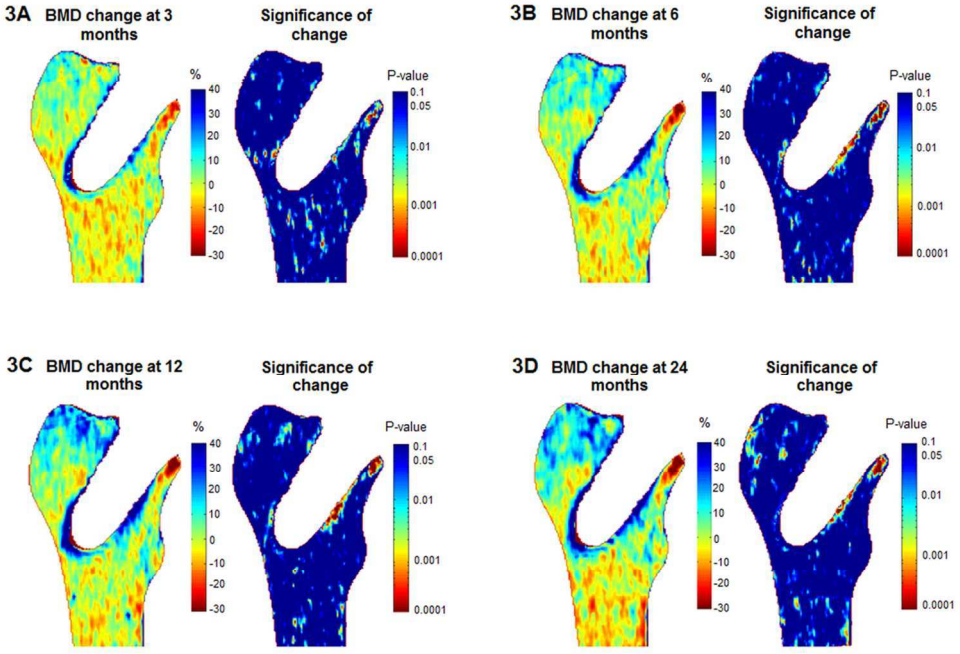

Figure 3
115x78mm (300 x 300 DPI)