Title: Spatial Mapping of Humeral Head Bone Density

Abstract: Background: Short stem humeral replacements achieve fixation by anchoring to the metaphyseal trabecular bone. Fixing the implant in high density bone can provide strong fixation and reduce the risk of loosening. However, there is a lack of data mapping the bone density distribution in the proximal humerus. The aim of the study was to investigate the bone density in proximal humerus.

Methods: Eight CT scans of healthy cadaveric humeri were used to map bone density distribution in the humeral head. The proximal humeral head was divided into twelve slices parallel to the humeral anatomical neck. Each slice was then divided into four concentric circles. The slices below the anatomical neck, where short stem implants have their fixation features, were further divided into radial sectors. The average bone density for each of these regions was calculated and regions of interest were compared using a repeated measures ANOVA with significance set at p<0.05.

Results: Average apparent bone density was found to decrease from proximal to distal regions leaving the majority of higher bone density proximal to the anatomical neck of the humerus (p<0.05). Below the anatomical neck, bone density increases from central to peripheral regions where cortical bone eventually occupies the space (p<0.05). In distal slices below the anatomical neck, a higher bone density distribution in the medial calcar region was also observed.

Conclusion: This study indicates that it is advantageous to preserve some bone above the anatomical neck and epiphyseal plate at the periphery to provide improved fixation.
Dear Editor,

The manuscript of the current work has been read and approved by all authors. The authors confirm that this study has not been published elsewhere and that it represents honest work.

The corresponding author of this work is:

Hamidreza Alidousti,
h.alidousti@imperial.ac.uk
Department of Mechanical Engineering,
Imperial College London,
London, UK, SW7 2AZ

Yours faithfully,

Hamidreza Alidousti 28/09/2016
Joshua W Giles 28/09/2016
Roger JH Emery 28/09/2016
Jonathan Jeffers 28/09/2016
19 November 2013

Dr Hamidreza Alidousti
Research Associate
Imperial College London
Room 312, Department of Mechanical Engineering
Imperial College London
South Kensington, London
SW7 2AZ

Dear Dr Alidousti

Study title: Cadaveric testing of a novel Total Shoulder Replacement (TSR) to assess the kinematics and the implant-bone mechanical fixation

REC reference: 13/LO/1839
IRAS project ID: 132972

The Proportionate Review Sub-committee of the NRES Committee London - Fulham reviewed the above application on 18 November 2013.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager, Miss Shehnaz Ishaq, nrescommittee.london-fulham@nhs.net

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.
Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
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<tr>
<td>Evidence of insurance or indemnity</td>
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<td>29 July 2013</td>
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<tr>
<td>Investigator CV</td>
<td>Dr Alidousti</td>
<td></td>
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<td>Letter from Sponsor</td>
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<td>12 July 2013</td>
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<tr>
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<td>10 May 2013</td>
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<tr>
<td>REC application</td>
<td>3.5</td>
<td>11 November 2013</td>
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Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website. Information is available at National Research Ethics Service website > After Review

Please quote this number on all correspondence

13/LO/1839

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee’s best wishes for the success of this project.

Yours sincerely

Signed on behalf of:
Dr Frank Miskelly
Vice-Chair (Chaired the meeting)

Email: nrescommittee.london-fulham@nhs.net

Enclosures: List of names and professions of members who took part in the review

“After ethical review – guidance for researchers”

Copy to: Christine Buicke, R&D Department, Imperial College London

A Research Ethics Committee established by the Health Research Authority
NRES Committee London - Fulham

Attendance at PRS Sub-Committee of the REC meeting on 18 November 2013

Committee Members:

<table>
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<tr>
<th>Name</th>
<th>Profession</th>
<th>Present</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Dr Kanagasabai Ganeshaguru</td>
<td>Retired Scientist</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Dr Shaun Griffin</td>
<td>Director of Communications and Public Affairs</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Dr Frank Miskelly (Chaired the meeting)</td>
<td>Physician (Vice-Chairman)</td>
<td>Yes</td>
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Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miss Shehnaz Ishaq</td>
<td>REC Manager</td>
</tr>
</tbody>
</table>
Dear Editor,

Conflict-of-Interest Statements

I, Hamidreza Alidousti, declare that I may receive benefits from patent 1512277.3 (pending) related to this work. I have no other conflict of interest to declare.

The institution of the author has received funding from Wellcome Trust for this study. Imperial college London and Wellcome Trust may receive benefits from patent 1512277.3 (pending) related to this work. Wellcome Trust has not been involved in data collection, data analysis, or the preparation of or editing of the manuscript.

Yours faithfully,

Hamidreza Alidousti

26/10/2016
Dear Editor.

Conflicts-of-Interest Statements

I have no conflict of interest to declare related to this work.

Yours faithfully,
Joshua W Giles 26/10/2016

[Signature]
Dear Editor.

Conflict-of-Interest Statements

I, Roger JH Emery, declare that I may receive benefits from patent 1512277.3 (pending) related to this work. I have no other conflict of interest to declare.

Yours faithfully,

Roger JH Emery 26/10/2016
Dear Editor.

Conflict-of-Interest Statements

I, Jonathan Jeffers, declare that I may receive benefits from patent 1512277.3 (pending) related to this work. I have no other conflict of interest to declare.

Yours faithfully,

Jonathan Jeffers

26/10/2016
Review #1

The authors would like to thank the reviewer for her/his valuable comments which greatly helped to improve the manuscript. We would also like to express our gratitude towards the positive comments by the reviewer. We are extremely glad that she/her finds our work with clinical impact and helpful to implant design applications - Please, find below the response to each comment:

Comment 1: The age and condition of the specimens may have an impact on the conclusions if in fact the bone density distribution changes with age and the development of arthritis. An excellent follow-up study would be to repeat it with aged, arthritic specimens or preoperatively in actual patients.

Answer: We agree with the reviewer’s comment. As the result of this comment, we will, indeed, carry out a future follow-up study to investigate the density distribution in actual patients, as we routinely CT scan patients pre-operatively for planning purposes. The plan to carry out this future work is now added to the manuscript discussion. Please see page 13, lines: 303-304 in the revised manuscript.

Comment 2: The tables are helpful and appropriate. Using color to define the regions based on bone density would be helpful if that technology is available and the Journal is willing to publish color figures.

Answer: We agree with the reviewer that adding colours to the figures is helpful particularly when the paper is read on the computer screen. We have changed Figure 3, 4 and 5 to a Parula colour map which is colour on the screen, but the greyscale is also distinct if printed on a b/w printer and is colourblind friendly.
Review #2

The authors would like to thank the reviewer for her/his valuable comments which greatly helped to improve the manuscript. We would also like to express our gratitude towards the positive comments by the reviewer - Please, find below the response to each comment:

Comment 1 - Despite significant differences in bone density, and therefore the potential micro-motion which may occur to inhibit bony ingrowth, the question that remains, is the biologic activity and osteointegration potential from the surrounding bone correlated with bone mineral density?

Answer – This is a very valid point raised by the reviewer. We cannot comment on the biological activity and the osteointegration potential of the surrounding bone based on our CT scans. However, Shah et al. 4, using osteoblasts derived from age-matched and paired humeral head samples with Osteoarthritis (OA) and Osteoporosis (OP), showed that cortical and subchondral bone showed greater pro-angiogenic (higher levels of VEGF-A mRNA and protein release) capacity and fracture healing characteristics when compared to trabecular bone. Their trabecular bone sample taken from the central regions distal to the anatomical neck also consistently showed slower osteoblasts proliferation. These findings suggest that denser proximal (close to subchondral bone) and peripheral bone (close to cortical bone) may also benefit from this greater biological activity and, therefore, have greater osteointegration potential when compared to the central and distal cancellous bone. This discussion is now added to the manuscript. Please see page 12, lines: 287-296.

Comment 2 - how is the 150 microns of micromotion translatable to the shoulder, rather than in weightbearing joints?

Answer – There is a lack of agreement within the literature on the maximum level of micromotion that should exist to promote implant osteointegration. However, the measured value of 150 µm as a threshold value for the bone growth is commonly accepted regardless of the joint in use. This value was established by Jasty et al 2 and Pillar et al 3 who measured in-vivo skeletal responses to different magnitudes of relative motion between a cylindrical porous implant and the surrounding bone in canine models. These experiments and those similar to it were displacement driven and thus independent of loads that may occur in a joint like shoulder. However, as described in the manuscript (page 2, lines: 49-51), Favre et al. 1, using a short stem device in cadaveric humeri, have measured micromotions up to 270 µm under 850 N load which is around 120% of the body weight (BW) of an averaged patient (70 kg). This load is easily reached when putting a 2 kg object above head according to instrumented humeral implants which measure in-vivo loading 5, due to the lever arm created by the arm length and tension in the deltoid and the rotator cuff muscles.
In addition, in our recent experiment (not published yet) on cadaveric humeri implanted with a short stem device, we also measured micromotions of up to 300 µm under similar loading conditions. These findings demonstrate that the quoted value of 150 µm may be relevant in the shoulder before the secondary fixation (osteointegration) takes place. This discussion is now added to manuscript. Please, see page 11 lines: 260-263.

References


Humeral head bone density spatial distribution

Spatial Mapping of Humeral Head Bone Density

Authors:

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The institution of the authors has received funding from Wellcome Trust for this study.

Disclaimer:

Hamidreza Alidousti may receive benefits from patent 1512277.3 (pending) related to this work

Joshua W Giles: none

Roger JH Emery may receive benefits from patent 1512277.3 (pending) related to this work

Jonathan Jeffers may receive benefits from patent 1512277.3 (pending) related to this work

This study has been conducted according to the ethics approval (REC reference: 13/LO/1839, IRAS project ID: 132972) from National Research Ethics Service (NRES) - a copy of the letter from the ethical committee approving this study has been submitted.

Acknowledgement

This work was funded by the Translation Award received from Wellcome Trust.
Abstract

Background: Short stem humeral replacements achieve fixation by anchoring to the metaphyseal trabecular bone. Fixing the implant in high density bone can provide strong fixation and reduce the risk of loosening. However, there is a lack of data mapping the bone density distribution in the proximal humerus. The aim of the study was to investigate the bone density in proximal humerus.

Methods: Eight CT scans of healthy cadaveric humeri were used to map bone density distribution in the humeral head. The proximal humeral head was divided into twelve slices parallel to the humeral anatomical neck. Each slice was then divided into four concentric circles. The slices below the anatomical neck, where short stem implants have their fixation features, were further divided into radial sectors. The average bone density for each of these regions was calculated and regions of interest were compared using a repeated measures ANOVA with significance set at p<0.05.

Results: Average apparent bone density was found to decrease from proximal to distal regions with the majority of higher bone density proximal to the anatomical neck of the humerus (p<0.05). Below the anatomical neck, bone density increases from central to peripheral regions where cortical bone eventually occupies the space (p<0.05). In distal slices below the anatomical neck, a higher bone density distribution in the medial calcar region was also observed.

Conclusion: This study indicates that it is advantageous with respect to implant fixation to preserve some bone above the anatomical neck and epiphyseal plate, and to use the denser bone at the periphery.

Level of evidence: Basic science study
Humeral head bone density spatial distribution

Keywords: Shoulder arthroplasty; humeral bone density; short-stem devices; implant fixation; humeral component; implant design; implant loosening
Humeral head bone density spatial distribution

Introduction

Short stem humeral component designs have been introduced by several manufacturers in the past few years.\textsuperscript{6,8} The benefits of this type of design (Figure 1) include decreased bone resection compared to conventional stemmed implants and the ability to replicate the native humeral head centre without compensating for a patient’s variable humeral shaft offset.\textsuperscript{2} A drawback of such designs is that they rely on a smaller proximal region for fixation with a less advantageous lever arm, which is not located as far down the shaft of the humerus, when compared to traditional stemmed designs. Currently available short stem designs resect the humeral head and achieve fixation in bone distal to the resection plane in the trabecular metaphyseal region. The density of the bone in this region is therefore important for achieving adequate component fixation. In fact, Favre et al.\textsuperscript{3}, using cadaveric humeri, showed that in a short stem device, micromotion between bone and implant may increase significantly with decreased apparent bone density. They showed that, when bone density is lower than 0.1 g.cm\textsuperscript{-3}, an implant may experience micromotions above the 150 µm threshold accepted to result in bone growth.\textsuperscript{7,11}

A number of studies have investigated the bone density distribution in the proximal humerus. A summary of their methodologies and findings is shown in Table 1. In a study on dissected proximal humeri using bone mineral densitometry and an indention test, Saitoh et al.\textsuperscript{14} showed that the proximal part of the humeral head exhibited the greatest amount of bone mineral density and the humeral neck had approximately one half the bone mineral density of the humeral head. In addition, they also showed that the cancellous bone of the neck had only one third the mechanical strength of the humeral head in the indention test. In a volumetric bone mineral density assessment of 20 cadaveric bones, Tingart et al.\textsuperscript{16} showed that trabecular bone has significantly higher density in the proximal-posterior portion of the
articular surface. Yamada et al. 21, performed a Computer Tomography (CT) study of forty patients and found that bone density was higher on the medial side of the humeral head, especially near the articular region. Hepp et al. 5 investigated bone strength rather than density by slicing 24 cadaveric humeri and measuring bone strength by indentation. They showed that medial and posterior aspects of the proximal humerus had the highest bone strength. Additionally, they found that the greater and lesser tuberosities and the central area of the proximal head had the lowest bone strength. Barvencik et al.1 studied age related changes in bone density in 60 cadaveric proximal humeri. They investigated bone density using X-rays and found the most superior and medially located part of the humerus had highest bone density independent from age. They also found that the most prominent decrease in bone density due to age was observed in the region of the greater tuberosity.

These studies provide valuable information on the spatial distribution of bone in the proximal humerus for screw fixation, rotator cuff repair suture anchors or for conventional stemmed humeral devices. However, they report data in the transverse plane (more appropriate for conventional stemmed humeral devices) or with limited data resolution in this volume of interest. Hepp et al. 5 reported strength from 5 points in four transverse slices in the proximal humerus, Yamada et al. 21, divided the CT data into two areas (medial and lateral) for transverse slices of the proximal humerus and Barvencik et al. 1 assessed a single coronal slice of the proximal humerus. Tingart et al. 16, did report their data relative to the humeral neck, but only in one slice which was perpendicular to the long axis of the shaft. A summary of the measurement location of these studies is shown in Table 1. As a result, the data provided by these studies are of limited use in relation to short proximally fixed humeral designs which are orientated in the plane of the head/neck junction, with fixation features protruding circa 20 - 40 mm perpendicular to that plane. For such devices, the spatial density map therefore needs to be reported in a reference frame relative to the anatomical neck and
Humeral head bone density spatial distribution

provide high resolution density mapping in the volume of bone proximal to this plane, and 20 - 40 mm distal to this plane.

A spatial map of humeral bone density in the volume of bone where devices with proximal fixation achieve fixation would therefore be useful to surgeons by providing a guide for the positioning of anchoring features of existing implants, and could prove to be a critical resource for implant designers seeking to improve the fixation features of future humeral components by utilising denser regions of the bone. Therefore, the current study aims to provide a detailed map of bone density in the proximal humerus, specifically in the bone distal to the humeral neck where these devices achieve fixation. The null hypothesis is that there is no statistically significant relationship between the bone density and the spatial location in proximal-to-distal, central-to-peripheral and radial directions in the humeral head.
Humeral head bone density spatial distribution

Method

Following ethics approval from the Research Ethics Committee (13/LO/1839), eight CT scans of independent cadaveric humeri specimens with mean ± SD age = 71 ± 10 (range: 59-83, four male) were used. There was no evidence of degenerative joint disease or osteoporosis in the specimens. The CT scans were carried out using a Toshiba Aquilion 32 machine. Standard phantoms of delrin, nylon and polypropylene provided by the manufacturer were used to calibrate the machine for bone, soft tissue and fat according the manufacturer’s protocol. Scans had a resolution of approximately 0.5 × 0.5 × 0.9 mm and were manually segmented in the Mimics software package (version 15.0, Materialise, NV) to generate solid models. The solid models were then discretised into 1mm tetrahedral elements in the 3-Matic software package (version 7.0, Materialise, NV), and material properties were assigned based on the local Hounsfield unit (HU) from the CT scan. A rigid polyurethane foam phantom with a known density of 0.29 g.cm\(^{-3}\) provided a reference to calibrate Hounsfield values and ensured consistency between CT scans. The apparent bone density was calculated using the recorded HU values and the relationship described by Rho et al.\(^{13}\) in which CT value and the apparent bone density in the proximal humerus were found to follow the formula:

\[
\rho (g. cm^{-3}) = 0.131 + 0.000624 \times HU
\]

where, apparent bone density is defined by wet weight divided by volume of the overall physical dimension of a given specimen. For each CT scan, the lower limit which distinguished the fatty marrow from bone tissue was established. Those cloud points which fell below this limit were excluded from the analysis.
Humeral head bone density spatial distribution

In Matlab (R2015a, The MathWorks Inc., Natick, MA), each element centroid was calculated and the corresponding apparent bone density in that element was assigned to its centroid. This provided a cloud of points in space with density values. The data were then rearranged and grouped by dividing the humeral head into twelve slices parallel to the humeral neck starting from the most proximal region to the distal regions beneath the epiphyseal plate (Figure 2). The humeral neck was identified by an experienced surgeon based on anatomical landmarks. Slices were made such that the sixth slice coincided with the anatomical neck. Each slice was then divided into four concentric zones (Figure 3). Using the distal to proximal and concentric sub-divisions, the overall spatial variation and specific interactions between geometric variables were investigated using descriptive and inferential statistics (see statistics section below).

The majority of current short stem implants place their fixation entities in the bone below the humeral anatomical neck without recommending an optimal orientation. Therefore, to investigate whether there is a meaningful difference in the apparent bone density at different orientations within each slice, the concentric zones in this distal region were further divided into six radial sectors (Figure 4) and assessed using descriptive and inferential statistics. For each of these sub-regions, apparent bone density values were calculated by averaging the density values of the cloud of points located within their volume. In deciding on the number of sub-volumes - and thus their size - it was ensured that the average value calculated from the cloud of points for each sub-volume did not mask important local variations in properties. This was achieved by defining the number of sub-volumes using the criteria that the standard deviation of the values of all points within a sub-volume must not exceed 10% of the average.
To provide a comprehensive understanding of the spatial mapping of the calculated apparent bone density values, they were first assessed using descriptive statistics for all of the above described sub-divisions (i.e. 12 slices with 4 concentric zones on each slice). Subsequently, statistical differences in observed spatial variations were analysed using 2 two-way Repeated Measures Analyses of Variance (RM-ANOVA) in SPSS 22 (IBM, Armonk, NY, USA) with factors of: (a) proximal to distal slices (3 levels) and concentric zones (4 levels), (b) concentric zones (4 levels) and radial sectors (6 levels). For (a), the 12 proximal to distal slices were grouped and averaged as blocks of four (hereafter termed proximal, middle, and distal) as these were typically 1mm thick and the analysis of statistical difference for regions of this small size was not considered clinically meaningful. For (b), only the region below the anatomical neck was considered, as this is where current short stem fixation occurs, and the values of these six slices were averaged together as implant fixation features pass through all of these. For each RM-ANOVA, significance was set at p<0.05, as well, follow-up post-hoc tests with a Bonferroni correction and analyses of interactions were performed when appropriate. Power analysis indicated that a sample size of equal eight humeri was required to achieve 80 percent power for each of the above described RM-ANOVA statistical analyses. For this power analysis we chose our clinically meaningful difference in bone density to be 15% which falls between the 10 & 20% values previously reported in the literature and our group standard deviations were ±0.037 g.cm⁻³ as taken from pilot specimens.
Results

Considering each proximal to distal slice as a whole, it was found that apparent bone density was at its maximum at Slice 1 (0.45 g.cm$^{-3}$), its minimum at Slice 8 (0.20 g.cm$^{-3}$), just below the anatomical neck, and increased to 0.24 g.cm$^{-3}$ by the most distal slice (Figure 2).

When slices were sub-divided into four concentric zones (Figure 3), it was observed that, by moving from proximal to distal, changes in bone density differed in the central and peripheral regions. The peripheral zone (Zone 4) which contains the cortex had the highest density value in all slices, but a trend for increasing density from Zone 1-3 was also observed (i.e. the density increased progressively from the central to the peripheral of the bone). This effect is a result of the continual decrease in bone density in the central zones from proximal to distal in contrast to that of the peripheral zones’ where, after decreasing, density starts increasing in regions below the anatomical neck, from Slice 8 to 12 (Figure 3).

Statistical comparisons

a) Statistical analysis of these data using two-way RM-ANOVA rejected the null hypothesis and demonstrated a number of important regional trends and statistically significant differences. Moving from proximal to distal in the humeral head was found to produce a significant main effect on bone density (both p<0.001) (Figure 5). Specifically, when averaged across all concentric zones, the proximal region was significantly more dense (0.34±0.06 g.cm$^{-3}$) than the middle (0.22±0.04 g.cm$^{-3}$, p<0.001) and distal (0.21±0.03 g.cm$^{-3}$, p<0.001) regions. Similarly, when averaged across all proximal-to-distal regions, all concentric zones were significantly different from one another (differences: 0.06-0.22±0.02-0.04, 0.001<p<0.001) except zone 1 to 2 (difference: 0.01±0.01, p=0.059). However, it was also found that proximal-to-distal and central-to-peripheral positioning significantly interact (p<0.001) such that bone density significantly reduces in concentric zones 1 and 2 from
Humeral head bone density spatial distribution

approximately 0.28 g.cm\(^{-3}\) to 0.1 g.cm\(^{-3}\) by moving from proximal to distal, but for zones 3 and 4 there is a characteristic decrease and increase from proximal to middle and middle to distal, respectively. However, in the middle region of the humerus, where the anatomical neck is located, apparent bone density in zone 3 drops below 0.2 g.cm\(^{-3}\) and in the distal region it has a value of just above 0.2 g.cm\(^{-3}\). More detailed analysis of this interaction found that there were numerous significant differences between the various levels of each of the two factors with proximal and distal regions producing similar patterns (if not magnitudes) of differences and only zone 4 being different from the others in the middle region.

b) As mentioned previously, to further investigate bone density variations in distal regions, where implant fixation entities are normally placed, six slices below the anatomical neck were averaged together and then split into four concentric zones and further sub-divided into six radial sectors (Figure 4). This two-way RM-ANOVA rejected the null hypothesis and found that both the concentric zone (p<0.001) and radial sector (p<0.001) of a bone region had a significant main effect on bone density. With respect to the main effect of the radial sector, it was found that bone density increases from its minimum at the most lateral sector in the vicinity of the greater and lesser tuberosities (Sector E: 0.17±0.04 g.cm\(^{-3}\)) as you rotate in either direction until it reaches its maximum in the medial calcar (Sector B: 0.25±0.05 g.cm\(^{-3}\)). This pattern resulted in significant differences between Sector E and all others (differences: 0.06-0.09±0.02-0.04, 0.003≤p≤0.049) except Sector D (difference: 0.02±0.3, p=1.000), which is adjacent. Additionally, Sector A was significantly more dense than Sector D (difference: 0.06±0.03, p=0.026). Furthermore, there was a significant interaction between the two factors (p=0.004) such that there were no statistically significant differences between radial sectors in central zones; however, in peripheral regions (zone 3 and 4), there were significant differences and each zone demonstrated the characteristic pattern described for the main effect above (i.e. lower density laterally and greater medially).
Humeral head bone density spatial distribution

Discussion

The current study showed that apparent bone density is higher proximal to the anatomical neck of the humerus. Apparent bone density also increases from central to peripheral regions. This difference in bone density from central to peripheral zones is more pronounced in regions below the anatomical neck. These regions of bone are therefore most suitable to achieve fixation of proximally fixed humeral implant designs. Furthermore, below the anatomical neck, bone density has the greatest density in the medial calcar region (i.e. the three to nine o’clock positions on the clock face) and the lowest at the lateral humeral head adjacent to the greater and lesser tuberosities (i.e. the eleven to one o’clock positions). Proximally fixed humeral components usually have a cruciform fixation keel that can be positioned to avoid this low density region.

The current findings are in agreement with the finding of Saitoh et al.\textsuperscript{14} who showed that the mineral bone density in humeral neck was approximately one half the bone mineral density of the humeral head (Figure 5). This study is also comparable to that of Barvencik et al.\textsuperscript{1} who showed higher density in proximal regions when a slice of the proximal humerus was viewed in the coronal plane. Yamada et al.\textsuperscript{21} also found high local bone density on the medial side the humerus and showed that regions in the vicinity of the lesser and greater tuberosities contained less bone tissue. Similarly, Hepp et al.\textsuperscript{5} showed higher densities in the medial and posterior regions of the proximal humerus. The increase in apparent bone density from central to periphery regions demonstrated in this study is also in agreement with earlier findings that the strength and rigidity of cancellous bone significantly increases within 2 to 5 mm of the cortical wall.\textsuperscript{10} Our data indicates that this is more evident in distal regions where a sharp increase in density is observed from zone 3 to 4.
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Short stem implants are designed to give surgeons greater access to the glenoid compared to resurfacing devices while preserving more bone than traditional stemmed implants; however, the disadvantage of these implants is that they must achieve fixation over a smaller surface area and with a less advantageous lever arm. Current generation short stem designs require the entire humeral head to be resected at the anatomical neck. Our data indicates this may sacrifice regions of higher quality bone proximal to the anatomical neck that could be utilized to achieve better fixation and thereby allow for lower profile fixation features; for example a mid head resection that allows access to the glenoid whilst retaining some bone proximal to the anatomic neck. In addition, the majority of short stem designs consist of a primary central fixation keel below anatomical neck, with fins or webs extending from this central feature. The current study shows that below the anatomical neck, the central portion of the humerus may have a density just around 0.1 g.cm\(^{-3}\) which has been shown to be an indication for increased micromotion above the commonly accepted value of 150 \(\mu m\). \(^3\) This micromotion threshold may be exceeded in the shoulder for short stem devices, prior to osseointegration for normal activity. Telemeterised implant data indicates the joint force can reach 850N (120\% body weight of 70kg patient) by placing a 2kg object on a shelf\(^{18}\), which has been shown to create micromotions up to 270 \(\mu m\) for a short stem device\(^3\). Our data indicates the peripheral bone has greater density, and this also may be utilized for lower profile peripheral fixation features of the humeral component. Our data also shows that the highest density bone is located in the outer third and fourth concentric rings of every slice, particularly those located below the anatomical neck. This observation may suggest that any peripheral fixation should have its features located at around 75\% of the radial distance extending from the implant centre to its rim. Since the bone slices are always divided into four concentric regions regardless of the patient’s size and shape variability, the denser bone will not be missed in some individual for such a peripheral design. Locating fixation features
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in the densest bone may extend the indication for humeral replacement procedure in patients with decreased bone density. In fact, Hall and Rosser 4 showed loss of bone substance due to osteoporosis occurs centrally beneath the epiphyseal plate and in the greater tuberosity and the peripheral regions remain less affected.

Wirth et al. 19, using Finite Element (FE) simulations developed from micro-CT scans of the humeral trabecular bone, has demonstrated that an implant-bone construct located in the central region of the humerus trabecular bone has less structural stiffness than those placed peripherally. In addition, Favre et al. 3, using cadaveric humeri and displacement measuring transducers, has shown that micromotion in short stem designs significantly increases as the trabecular apparent bone density decreases. The data in the current study may therefore be useful for implant design, but it also is useful for positioning existing designs. It may be advantageous to place at least one of the peripheral fixation entities in the stronger bone in the medial and posterior regions. This may be especially advantageous for patients who experience a marked decrease in bone density in the region of the greater tuberosity due to age while their bone density remains unchanged in the medial and posterior regions independent of age and sex as described by Barvencik et al. 1. In addition, Shah et al. 15, using osteoblasts derived from age-matched and paired humeral head samples with Osteoarthritis (OA) and Osteoporosis (OP), showed that cortical and subchondral bone showed greater pro-angiogenic (higher levels of VEGF-A mRNA and protein release) capacity and fracture healing characteristics when compared to trabecular bone. Their trabecular bone sample taken from the central regions distal to the anatomical neck also consistently showed slower osteoblasts proliferation. These findings suggest that denser proximal (close to subchondral bone) and peripheral bone (close to cortical bone) identified in the current work may also benefit from this greater biological activity and, therefore, have greater osteointegration potential when compared to the central and distal cancellous bone.
The current study has a number of limitations. Firstly, the study includes a small sample size of eight humeri. However, our power analysis indicated that this was sufficient to identify clinically significant differences of 15% in bone density. Secondly, the specimens were exclusively healthy joints, however, the proximally fixed devices discussed in the current study are aimed as an earlier intervention than conventional TSA, thus when these devices are used the bone will not have reached the deterioration associated with end stage disease. **However, a future follow-up study will use the same methodology to investigate density distribution preoperatively in actual patients.** Thirdly, apparent bone density was not directly measured through in-vitro experiments but instead using CT data; however, Rho et al. found a strong correlation between CT based apparent density and physically measured apparent density of the proximal humerus. It has also been shown that bone density is a good predictor of implant performance and can predict bone Young’s modulus with a good correlation. This was confirmed by the regions of high bone density found in this study which correspond to the regions with higher mechanical strength shown by Hepp et al. Fourthly, our study did not distinguish between the cortical and trabecular bone in the higher density peripheral region (Concentric zone 4). However, the trend of bone density increase from central to periphery clearly demonstrates higher bone density in the trabecular bone in the vicinity of the cortical bone as suggested by Pilliar et al. In addition, the thickness of the cortical shell in proximal humerus was measured to vary between 1-2 mm in all specimens and the highest thickness measured is still only approximately one fifth of the thickness of the outer concentric zone (zone 4). This indicates that a large portion of the concentric zone 4 is occupied by trabecular bone and, therefore, the higher density in this region is not wholly attributable to the cortical shell. Furthermore, the increase in bone density in the peripheral regions is strongly evident in zone 3 where there is no cortical bone present.
Conclusions

In conclusion, this study is the first to comprehensively map humeral bone density and has shown that there are significant regional differences, with the most pronounced effects being stronger bone proximally and peripherally as well as in the medial calcar region. Therefore, any new humeral implants should utilise these stronger regions of bone located above the anatomical neck, which have also shown to exhibit biologically better osteointegration properties\textsuperscript{15}, and at the periphery by incorporating strategically located fixation features.
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References


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Figures

Figure 1: Diagram of the most common short stem humeral components. The hemispherical head is assembled to a variety of stem designs shown in the figure using a tapper fit mechanism. The stem is press-fitted into the cancellous bone beneath the anatomical neck cut.

Figure 2: Variation of bone density from the proximal to distal region across slices parallel to the anatomical neck. The range and the orientation of the slices are shown, with the anatomical neck at slice 6.

Figure 3: Variation of bone density from central to peripheral zones for each slice parallel to the anatomical neck. The range and the orientation of the slices are shown, with the anatomical neck at slice 6.

Figure 4: Graph of mean bone density stratified by concentric zone (1-4) and radial sectors (A-F). Asterisks (*) and brackets represent significant comparisons (p<0.05) between radial sectors for a given concentric zone. Also, note that data are for the average of the six slices distal to the anatomical neck.

Figure 5: Graph of mean bone density stratified by proximal-to-distal (proximal, middle, distal) position and concentric zone (1-4). Asterisks (*) and brackets represent significant comparisons (p<0.05) between concentric zones for a given Proximal-to-Distal region. Also, note that slice data were grouped and averaged into distal, middle, and proximal regions in order to make comparisons more clinically meaningful as described in the Statistics section.
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Tables

Table 1 – Schematics of studies and their methodologies for carrying out bone density and strength measurement for the proximal humeral head.
Figure (1)
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Figure (2)
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The graph shows the apparent bone density (g.cm\(^{-3}\)) as a function of slice number. The density decreases from proximal to distal, with slice 1 having the highest density and slice 12 having the lowest density. The error bars indicate the variability in the measurements.
Figure (4):
Click here to download high resolution image
<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barvencik et al [1]</td>
<td>Bone mineral measurement using Histomorphometric analysis and X-rays in A to L regions on one centered coronal humeral head slice</td>
<td>The most superior and medially located part of the humerus (C, B and F) had highest bone density</td>
</tr>
<tr>
<td>Hep et al. [5]</td>
<td>Bone mineral measurement using Histomorphometric analyses for 1, 3, 5 and 7 slices</td>
<td>Medial (A) and posterior (B) aspects of the proximal humerus had the highest bone strength</td>
</tr>
<tr>
<td></td>
<td>Indentation test on 2, 4, 6 and 8 slices in A to E regions</td>
<td>The greater (E) and lesser (D) tuberosities and the central (C) area of the proximal head had the lowest bone strength</td>
</tr>
<tr>
<td>Siatoh et al. [13]</td>
<td>Bone mineral densitometry on the entire region of each three slices</td>
<td>Bone bove anatomical neck (1) showed twice bone mineral and three times higher mechanical strength than bone of the humeral neck (3). Posteroinferior regions were mechanically stronger than other regions</td>
</tr>
<tr>
<td></td>
<td>Indentation test on three slices in A to I regions</td>
<td></td>
</tr>
<tr>
<td>Tingart et al. [15]</td>
<td>Bone mineral densitometry on the entire region of each six slices</td>
<td>Bone has significantly higher density in the proximal (1, 2 and 3)-posterior (D and E) portion of the articular surface</td>
</tr>
<tr>
<td></td>
<td>Regional bone mineral densitometry for one head middle slice in regions A to G</td>
<td></td>
</tr>
<tr>
<td>Yamada et al. [19]</td>
<td>Bone density measurement based on HU values on each slice CT in the region shown</td>
<td>Bone density was higher on the medial side (A) of the humeral head, especially near the articular region</td>
</tr>
<tr>
<td></td>
<td>Regional density measurement in each slice for A and B regions</td>
<td></td>
</tr>
</tbody>
</table>