2019 Interdisciplinary Symposium on Osteoporosis

Friday, May 17, 2019
1:15 pm – 2:15 pm

Bone Modeling: An Old Idea Revisited with Implications for Osteoporosis Treatment

David Dempster, PhD, FRMS

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Modeling-based Bone Formation: An Old Concept Revisited
- with Implications for the Treatment of Osteoporosis

David W. Dempster, BSc (Hons), PhD, FRMS

Columbia University
and
Helen Hayes Hospital
New York

ISO2019 La Jolla, CA, May 17, 2019
Disclosures

- Eli Lilly & Co.: Consultant, Research Grants
- Amgen Inc.: Consultant, Speaker’s Bureau, Research Grants
- Radius Health: Consultant, Speaker’s Bureau, Research Grants
Cortical and Cancellous Bone

80% of the human skeleton is Cortical Bone\(^1\)

- **Thoracic spine**: >75% cancellous
- **Lumbar spine**: >66% cancellous
- **Femoral neck**: 75% cortical, 25% cancellous
- **Trochanter**: 50% cortical, 50% cancellous
- **1/3 distal radius**: >95% cortical
- **Ultradistal radius**: 75% cortical, 25% cancellous


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Bone is a complex, continuously remodeled tissue

- The adult skeleton is completely regenerated every 10 years
- 3-4 million bone remodeling units (BRUs) are initiated each year
- 1 million BRUs are actively engaged in bone turnover at any time

Bone Remodeling

- Replacement of old or damaged bone with new bone
  - Osteoclasts and osteoblasts in the same remodeling units
  - Persists for a lifetime
  - Abnormalities cause low or high bone mass syndromes

Courtesy of Roberto Civitelli, MD
Remodeling on Endocortical, and Periosteal and Cancellous Surfaces
Hemi-osteonal Remodeling on Endocortical, Periosteal and Cancellous Surfaces

Dempster et al, JBMR 2001; 16:846
Intracortical Remodeling
Osteonal Remodeling in Cortical Bone
Osteonal Remodeling in Cortical Bone

Clopton Havers, 1691

Reprinted from The Lancet, Dempster DW, Lindsay R. 1993;341:797-801. Copyright 2011, with permission from Elsevier.
Osteonal Remodeling in Iguanodon Bone from the Cretaceous Period (~130 M yr)

Image courtesy of Tim Skerry and John Currey.
Functions of Remodeling

- Calcium homeostasis (long-term)
- Maintain mechanical strength
- Acid/base balance
- Release growth factors
- Provide reservoir of labile mineral (short-term homeostasis)
- Replace osteocytes
- ???
Functions of Remodeling

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• Maintain mechanical strength
• Acid/base balance
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• Provide reservoir of labile mineral (short-term homeostasis)
• Replace osteocytes
• ????
Tiktaalik

“From Fins to Limbs”

National Science Foundation
University of Chicago
Remodeling Participates in Mineral Homeostasis

Before antler formation

During antler formation

After antler formation

Remodeling Maintains Mechanical Strength
“Excessive Repair is a Risky Business”


Dempster et al, *JBMR* 1986;1:15
Targeted Remodeling

- Excessive strain causes regional microdamage
- Targeted remodeling removes a volume of bone that greatly exceeds that of damaged region
- Resulting volume deficit increases strain in neighboring bone


B. Martin, JOR 1995
Age-Related Changes in the Human Femoral Midshaft

Skeletal Integrity

Calcium Homeostasis

Images courtesy of Dr. David Cooper. University of Saskatchewan.
Bone Modeling

- The shaping of bone segments and their movement through space
  - Defines skeletal development and growth
  - Osteoblasts and osteoclasts need not be anatomically and temporally tethered
  - Abnormalities cause skeletal dysplasias or dismorphysms

Courtesy of Roberto Civitelli, MD
The Erlenmeyer Flask Deformity


Jean-François Ganghoffer (2011).
Tibial Modeling after Fibula Harvesting

A Touch of Frost

Hattner, Epker and Frost, Nature 1965
“…3.3% of the cement lines that were smooth could represent bone being formed without previous resorption…”

‘…they could also represent “overflow” of formation processes extending beyond the perimeter of the bone formation preceded by resorption…”

75 normal subjects, aged 20-75 (ribs, femoral heads, iliac crests, humeri, and vertebrae)

Rat Bone: Modeling or Remodeling?

Trabecular and Endocortical Bone Surfaces in the Rat: Modeling or Remodeling?

REINHOLD G. ERBEN
Institute of Physiology, Physiological Chemistry, and Animal Nutrition, University of Munich, Germany

ABSTRACT Background: There is conflicting evidence as to whether bone resorption and bone formation are coupled in the site-specific manner that is typical of bone remodeling in the rat. The aim of this study was to elucidate this controversy further by analysis of tibial and vertebral cancellous and endocortical bone in rats of different age groups with a combination of in vivo fluorochrome labeling with cement line staining.

Rat Bone: Modeling or Remodeling?

Erben et al, Anat Rec 1996
Trabecular Mini-modeling in Human Bone

34 normal subjects undergoing THR

Table 1
Histomorphometric data for minimodeling (mean ± SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>In 34 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.M1/BS (mm)</td>
<td>0.053 ± 0.085</td>
</tr>
<tr>
<td>N.M1/TV (mm²)</td>
<td>0.113 ± 0.193</td>
</tr>
<tr>
<td>N.M1/BV (mm²)</td>
<td>0.906 ± 1.360</td>
</tr>
<tr>
<td>M1.BV/TV (%)</td>
<td>0.084 ± 0.156</td>
</tr>
<tr>
<td>M1.BV/BV (%)</td>
<td>0.639 ± 1.096</td>
</tr>
<tr>
<td>M1.OV/BV (%)</td>
<td>0.152 ± 0.328</td>
</tr>
<tr>
<td>M1.OV/OV (%)</td>
<td>9.03 ± 12.59</td>
</tr>
<tr>
<td>M1.OV/M1.BV (%)</td>
<td>21.5 ± 8.1</td>
</tr>
<tr>
<td>M1.BS/BS (%)</td>
<td>1.46 ± 2.43</td>
</tr>
<tr>
<td>M1.OS/BS (%)</td>
<td>1.36 ± 2.29</td>
</tr>
<tr>
<td>M1.OS/M1.BS (%)</td>
<td>94.0 ± 30.6</td>
</tr>
</tbody>
</table>

M1 = Mini-modeling

Kobayashi et al, Bone 2003
PTH - Discovery of Anabolic Action

1929: Bauer, Aub, and Albright
Parathyroid extract increased trabecular number in growing rats
(J Exp Med. 1929;49:145-161.)

1932: Selye
Histological evidence that parathyroid extract stimulates bone formation
(Endocrinology. 1932;16:547-558.)
“This experiment shows that if parathyroid hormone is administered in very small doses it will lead to a stimulation of the osteoblasts and thereby to bone apposition without previous osteoclast formation...”

Hans Selye, 1932
Cycle 1 labeling (3:12:3): Declomycin (Declo) 150 mg, 4 times a day for 3 days. The doses were repeated after 12 days of no antibiotic.

Cycle 2 labeling (3:12:3): Tetracycline (Te) 250 mg, 4 times a day for 3 days. The doses were repeated after 12 days of no antibiotic.
Early Effects of Teriparatide on Bone Formation

“...bone apposition without previous osteoclast formation...”

Lindsay R et al, JBMR 2006
Quadruple Labels in Teriparatide-Treated and Control Subjects

Lindsay R et al, JBMR 2006
Early Effects of Teriparatide on Bone Formation

“…they could also represent “overflow” of formation processes…”
Long Term Effects of DMAB on BMD

**Hypothesis:** As bone remodeling is persistently low, these bone mass increases may result from a remodeling-independent mechanism to accrue bone matrix.

16-Month Bone Quality Study in OVX Cynomolgus Monkeys

Mature (9+ year old) cynos:

- **Group 1**: Sham + vehicle
- **Group 2**: OVX + vehicle
- **Group 3**: OVX + DMAb (25 mg/kg)
- **Group 4**: OVX + DMAb (50 mg/kg)

(All groups dosed Q4W)

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**Femur Neck Mineralizing Surface**

- **Mean ± SE; n = 14 - 20/group; *P < 0.05 vs OVX, ^P < 0.05 vs Sham**

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**Femur Neck Strength**

- **Kostenuik et al, Bone 2011**
Fluorochrome Labeling: Femur Neck

Fluorochrome Labels
1. Tetracycline (6 mo)
2. Alizarin (12 mo)
3. Calcein (16 mo)

TRABECULAR BONE
Superior Endocortex

Cortical Periosteum
Inferior Periosteum

DMAb 25 mg/kg

Ominsky et al, JBMR 2015
Additional Examples of Stacked Labels in Sham and DMAb-treated Animals

Stacked labeling on one or both surfaces was observed in 65% of Sham and 70% of DMAb–treated samples

Ominsky et al, JBMR 2015
Effects of DMAb on Bone Formation in Cynomolgus Monkeys – 9th Rib

Ominsky et al, JBMR 2015
Effects of DMAb on Bone Formation in Cynomolgus Monkeys - Rib

Ominsky et al, JBMR 2015
Effects of DMAAb on Bone Formation in Cynomolgus Monkeys – 9th Rib

Remodeling-based formation

$\text{Mean} \pm \text{SEM}; \ *p<0.05 \text{ vs VEH}$

Ominsky et al, *JBMR* 2015
Hypothetical Model of the Potential Contributions to BMD Increases with Denosumab

Ominsky et al. *JBMR*, 2015
Effect of Teriparatide on Bone Formation in the Human Femoral Neck

Felicia Cosman, David W. Dempster, Jeri W. Nieves, Hua Zhou, Marsha Zion, Catherine Roimisher, Yvonne Houle, Robert Lindsay, and Mathias Bostrom

Regional Bone Center, Helen Hayes Hospital (F.C., D.W.D., J.W.N., H.Z., N.Z., C.R., R.L.), West Haverstraw, New York 10993; Department of Medicine (F.C., R.L.), Department of Pathology (D.W.D.), and Department of Epidemiology (J.W.N.), Columbia University, New York, New York 10032; and Department of Orthopedics (Y.H., M.B.), Hospital for Special Surgery, New York, New York 10021

Purpose: Teriparatide (TPTD) improves bone mass and microstructure resulting in reduced risk of vertebral and nonvertebral fractures. However, hip bone mineral density improvements are modest and there are no data confirming that TPTD reduces hip fracture risk. To study the effects of TPTD on the proximal femur, we performed a double-blind trial of TPTD vs placebo (PBO) in patients with osteoarthritis from whom femoral neck (FN) samples were obtained at total hip replacement (THR) surgery.

Methods: Participants were randomly assigned to receive TPTD or PBO for an average of 40 days before THR. Double tetracycline labeling was initiated 21 days prior to THR to allow histomorphometric assessment of bone formation. During the THR, an intact sample of the FN was procured, fixed, and sectioned transversely. Serum levels of bone turnover markers were measured at baseline and during the THR. Standard histomorphometric parameters were measured and calculated on four bone envelopes (cancellous, endocortical, intracortical, and periosteal). The primary outcome measure was bone formation rate/bone surface (BFR/BS).

Tetracycline Labels with PBO and TPTD in Human Femoral Neck

J Clin Endocrinol Metab 101: 1498 –1505,
Effect of DMAb Treatment on Bone Remodeling and Modeling in the Human Femoral Neck
Remodeling- and Modeling-Based Bone Formation With Teriparatide Versus Denosumab: A Longitudinal Analysis From Baseline to 3 Months in the AVA Study

David W Dempster,1,2 Hua Zhou,1 Robert R Recker,3 Jacques P Brown,4 Christopher P Recknor,5 E Michael Lewiecki,6 Paul D Miller,7 Sudhaker D Rao,8 David L Kendler,9 Robert Lindsay,1,2 John H Krege,10 Jahangir Alam,10 Kathleen A Taylor,11 Thomas E Melby,12 and Valerie A Ruff11

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3Department of Medicine, Division of Endocrinology, School of Medicine, Creighton University, Omaha, NE, USA
4Rheumatology and Bone Diseases Research Group, CHU de Québec (CHUL), Research Centre and Department of Medicine, Laval University, Quebec City, Canada
5United Osteoporosis Centers, Gainesville, GA, USA
6New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, USA
7Department of Medicine, Colorado Center for Bone Research, Lakewood, CO, USA
8Bone & Mineral Research Laboratory, Henry Ford Hospital, Detroit, MI, USA
9Department of Medicine (Endocrinology), University of British Columbia, Vancouver, Canada
10Muiti-Disciplinary Neuroendocrine Center (MIDNISC), Laval University, Quebec City, Canada
11Department of Medicine, West Virginia University, Morgantown, WV, USA
12Department of Medicine, University of California, San Francisco, CA, USA
Intact PTH and Bone Turnover Markers

*\(p=0.01\) for within treatment group comparison from baseline to each time point using t-test
†\(p<0.001\) for within treatment group comparison from baseline to each time point

Abbreviations: iPTH = intact parathyroid hormone; P1NP = procollagen type 1 N-terminal propeptide; CTX = carboxyterminal cross-linking telopeptide of type 1 collagen; SE = standard error

Results – Histomorphometry

Values are medians with interquartile range. *p<0.001 for between treatment group comparison at baseline or Month 3 in each envelope †p<0.001 for within treatment group comparison from baseline to Month 3 in each envelope ¥p<0.01 for within treatment group comparison from baseline to Month 3 in each envelope. ±p<0.05 for between treatment group comparison at baseline or Month 3 in each envelope.

Abbreviations: MS/BS = mineralizing surface/bone surface; MAR = mineral apposition rate; BFR/BS = bone formation rate per bone surface.
Cartoon Illustrating Three Types of Bone Formation

RBF = Remodeling-based formation

MBF = Modeling-based formation

oMBF = Overflow Modeling-based formation

Dempster DW et al. Longitudinal Effects of Teriparatide or Zoledronic Acid on Bone Modeling- and Remodeling-Based Formation in the SHOTZ Study. J Bone Miner Res. 2017 Nov 30. 10.1002/jbmr.3350. [Epub ahead of print]
Results – Bone Formation from Baseline to 3 Months Within Groups

*<0.05; **<0.0001 for within group p-value by paired t-test
Modeling in Monkeys Treated with Sclerostin Antibody

Ominsky et al, *JBMR* 2014

Trabecular Envelope

Endocortical Envelope
**Effects of Romosozumab in Postmenopausal Women With Osteoporosis After 2 and 12 Months: Bone Histomorphometry Substudy**

Pascale Chavassieux¹, Roland Chapurat¹, Nathalie Portero-Muzy¹, Pedro Garcia², Jacques P. Brown³, Stéphane Horlait⁴, Cesar Libanati⁵, Rogely Boyce⁶, Andrea Wang⁶, Andreas Grauer⁶

¹INSERM UMR 1033, Université de Lyon, Lyon, France; ²Hospital Universitario de Monterrey, Monterrey, Mexico; ³CIL de Quebec Research Center and Laval University, Quebec, Canada; ⁴Amgen, Thousand Oaks, California

<table>
<thead>
<tr>
<th></th>
<th>Month 2</th>
<th>Month 12</th>
<th></th>
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<tr>
<td></td>
<td>median (Q1, Q3)</td>
<td>median (Q1, Q3)</td>
<td>p-value</td>
<td>median (Q1, Q3)</td>
<td>median (Q1, Q3)</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>Placebo (N = 14)</td>
<td>Romosozumab (N = 15)</td>
<td></td>
<td>Placebo (N = 31)</td>
<td>Romosozumab (N = 39)</td>
<td></td>
</tr>
<tr>
<td>Cn-BV/TV (%)</td>
<td>12.3 (10.9, 17.0)</td>
<td>15.5 (9.0, 19.1)</td>
<td>0.98</td>
<td>11.4 (9.4, 15.5)</td>
<td>15.4 (11.0, 20.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cn-Tb.Th (µm)</td>
<td>99.5 (85.0, 133.4)</td>
<td>105.9 (95.8, 125.4)</td>
<td>0.35</td>
<td>100.2 (86.1, 125.2)</td>
<td>132.0 (101.9, 158.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cn-W.Th (µm)</td>
<td>31.7 (30.4, 33.9)</td>
<td>31.6 (30.7, 33.6)</td>
<td>0.91</td>
<td>29.5 (27.8, 32.3)</td>
<td>31.8 (30.8, 34.1)</td>
<td>0.014</td>
</tr>
<tr>
<td>Cn-MS/BS (%)</td>
<td>2.3 (0.7, 3.1)</td>
<td>5.6 (3.7, 8.4)</td>
<td>0.002</td>
<td>3.0 (0.9, 5.4)</td>
<td>0.6 (0.0, 2.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cn-BFR/BS (µm³/µm²/year)</td>
<td>5.2 (2.9, 7.2)</td>
<td>12.1 (7.3, 16.1)</td>
<td>0.004</td>
<td>6.8 (2.7, 13.2)</td>
<td>1.6 (0.9, 6.5)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

ASBMR 2018
Romosozumab – CT and Biochemical Markers

https://www.fda.gov/media/121255/download

Lewiecki EM, et al J Clin Endocrinol Metab. 2018 Sep 1;103(9):3183-3193.
Modeling and Remodeling in Osteoporosis and Following Treatment

Summary I

• Bone remodeling plays an important role in calcium homeostasis and maintenance of skeletal integrity – as we age, these functions may be in conflict.

• Modeling-based bone formation (MBF) in the adult skeleton has been largely ignored.

• MBF persists in the ileum and femur of adult humans. Under normal conditions, MBF in cancellous bone represents a tiny fraction of total bone formation. Other surfaces and skeletal sites need to be explored.
Summary II

• MBF is the most efficient mechanism to increase bone mass in osteoporosis. However, it does not replace older bone and does not replenish the osteocyte pool.

• Potent antiresorptive agents (e.g., DMAb) may be permissive to MBF and, coupled with a low rate of remodeling, may account for prolonged gains in bone mass with such agents.

• Anabolic agents (e.g., PTH 1-34; Scl Ab’s) stimulate modeling in both cancellous and cortical bone.
Thank You!

College of Physicians and Surgeons of Columbia University, New York