Isn’t It Ironic:
BMPs and the Relationship Between Iron and Bone

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General Outline

Iron & Osteopenia

Lactoferrin

Iron

Bone

BMPs

Hepcidin and HJV/BMP/SMAD4
Iron & Bone: Hereditary Hemochromatosis

- Autosomal recessive disorder
- Due to common mutation in HFE gene
- Low clinical penetrance
- Hepatic iron overload
- Low hepcidin levels
Iron and Osteopenia

- Sickle Cell Disease
- Thalassemia
- HH
- Transfusion iron overload
- Post-menopause
Bone Disease in Hemochromatosis

- Fractures
  - case reports
- Osteoporosis
  - 29-34%
- Osteopenia
  - 71-79%
Stainable bone iron in undecalcified, plastic-embedded sections. Occurrence in man related to the presence of "free" iron
H Laeng, T Egger, C Roethlisberger and H Cottier

- 2.3% of 1536 iliac crest biopsies in patients without HH
- 4/4 with HH
- 11/15 vertebral bone fragments with HH
- Correlates with presence of NTBI
- Found at “osteoid seam”

Iron Lactate-Induced Osteopenia in Male Sprague-Dawley Rats

Shuuichi Matsushima,¹,² Mariko Hoshimoto,¹ Mikinori Torii,¹ Kiyokazu Ozaki,² and Isao Narama²

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²Research Institute of Drug Safety, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka, 573-0101, Japan
Hemochromatotic Salers Cattle

Salers kindred with hemochromatosis

- Phenotypically normal male, female
- Phenotypically normal male, female – presumed carrier
- Hemochromatosis-affected female
Hemochromatotic Salers Cattle
Skeletal Changes in Hemochromatosis of Salers Cattle

R. W. Norrdin, K. J. Hoopes, and D. O’Toole

Iron, ppm

<table>
<thead>
<tr>
<th>Inner cortex</th>
<th>Outer cortex</th>
</tr>
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<tbody>
<tr>
<td>5.36</td>
<td>9.76</td>
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</table>

Wild Type Hemochromatosis
Age-associated Iron Accumulation in Bone: Implications for Postmenopausal Osteoporosis and a New Target for Prevention and Treatment by Chelation

Liu G, Men P, Kenner GH, Miller SC

- Ovarectomized rat model of postmenopausal osteoporosis
- Severity of osteoporosis associated with iron accumulation in bone
- Mitigated by bone-targeted chelator

Biometals. 2006 May 11
Potential Mechanisms for Iron-Related Osteopenia

- Hypogonadism
- Hyperparathyroidism
- Iron toxicity
- “Unknown factor”
Lactoferrin Is a Potent Regulator of Bone Cell Activity and Increases Bone Formation in Vivo

JILLIAN CORNISH, KAREN E. CALLON, DORIT NAOT, KATE P. PALMANO, TATJANA BANOVIC, USHA BAVA, MAUREEN WATSON, JIAN-MING LIN, P. C. TONG, QI CHEN, VINCENT A. CHAN, HELEN E. REID, NICK FAZZALARI, HEATHER M. BAKER, EDWARD N. BAKER, NEILL W. HAGGARTY, ANDREW B. GREY, AND IAN R. REID

- **Lactoferrin**
  - Member of transferrin family
  - Iron binding protein
  - Produced by exocrine glands, neutrophils

- **Anabolic to bone**
  - Stumulator of osteoblast proliferation, differentiation
  - Inhibitor of osteoclastogenesis

Endocrinology 145(9):4366–4374, 2004
General Outline

Iron & Osteopenia
Lactoferrin

Iron

Bone

Hepcidin and
HJV/BMP/SMAD4

BMPs
A role of SMAD4 in iron metabolism through the positive regulation of hepcidin expression

Rui-Hong Wang,¹, ⁵ Cuiling Li,¹, ⁵ Xiaoling Xu,¹ Yin Zheng,¹ Cuiying Xiao,¹ Patricia Zerfas,² Sharon Cooperman,³ Michael Eckhaus,² Tracey Rouault,³ Lopa Mishra,⁴ and Chu-Xia Deng¹, *
Loss of Hepcidin Regulation in Haptocellular SMAD4 KO Mice
BMPs Regulate Hepatocellular Hepcidin Expression
Bone morphogenetic protein signaling by hemojuvelin regulates hepcidin expression

Jodie L Babitt¹, Franklin W Huang², Diedra M Wrighting², Yen Xia¹, Yisrael Sidi³, Tarek A Samad⁴, Jason A Campagna⁴, Raymond T Chung⁵, Alan L Schneyer⁵, Clifford J Woolf⁴, Nancy C Andrews²,⁶ & Herbert Y Lin¹
<table>
<thead>
<tr>
<th>Name(^a)</th>
<th>Alternative name</th>
<th>Potential functions</th>
<th>Bone induction model studied</th>
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<tr>
<td>BMP-2</td>
<td>BMP-2A</td>
<td>Cartilage and bone morphogenesis</td>
<td>Rodent, subcutaneous</td>
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<tr>
<td>BMP-3</td>
<td>Osteogenin</td>
<td>Bone formation</td>
<td>Rodent, subcutaneous</td>
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<tr>
<td>BMP-3B</td>
<td>GDF-10</td>
<td>Bone formation</td>
<td>NS</td>
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<td>BMP-4</td>
<td>BMP-2B</td>
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<td>OP-1</td>
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<td>OP-2</td>
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<td>–</td>
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<td>Ligament and tendon development</td>
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<td>Cartilage development and hypertrophy</td>
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<td>BMP-14</td>
<td>GDF-5, CDMP-1, CDMP-2</td>
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<td>NS</td>
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<td>TGF-β1</td>
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<td>NS</td>
<td>Primate, intramuscular</td>
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<tr>
<td>TGF-β2</td>
<td>–</td>
<td>NS</td>
<td>Primate, intramuscular</td>
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</tbody>
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Effect of BMPs on Hepcidin mRNA in HuH7 Cells
TGFB and BMP Regulation of Hepcidin in Human Hepatoma (HuH7) Cells

hepcidin mRNA (relative to control)

Control | BMP | TGF

* Significance indicated by asterisk.
Effect of Iron on BMP-Induction of Hepcidin Expression
Effect of Iron on TGFβ Signaling in HuH7 Cells

![Graph showing effect of iron on hepcidin mRNA expression](image)
NTBI in Hemochromatosis

Transferrin Saturations

- Transferrin saturation (%)
- +/- m/m

NTBI

- µM Fe
- +/- m/m

* Indicates statistical significance.
Increased NTBI and Decreased Hepcidin

- HFE, Tfr2, HJV associated HH
- Atransferrinemia
- Acute hemolysis
Increased NTBI, Decreased Hepcidin, Osteopenia

• HH
• Sickle cell
• Beta thalassemia
Speculative Model

• Holotransferrin increases hepcidin
• Elemental iron decreases BMP signaling
• In iron overload, increased elemental iron attenuates BMP signaling
• Decreased BMP signaling leads to
  – Decreased hepcidin
  – Osteopenia