Reduced bone formation in UK Gulf War veterans: a bone histomorphometric study

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Methods: Iliac crest bone biopsies were obtained from 17 Gulf War veterans who were seeking litigation and compared with those of 13 age and sex matched healthy controls. Bone histomorphometry was performed using image analysis.

Results: Cancellous bone area was significantly lower in Gulf War veterans than in control subjects (p = 0.027) and this was associated with a significantly reduced mineral apposition rate (p = 0.002), mean wall width (p < 0.0001), and bone formation rate at the tissue level (p < 0.0001).

Conclusions: These results demonstrate that in this group of Gulf War veterans there was a significant reduction in bone formation at both the cellular and tissue level and this was associated with a reduction in cancellous bone area. The cause of these abnormalities is unknown but might be related to potentially harmful exposures during service in the Gulf War or to changes in life style as a result of chronic ill health. The clinical relevance of the observed reduction in bone formation remains to be established.

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The mean distance between double labels was measured directly at ×312 magnification. Measurements were made at approximately four equidistant points along each double label. A minimum of 20 labels was measured for each biopsy on a minimum of six sections.

Mineral apposition rate (MAR) was calculated as:

\[ \text{MAR (µm/day)} = \frac{L.Wi}{LP} \]

where L.Wi is the interlabel width and LP is the labelling period (12 days).

The tissue based bone formation rate (BFR/B.Pm) was calculated as follows:

\[ \text{BFR/B.Pm (µm²/µm²/day)} = \text{MAR} \times \left( \frac{M.Pm}{B.Pm}\% \right). \]

Activation frequency was calculated as:

\[ \text{Acf (/year)} = \frac{\text{BFR/B.Pm}}{W.Wi}. \]

Strut analysis, trabecular bone pattern factor, and marrow star volume were assessed as reported previously.\(^{13}\) Control data were obtained from 13 healthy men who formed part of an earlier study of normal bone,\(^{13}\) in which iliac crest biopsies were obtained from normal subjects during general anaesthesia for a minor surgical procedure. The mean age of these controls was 36.6 years (range, 19–51). Results of histomorphometric analysis performed previously using an eye piece graticule and micrometre were used because sections were no longer available from this cohort. The measurements in biopsies from the controls and Gulf War veterans were made by the same observer (SV). Statistical analysis was performed using an unpaired Student’s t test after log transformation of the data. Results are expressed as the mean (SD).

**RESULTS**

**Demographic details and bone mineral density**

The age of the veterans at the time of the study ranged between 27 and 51 years (mean, 34.9). They had spent between two and four months in the Gulf during the war and most had spent time in a blackadder camp where there was obvious spraying of organophosphates. At least four were aware of exposure to sarin but it was not possible to obtain an accurate vaccination history. All but one complained of musculoskeletal symptoms (most commonly arthralgia) but none had a history of low trauma fracture. Seven of the men were regular cigarette smokers, six of whom smoked more than 15 daily, and four had an alcohol intake in excess of 10 alcohol units weekly (16, 40, 40, and 50 units, respectively).

The mean bone mineral density in the lumbar spine (L2–4), expressed as a Z score, was +0.55 (range, −1.6 to +2.3) and in the proximal femur (femoral neck) was +0.45 (range, −0.7 to +1.9). None of the men had osteoporosis as defined by a T score below −2.5.\(^{16}\) Body weight ranged between 64 and 120 kg (mean, 85.2).

**Table 1 Gulf war group v controls**

<table>
<thead>
<tr>
<th>Indices</th>
<th>Gulf war group</th>
<th>Control group</th>
<th>p Value (log transformed independent t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>17</td>
<td>13</td>
<td>&lt;0.599</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.9 (6.4)</td>
<td>36.6 (10.7)</td>
<td>&lt;0.027</td>
</tr>
<tr>
<td>Trabecular bone area (%)</td>
<td>20.5 (5.3)</td>
<td>25.3 (6.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Osteoid perimeter (%)</td>
<td>8.5 (4.5)</td>
<td>23.7 (10.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mineralising perimeter (%)</td>
<td>4.5 (3.1)</td>
<td>11.3 (5.8)</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>Mineral apposition rate (µ/day)</td>
<td>0.58 (0.19)</td>
<td>0.77 (0.12)</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Bone formation rate (µm²/µm²/day)</td>
<td>0.028 (0.021)</td>
<td>0.087 (0.044)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Activation frequency (/year)</td>
<td>0.24 (0.16)</td>
<td>0.54 (0.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Eroded perimeter (%)</td>
<td>5.98 (2.64)</td>
<td>1.87 (0.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wall width (µm)</td>
<td>42.5 (4.3)</td>
<td>57.8 (7.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean (SD).

**DISCUSSION**

Our results demonstrate that in this group of Gulf War veterans there was a significant reduction in bone formation, both at the cellular and tissue level, in association with a reduction in cancellous bone area. Although the eroded perimeter was increased compared with the controls, this was generally of a small magnitude and the scarcity of osteoclasts in association with resorption cavities indicates that reduced bone formation rather than increased resorption was the most likely cause of the observed increase.

“it is of interest that the bone abnormalities observed in these Gulf War veterans were similar to those recently reported in agricultural workers with chronic organophosphate exposure as a result of sheep dipping”

The control values used in our study were obtained from healthy men in whom bone biopsies had been obtained previously.\(^{13}\)\(^{17}\) Because of the time that had elapsed between that study and our present one, it was not possible to obtain and quantify fresh sections so that the results of an earlier histomorphometric analysis made by the same observer (SV) were used. Although some differences may arise as a result of inter-method variations,\(^{13}\)\(^{17}\) these are generally small and cannot explain the observed differences between the Gulf War
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Take home messages

- In this group of Gulf War veterans, cancellous bone area was significantly reduced and this was associated with a significant reduction in mineral apposition rate, mean wall width, and bone formation rate at the tissue level.
- The cause of these abnormalities is unknown but might be related to potentially harmful exposures during service in the Gulf War (such as exposure to organophosphates or pyridostigmine) or to changes in lifestyle as a result of chronic illness.
- The clinical relevance of the observed reduction in bone formation remains to be established.

veterans and controls, particularly with respect to indices such as wall width, mineral apposition rate, and mineralising surface. The cause of the reduction in bone formation seen in these biopsies cannot be ascertained from our study. One possibility is that changes in the lifestyle of these subjects may have been responsible— for example, tobacco and excessive alcohol consumption and reduced levels of physical activity. However, in this cohort there was no clear relation between any of these variables and indices of bone remodelling and turnover. Alternatively, it is possible that the abnormalities may have arisen as a result of one or more of the chemical exposures experienced by the veterans. It was not possible to ascertain precisely either the nature or degree of these in this cohort, but nearly all have a history of definite or probable organophosphate exposure and, in addition, pyridostigmine was widely used by servicemen during the Gulf War. It has recently been reported that acetylcholinesterase is expressed by osteoblasts; its presence in bone matrix along cement lines and in osteoid indicates that it may have an extracellular role in bone. Furthermore, the demonstration of Cbfa-1 and other osteogenic factor binding motifs on the acetylcholinesterase gene promoter also indicates a role for acetylcholinesterase in bone formation and provides a potential mechanism for reduction in bone formation in individuals exposed to organophosphates. In this context, it is of interest that the bone abnormalities observed in these Gulf War veterans were similar to those recently reported in agricultural workers with chronic organophosphate exposure as a result of sheep dipping.

The clinical relevance of the observed changes in bone formation is unclear. Reduced bone formation at the cellular level is associated with trabecular thinning which, although initially associated with the preservation of cancellous bone architecture, will eventually progress to trabecular penetration with loss of connectivity. In addition, low bone turnover results in an increase in bone age and increased secondary mineralisation, changes that may lead to increased microdamage and reduced mechanical strength.

References

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