Avascular necrosis associated with fracture of the femoral neck after hip resurfacing

HISTOLOGICAL ASSESSMENT OF FEMORAL BONE FROM RETRIEVAL SPECIMENS

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The cause of fracture of the femoral neck after hip resurfacing is poorly understood. In order to evaluate the role of avascular necrosis we compared 19 femoral heads retrieved at revision for fracture of the femoral neck and 13 retrieved for other reasons.

We developed a new technique of assessing avascular necrosis in the femoral head by determining the percentage of empty osteocyte lacunae present. Femoral heads retrieved as controls at total hip replacement for osteoarthritis and avascular necrosis had 9% (SD 4; n = 13) and 85% (SD 5; n = 10, p < 0.001) empty lacunae, respectively.

In the fracture group the percentage of empty lacunae was 71% (SD 22); in the other group it was 21% (SD 13). The differences between the groups were highly significant (p < 0.001).

We conclude that fracture after resurfacing of the hip is associated with a significantly greater percentage of empty osteocyte lacunae within the trabecular bone. This indicates established avascular necrosis and suggests that damage to the blood supply at the time of surgery is a potent risk factor for fracture of the femoral neck after hip resurfacing.

Hip resurfacing is an alternative to conventional total hip replacement (THR), particularly in the younger patient. The main indication for early revision after resurfacing through the standard posterior approach is fracture of the femoral neck.1-8

There is evidence that mechanical risk factors such as notching of the superior part of the femoral neck during implantation,6,9-13 incomplete seating4,6,11,13,14 or varus alignment of the femoral component6,9,10,15 and post-operative lengthening of the femoral neck16 are not always the primary reasons for fracture.2,17 Instead, avascular necrosis (AVN) has been suggested as a common cause.2,13,18 Such proposals accord with evidence of disturbance and, in some cases, complete interruption of the blood supply to the femoral head and neck during surgery through a standard posterior approach.19-21 The duration of such ischaemia and its effect on the viability of the bone remains uncertain.19,22,23

It is generally accepted that AVN can be recognised by loss of osteocytes from the lacunae in trabecular bone.24 The osteocyte differential count is the ratio of normal osteocytes to empty lacunae25-34 and is an established method of evaluating the viability of trabecular bone. For example, Usui et al34 when investigating osteocyte changes in rabbits under ischaemic conditions, reported a gradual rise in the proportion of empty osteocyte lacunae with increasing time of ischaemia. An assessment of human auditory ossicles revealed a negative correlation between the proportion of empty lacunae and local vascularity.28 Widespread loss of osteocytes has been seen in tibiae of patients with severe peripheral vascular disease.35 Despite a well-documented relationship between ischaemia of bone and an increasing proportion of empty osteocyte lacunae, to our knowledge, the osteocyte differential count has not previously been employed or validated for use in the assessment of AVN in femoral bone.

The aim of our study was to validate the osteocyte differential count for the assessment of AVN in the femoral head. We then planned to determine the proportion of empty osteocyte lacunae in samples from the femoral head in hip resurfacings that had failed due to fracture in order to see whether there was an association between AVN and fracture. Finally, we wished to assess osteocyte viability in samples from the femoral head in hip resurfacings which had failed for reasons other than fracture, and compare this to the fracture group.

Materials and Methods

Histological samples of 55 femoral heads from 55 patients were studied. They were classified into four groups: fracture, other, control-OA and control-AVN.
There were two assessment groups. The first consisted of specimens from the femoral head from resurfaced hips which had failed because of fracture of the neck (fracture; n = 19). The second contained resurfaced hips which had failed for reasons other than fracture (other; n = 13).

Specimens retrieved from femoral heads obtained during THR for advanced osteoarthritis and which were presumed not to be avascular, served as a negative control (control-OA; n = 13). Specimens from heads retrieved during THR for established AVN served as a positive control (control-AVN†; n = 10).

The fracture group was divided into two subgroups: fracture less than one month after the index procedure (late-fracture; n = 13) and fracture more than one month after the index procedure (late-fracture; n = 13). In the other group revision was required for pseudotumour in six cases (subgroup pseudotumour), for loosening of a component in four cases, and for infection, dislocation and implant fracture in one case each (subgroup other-non-pseudotumour; n = 7).

Table I gives an overview of the patient demographics in the groups and subgroups. The hip resurfacing implants used were the Birmingham Hip Resurfacing (Smith & Nephew, Birmingham, United Kingdom) and Conserve Plus (Wright Medical, Memphis, Tennessee). Each operation was performed through a posterior approach.

All specimens were processed using a standard protocol for the assessment of AVN in trabecular bone using light microscopy.36-38 After surgical extraction, samples were taken from within the femoral head, fixed in 10% phosphate-buffered formalin for 24 hours and decalcified with 5% nitric acid. Dehydration was performed by transferring samples through baths of progressively more concentrated alcohol. The samples were then embedded in wax (Formula R, Surgipath Europe Ltd, Peterborough, United Kingdom) for sectioning.

Thin sections (5 μm) were obtained using a bone microtome (RM 2135, Leica Microsystems Ltd, Milton Keynes, United Kingdom), and stained with Meyer haematoxylin and 1% aqueous eosin (Raymond Lamb, Eastbourne, United Kingdom). They were then analysed using light microscopy (Olympus DP 70 Microscope, Hamburg, Germany) combined with cell counting software (Cell F Soft Imaging System, Olympus Soft Imaging Solutions, Münster, Germany).36 All control sections and the majority of sections in the assessment group were cross-sections of the femoral head; the remainder were core biopsies. For microscopic assessment, each section was divided into four quadrants. In each quadrant, beginning with the left lower quadrant (Q1) and continuing clockwise (Q2 to Q4), one assessment field (field size 0.88 mm × 0.67 mm; magnification ×100) was chosen. One additional randomly selected field (Q5) within the same section was also selected.

The percentage of empty osteocyte lacunae in each quadrant was determined using the method of Humphreys et al.39 Each lacuna containing an osteocyte that filled more than 50% of its overall area was considered to contain a viable osteocyte (Fig. 1a). The remaining lacunae were considered empty and the osteocytes were deemed to be dead (Fig. 1b).39-41

For each sample, the mean percentage of empty lacunae in the five quadrants was determined.40 Each sample was analysed by the same investigator (RTS), who was blinded to the underlying diagnosis. Artefacts, such as areas where bone marrow obscured the trabeculae or where trabeculae were crossed, were avoided.

Repeatability. Ten samples were analysed by two observers to assess inter-observer error and the analysis was repeated by one of the observers to determine the intra-observer error (n = 10). In addition, the second observer assessed the variability between different microscopic fields within identical sections (n = 10) and the variability between different sections of identical patient samples (n = 10). The results of these assessments were expressed as the SD of the measured difference, as described by Bland and Altman.42

Statistical analysis. The difference in the percentage of empty lacunae between the two control groups was examined, and the specificity and sensitivity of the osteocyte differential count given by the percentage of empty lacunae, were determined using a receiver operating characteristic analysis based on the data for these two groups. The primary outcome measure was the mean percentage of empty

Table I. Patient statistics in all reviewed groups and subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Male</th>
<th>Female</th>
<th>Left</th>
<th>Right</th>
<th>% Primary OA† (N)</th>
<th>% Other OA* (N)</th>
<th>Mean age index procedure (range)</th>
<th>Mean age revision procedure (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control-OA</td>
<td>13</td>
<td>6</td>
<td>7</td>
<td>9</td>
<td>4</td>
<td>100 (13)</td>
<td>0 (0)</td>
<td>73.9 (59 to 88)</td>
<td>Not revised</td>
</tr>
<tr>
<td>Control-AVN†</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>2</td>
<td>0 (0)</td>
<td>100 (10)</td>
<td>71.1 (55 to 90)</td>
<td>Not revised</td>
</tr>
<tr>
<td>Fracture</td>
<td>19</td>
<td>13</td>
<td>6</td>
<td>9</td>
<td>10</td>
<td>79 (15)</td>
<td>21 (4)</td>
<td>57.9 (37 to 73)</td>
<td>57.9 (37 to 73)</td>
</tr>
<tr>
<td>Fracture-early</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>80 (5)</td>
<td>20 (1)</td>
<td>60.4 (46 to 71)</td>
<td>60.4 (46 to 71)</td>
</tr>
<tr>
<td>Fracture-late</td>
<td>13</td>
<td>9</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>77 (10)</td>
<td>23 (3)</td>
<td>56.2 (37 to 73)</td>
<td>56.8 (37 to 73)</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>3</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>77 (10)</td>
<td>23 (3)</td>
<td>49.0 (20 to 65)</td>
<td>51.4 (23 to 66)</td>
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<tr>
<td>Pseudotumour</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>83 (5)</td>
<td>17 (1)</td>
<td>43.3 (29 to 58)</td>
<td>46.8 (33 to 61)</td>
</tr>
<tr>
<td>Other-non pseudotumour</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>71 (5)</td>
<td>29 (2)</td>
<td>53.8 (20 to 65)</td>
<td>55.2 (23 to 66)</td>
</tr>
</tbody>
</table>

* OA, osteoarthritis
† AVN, avascular necrosis
lacunae averaged across the quadrants in each section. The primary analysis was the comparison between heads revised for fracture and those for other causes. The Mann-Whitney U test was employed to compare data from different groups. For all tests, Statistical Package for Social Sciences version 15.0 was used (SPSS Inc., Chicago, Illinois). Statistical significance was set at \( p < 0.05 \).

**Results**

The results of inter- and intra-observer error, field and section variability measurements are summarised in Table II. The variability (SD 2) of measurements from two separate sections of the same femoral head was 7%.

The percentage of empty lacunae in samples from the negative control group Control-OA was 9% (SD 4) and in samples from the positive control group Control-AVN 85% (SD 5; Table III). The difference between the two control groups was highly significant \( (p < 0.001; \text{Table IV}) \) and the ranges were far apart (Fig. 2). The area under the receiver operating characteristic curve was 1.0. A threshold of 16.6% empty lacunae gave a 100% sensitivity for detecting AVN with a specificity of 92.3%: using a threshold of 47.2% gave 100% sensitivity with 100% specificity.

In the fracture group the percentage of empty lacunae was 71% (SD 22) and in the other group it was 21% (SD 13). The difference between these two groups was highly significant \( (p < 0.001; \text{Table IV, Fig. 2}) \).

In the fractures that occurred less than one month after the index procedure (fracture-early) the percentage of empty lacunae (48%, SD 19) was significantly lower \( (p = 0.001) \) than in the fractures occurring more than one month after the index procedure (fracture-late) (84%, SD 12; Tables III and IV).

Differences were also found within the other group (Table IV). The revisions for pseudotumour had significantly \( (p = 0.003) \) more empty lacunae than those for causes other than pseudotumour.

**Discussion**

Standard histological techniques tend not to be quantitative and are therefore open to large inter-observer errors. As a result, different histopathologists may interpret the same specimen differently. It is also difficult to compare findings from different centres. In order to address this, we developed a quantitative assessment for evaluating ischaemic bone change in the femoral head, based on the percentage.

![Fig. 1a](image1.png) ![Fig. 1b](image2.png)

Microscopic picture of a) viable osteocytes (white arrows) in osteoarthritic bone and b) empty osteocyte lacunae (white arrows) and appositional new bone formation (black arrow) after failure of hip resurfacing due to fracture.

<table>
<thead>
<tr>
<th>Table II. Repeatability measurements</th>
<th>Empty lacunae (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 10</strong></td>
<td></td>
</tr>
<tr>
<td>Intra-observer error (same microscopic field; same observer)</td>
<td>0.02</td>
</tr>
<tr>
<td>Inter-observer error (same microscopic field; different observer)</td>
<td>1.37</td>
</tr>
<tr>
<td>Field variability (different microscopic field; same section)</td>
<td>0.89</td>
</tr>
<tr>
<td>Section variability (different section; same patient)</td>
<td>2.10</td>
</tr>
<tr>
<td>Mean</td>
<td>0.91</td>
</tr>
<tr>
<td>SD</td>
<td>6.79</td>
</tr>
<tr>
<td>SD</td>
<td>2.39</td>
</tr>
<tr>
<td>SD</td>
<td>3.74</td>
</tr>
</tbody>
</table>
of empty osteocyte lacunae. The wide range between the positive and negative controls and a small inter-observer error demonstrate that this is a useful technique for quantifying AVN (Fig. 2). The receiver operating characteristic analysis also demonstrated that the technique has excellent sensitivity and specificity for detecting AVN, a threshold of 47.2% empty lacunae having 100% specificity and 100% sensitivity for detecting its presence.

The 19 samples retrieved after fracture of the femoral neck had a significantly higher mean percentage (71%) of empty osteocyte lacunae than those from osteoarthritic controls (9%; Fig. 2). If the fractures occurred after one month, 85% of the osteocyte lacunae were empty, whereas in fractures occurring before one month 48% of the lacunae were empty. The percentage of empty lacunae in the late fracture group was identical to the percentage observed in AVN controls (85%). This is powerful evidence to suggest that the femoral heads retrieved after fracture occurring more than one month after resurfacing, are avascular. In contrast, femoral heads retrieved after failure of resurfacing for other reasons have a percentage of empty osteocyte lacunae (21%) that is nearer the OA controls (9%) than the AVN controls (84%).

Our findings are substantiated by a review of the evidence in the literature. Meta-analysis of the results obtained from histological examination of femoral heads retrieved after revision of a hip resurfacing for fracture shows that avascular necrosis was present in 60% of cases. The incidence of AVN in bone samples retrieved for reasons other than fracture was 6% (Table V).13,22,43-50 None of the femoral heads retrieved after fracture had a primary diagnosis of AVN. Therefore, either AVN caused the fracture or the fracture caused AVN. A fracture could only cause AVN if it progressed slowly and interrupted the intraosseous blood supply to the head, rendering it avascular. As the blood supply to the head is predominantly extraosseous, it is unlikely that AVN is a result of the fracture. Therefore, we suggest
that damage to the blood supply at operation may lead to avascular necrosis and fracture.

Fractures after resurfacing tend to occur during normal activities of daily living and not as a result of trauma. For these to occur the bone must be substantially weakened. The mechanisms by which bone weakens soon after ischaemia are closely related to the processes of repair. Phemister\textsuperscript{51} termed this repair system, which after initiation requires months or years to be completed, ‘creeping substitution’. It involves revascularisation and ingrowth of osteogenic tissue which originates in vascularised bone in direct contact with the avascular region.\textsuperscript{52} Proliferating cells spread through the marrow spaces between the dead trabeculae, differentiate into osteoblasts, and subsequently form appositional new bone on the surface of dead trabeculae.\textsuperscript{53} At the same time, they initiate osteoclastic resorption of necrotic bone. Osteoclastic resorption, modulated by cytokines released from osteoblasts, is crucial for the balance of the repair processes. The bone may be markedly weakened if resorption occurs at the interface of the viable and dead bone, or if revascularisation and new bone formation in necrotic areas is prevented by the formation of a fibrous scar.\textsuperscript{54}

Rösingh, Steendijk and van den Hooff\textsuperscript{55} found evidence of this process in an experimental study conducted on rabbits, when they observed extensive resorption of avascular bone and deposition of new woven bone, three to six weeks after disruption of the blood supply to the femoral head.

In our study, samples from late fractures had a significantly higher proportion of empty lacunae than samples from fractures occurring within the first month after hip resurfacing. The proportion of empty lacunae gradually increased as the time since operation increased. The highest percentages of empty lacunae were seen between four weeks and eight months after the operation. Similar findings have been reported after experimental disruption of the blood supply in rabbits, and in fractures of the femoral neck not associated with resurfacing in humans.\textsuperscript{35,56} The reason for this is likely to be the time it takes for the effect of ischaemia to be seen under light microscopy. Changes of osteocyte morphology can be seen with the electron microscope up to four hours after the onset of ischaemia,\textsuperscript{57,58} and by review of chromatin mesh structures up to 12 hours later. Such early changes are not apparent under the light microscope for two to four weeks.\textsuperscript{34,56,59} An alternative explanation for the more normal appearance of the femoral head after fractures occurring within one month is that they were caused by mechanical weakening of the bone at surgery and not by AVN.

The proportion of empty lacunae in the other group differed significantly between the subgroups revised for a pseudotumour and for other modalities of failure (Fig. 3). The avascular changes in cases of pseudotumour were more pronounced. The most likely reason for this is that the increased intracapsular pressure caused by the cystic pseudotumour compromises the blood supply to the femoral head.

This study suggests that AVN of the femoral head can cause fractures of the neck after hip resurfacing. The AVN is likely to be a result of disruption of the blood supply to the femoral head at the time of operation. The deep branch of the medial femoral circumflex artery, which provides most of the blood supply to the femoral head, is divided in a standard posterior approach.\textsuperscript{19-21} Substantial weakening of the neck may occur as a result of the bone resorption, which forms part of the remodelling process in avascular areas of the femoral head and neck. It is therefore recommended that a surgical approach that preserves the blood supply, such as those of Hardinge or Ganz\textsuperscript{60-64} should be used. It is also possible to preserve the blood supply by using a modified posterior approach that does not disturb the anastomoses around the trochanter.\textsuperscript{64}

<table>
<thead>
<tr>
<th>Study</th>
<th>Fractures AVN</th>
<th>No AVN</th>
<th>Other causes of failure AVN</th>
<th>No AVN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bradley et al\textsuperscript{66}</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>2. Howie et al\textsuperscript{65}</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>65</td>
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<td>3. Campbell et al\textsuperscript{4}</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>4. Bogoch et al\textsuperscript{45}</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>5. Little et al\textsuperscript{53}</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>6. Head\textsuperscript{46}</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>7. Bell et al\textsuperscript{67}</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>8. Treacy et al\textsuperscript{48}</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>9. Daniel et al\textsuperscript{49}</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10. Pollard et al\textsuperscript{50}</td>
<td>1</td>
<td>0*</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>11. Furuya et al\textsuperscript{67}</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Total</td>
<td>16</td>
<td>9</td>
<td>27</td>
<td>134</td>
</tr>
</tbody>
</table>

* two fracture cases were excluded as no information regarding the outcome of histological assessment was provided

Table V. Literature evidence of the incidence of avascular necrosis (AVN) in retrieved bone samples after failure of hip resurfacing.

Box and whisker plot showing the percentage of empty lacunae in groups pseudotumour, other-non pseudotumour, fracture-early and fracture-late.
There are a number of limitations to this study. The microscopic fields assessed do not represent the entire bone of the femoral head, but evaluation of a number of samples obtained from different parts of the head gave similar results. Methods of histological preparation can influence the presence or absence of osteocytes within the bone.\textsuperscript{65} Nevertheless, the data from the different groups were consistent, suggesting that this was not an important problem. In order to avoid any possible misinterpretation of osteocyte viability during the counting process under the light microscope, we considered as viable only those lacunae that contained an osteocyte filling more than half its area. This may underestimate the percentage of viable osteocytes. However, if it does, the same underestimation applied to all measured groups and subgroups.\textsuperscript{41}

This study demonstrates that AVN is associated with fracture after hip resurfacing. The association is particularly high for fractures that occur more than one month after resurfacing. We believe that bone resorption resulting from the AVN, caused by damage to the blood supply at operation, weakens the bone and is an important cause of fracture. In early fractures the incidence of AVN is not so high, and so mechanical factors are likely to be more important.

**Supplementary material**

An XY scatterplot showing the percentage of empty osteocyte lacunae and fracture timing for individual cases in group fracture is available with the online version of this article on our website at www.jbjs.org.uk

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No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**References**

AVASCULAR NECROSIS ASSOCIATED WITH FRACTURE OF THE FEMORAL NECK AFTER HIP RESURFACING


