Lead Exposure and Osteoporosis

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University of Rochester School of Medicine and Dentistry
Dempster, DW et al, J Bone Miner Res 1986; 1:15-21
Impact of Osteoporosis

• 17% of women over age 50 years
• 6 million women have osteoporosis, and 17 million women have osteopenia
• 269,000 hospital discharges for hip fracture in 1991
• $10-15 billion per year
Impact of Osteoporosis

• Nearly 1/3 of patients with osteoporotic hip fractures enter a nursing home within a year
• 20% of patients die within 1 year after an osteoporotic hip fracture
Does lead poisoning cause osteoporosis?
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Criteria to Establish Causation

• The exposure must precede outcome.
• Studies show an association between exposure and outcome.
• The association shows a dose-response relation.
• The association is strong.
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# Lead and Bone Mineral Density

## NHANES Analysis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Female</th>
<th></th>
<th></th>
<th>Male</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>White</td>
<td>African-American</td>
<td>White</td>
<td>African-American</td>
<td></td>
</tr>
<tr>
<td>Adjusted mean (SE) BMD (g/cm²)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>0.789 (0.006)</td>
<td>0.898 (0.010)</td>
<td></td>
<td>0.961 (0.007)</td>
<td>1.036 (0.011)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>0.776&lt;sup&gt;b&lt;/sup&gt; (0.006)</td>
<td>0.882 (0.009)</td>
<td></td>
<td>0.944&lt;sup&gt;c&lt;/sup&gt; (0.006)</td>
<td>1.023 (0.010)</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>0.771&lt;sup&gt;b&lt;/sup&gt; (0.007)</td>
<td>0.873 (0.012)</td>
<td></td>
<td>0.934&lt;sup&gt;c&lt;/sup&gt; (0.009)</td>
<td>1.011 (0.013)</td>
<td></td>
</tr>
</tbody>
</table>

Lead and Bone Mineral Density
Occupationally Exposed Chinese

Sun Y. Am J Ind Med. 2008;51:436-442
# Lead and Bone Mineral Density

**Female Lead Smelters**

<table>
<thead>
<tr>
<th>Blood Lead Level Percentile</th>
<th>% Change in BMD from 1994 to 2000</th>
</tr>
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<tbody>
<tr>
<td>≥90 percentile</td>
<td>-10.38%</td>
</tr>
<tr>
<td>&lt;90 percentile</td>
<td>-1.33%</td>
</tr>
</tbody>
</table>

Potula V. Am JOEM. 2006;48:556-564.
Lead and Bone Mineral Density Study of Osteoporotic Fractures

<table>
<thead>
<tr>
<th>Level (μg/dl)</th>
<th>Low (≤3)</th>
<th>Medium (4–7)</th>
<th>High (≥8)</th>
</tr>
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<tbody>
<tr>
<td>N = 533</td>
<td>N = 122</td>
<td>N = 332</td>
<td>N = 79</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip [mean (SD)]</td>
<td>0.77 (0.13)</td>
<td>0.76 (0.13)</td>
<td>0.72 (0.12)</td>
</tr>
<tr>
<td>Femoral neck [mean (SD)]</td>
<td>0.65 (0.11)</td>
<td>0.66 (0.12)</td>
<td>0.62 (0.09)</td>
</tr>
<tr>
<td>Calcaneus [mean (SD)]</td>
<td>0.41 (0.09)</td>
<td>0.42 (0.09)</td>
<td>0.39 (0.09)</td>
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Lead and Fracture Incidence Study of Osteoporotic Fractures

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Lead and BMD in Mice

Beier EE. Environ Health Perspect. 2013;121:97-104
Lead & BMD in Mice

Lead & Bone Strength in Mice

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<th>Percent BMD of Exposed to Unexposed</th>
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<td>Khalil, 2008</td>
<td>0.770</td>
<td>0.720</td>
<td>0.94</td>
</tr>
<tr>
<td>Sun, 2008</td>
<td>0.757</td>
<td>0.739</td>
<td>0.97</td>
</tr>
<tr>
<td>Potula, 2006</td>
<td>1.065</td>
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Lead & Cartilage Formation

Lead & Cartilage Formation

Lead & Fracture Healing in Rats

Lead in Water

0 ppm

55 ppm

230 ppm
Lead & Fracture Healing in Rats

Chondrogenesis

Undifferentiated Mesenchyme → Cartilagenous Skeletal Template → Immature Chondrocytes

(+) Pb^{2+} (-)  

Endochondral Ossification

Bone Growth
Fracture Healing
Lead and Cartilage/Bone Formation

In a normal skeleton.....

Bone Resorption = Bone formation
Hypothesis

Bone Mineral Density

Fracture Threshold

Age

Males

Females

Hypothetical
Pb Exposed
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Today’s Random Medical News

According to a report released today...

CAN CAUSE

HYPERTHERMIA
HYPERPYRA
SPONTANEOUS
BREAST
DEPRESSION

IN

FOOD
SMOKING
EXERCISE
STRESS
RED WINE
COFFEE
COMPUTER TERMINALS
PAIN CARE

CHILDREN
TWIN
ARTHRITIS SUFFERERS
7 OUT OF 10 WOMEN

MEN 25-40
OVERWEIGHT SMOKERS
RATS
TWO-INCOME FAMILIES

Lead & BMD in Mice

Gruber H. Miner Electrolyte Metab. 1997;23:65-73
Lead & Fracture Healing in Rats

Lead & BMD in Rats

**Lead & Bone Turnover in Humans**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Blood lead levels</th>
<th>Calcaneus-bone lead levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤90th ( M )</td>
<td>&gt;90th ( M )</td>
</tr>
<tr>
<td>Calcium &amp; bone turnover markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml)</td>
<td>59.0</td>
<td>42.5*</td>
</tr>
<tr>
<td>Vitamin D (pg/ml)</td>
<td>45.7</td>
<td>25.1*</td>
</tr>
<tr>
<td>Ionized calcium (mg/dl)</td>
<td>4.9</td>
<td>5.1</td>
</tr>
<tr>
<td>Total calcium (mg/dl)</td>
<td>8.9</td>
<td>9.2**</td>
</tr>
<tr>
<td>Bone turnover markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary pyridinoline</td>
<td>47.2</td>
<td>77.8*</td>
</tr>
<tr>
<td>Urinary deoxypyridinoline</td>
<td>11.6</td>
<td>20.2*</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>17.0</td>
<td>9.9</td>
</tr>
</tbody>
</table>

Lead & BMD in Mice

# Lead & BMD in Mice

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>Exp</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tr* volume</td>
<td>21.8%</td>
<td>17.8%</td>
<td>0.041</td>
</tr>
<tr>
<td>Tr number</td>
<td>3.5</td>
<td>2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Tr thickness</td>
<td>64</td>
<td>56</td>
<td>0.028</td>
</tr>
<tr>
<td>Tr space</td>
<td>359</td>
<td>556</td>
<td>0.022</td>
</tr>
</tbody>
</table>

* Trabecular

Escribano A. Calcif Tissue Int. 1997;60:200-3