New Concepts on Bone Remodeling and Bone Modeling

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

Columbia University
Disclosures

Amgen, Inc.: Consultant, Grant Support, Speaker

Radius Health: Consultant, Grant Support, Speaker

Eli Lilly: Consultant, Grant Support, Speaker
2003 Santa Fe Bone Symposium

Symposium Faculty

B. Lawrence Riggs, MD • David W. Dempster, PhD
Laura K. Bachrach, MD • Kenneth D. Saag, MD

Guest Moderator

Paul D. Miller, MD

Symposium Director

E. Michael Lewiecki, MD
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

- Calcium homeostasis (long-term)
- Maintain mechanical strength
- Acid/base balance
- Release growth factors
- Provide reservoir of labile mineral (short-term homeostasis)
- Replace osteocytes
- ???
Tiktaalik
“From Fins to Limbs”
Remodeling Participates in Mineral Homeostasis

Before antler formation

During antler formation

After antler formation

Remodeling Maintains Mechanical Strength
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 dismorphisms

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

SUGGESTED SEQUENTIAL MODE OF CONTROL OF CHANGES IN CELL BEHAVIOUR IN ADULT BONE REMODELLING

By R. HATTNER, B. N. EPKER and Dr. H. M. FROST
Wayne State University College of Medicine, University of Detroit School of Dentistry, and Henry Ford Hospital, Detroit, Michigan

A SPECIFIC functional relationship between resorption lines reveals whether resorption has or has not occurred in 150 mineralized bones from 120 stereologically normal people aged 0 to 75 years. The sexes were...
“…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)

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>Bone structure</td>
<td></td>
</tr>
<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>Bone surfaces</td>
<td></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

**PTH - Discovery of Anabolic Action**

1929: Bauer, Aub, and Albright
Parathyroid extract increased trabecular number in growing rats

---

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....Dempster DW et al, JBMR 2006
Quadruple Labels in Teriparatide-Treated and Control Subjects
Early Effects of Teriparatide on Bone Formation

“...they could also represent “overflow” of formation processes…”

Lindsay R....Dempster DW et al, JBMR 2006
Effects of 12-24 Months TPTD on Modeling and Remodeling Osteons

Ma L…Marcus R et al, JBMR 2006
• Participants were randomly assigned to receive TPTD (n=21) or PBO (n=17) for an average of 40 days before THR. Double tetracycline labeling was initiated 21 days prior to THR.

• During the THR, an intact sample of the mid-femoral neck (FN) was procured, fixed and sectioned transversely.

Cosman F, Dempster DW, et al, JCEM 2016
Effects of TPTD on Bone Formation in the Hip

A Cancellous

B Endocortical

C Intracortical

D Periosteal

![Placebo](image1.png)

![Teriparatide](image2.png)

Cancellous

Endocortical

Intracortical

Periosteal

Cosman et al, JCEM 2016
Three Types of Bone Formation Assessed in Cancellous, Endocortical and Periosteal Envelopes.

Remodeling-based formation (MS.RBF/BS)

Modeling-based formation (MS.RBF/BS)

Overflow remodeling-based formation (MS.oRBF/BS)

Results: Bone Formation Types

Cancellous envelope

- **Modeling-based formation**: Mean ± S.E.
  - PBO: [Graph]
  - TPTD: [Graph]
  - \( p = 0.07 \)

- **Remodeling-based formation**: Mean ± S.E.
  - PBO: [Graph]
  - TPTD: [Graph]
  - \( p < 0.05 \)

- **Overflow remodeling-based formation**: Mean ± S.E.
  - PBO: [Graph]
  - TPTD: [Graph]
  - \( p < 0.02 \)

Endocortical envelope

- **Modeling-based formation**: Mean ± S.E.
  - PBO: [Graph]
  - TPTD: [Graph]
  - NS

- **Remodeling-based formation**: Mean ± S.E.
  - PBO: [Graph]
  - TPTD: [Graph]
  - \( p < 0.001 \)

- **Overflow remodeling-based formation**: Mean ± S.E.
  - PBO: [Graph]
  - TPTD: [Graph]
  - \( p < 0.005 \)

Values are Mean ± S.E.

Results: Bone Formation Types in Two Envelopes

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

Dempster et al, 2018

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)*

![Femur Neck Mineralizing Surface](image)

![Trabecular ROI](image)

![Femur Neck Strength](image)

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

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

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

Ominsky et al, JBMR 2015
Differential Effects of Teriparatide and Denosumab on Intact PTH and Bone Formation Indices: AVA Osteoporosis Study


**Context:** Denosumab-induced PTH elevation may stimulate early bone formation.

**Objective:** Our objective was to evaluate whether denosumab-induced changes of intact PTH (iPTH) result in early anabolic effects according to histomorphometry and bone turnover markers (BTMs) compared with teriparatide, an established anabolic agent.
Intact PTH and Bone Turnover Markers

66 biopsies were collected; TPTD=31, DMAb=35

**Abbreviations:** DEM = demeclocycline; TET = tetracycline

AVA: Bone Formation (Baseline, Month 3)

BFR/BS, bone formation rate/bone surface; MAR, mineral apposition rate; MS/BS, mineralizing surface/bone surface. †p<0.05 for between-treatment group comparison at baseline or month 3; *p<0.05 for within-treatment group comparison from baseline to month 3 in each envelope.

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

¹Regional Bone Center, Helen Hayes Hospital, West Haverstraw, NY, USA
²Department of Pathology and Cell Biology, College of Physicians and Surgeons of Columbia University, New York, NY, USA
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
¹⁰Multi-Center Study of the Efficacy and Safety of Denosumab (ESON)
¹¹Joule, multi-center, international, blinded, randomized, placebo-controlled study, Canada

Results – Bone Formation from Baseline to 3 Months Within Groups

*<0.05; **<0.0001 for within group p-value by paired t-test

Modeling-Based Bone Formation in the Human Femoral Neck in Subjects Treated With Denosumab

David W Dempster,1,2 Arkadi Chines,3 Mathias P Bostrom,4 Jeri W Nieves,1,2 Hua Zhou,2 Li Chen,3 Nico Pannacciulli,3 Rachel B Wagman,3 and Felicia Cosman1

1Columbia University, New York, NY, USA
2Helen Hayes Hospital, West Haverstraw, NY, USA
3Amgen Inc, Thousand Oaks, CA, USA
4Hospital for Special Surgery, New York, NY, USA

ABSTRACT
Denosumab is associated with continued gains in hip and spine BMD with up to 10 years of treatment in postmenopausal women with osteoporosis. Despite potent inhibition of bone remodeling, findings in nonhuman primates suggest modeling-based bone formation (MBBF) may persist during denosumab treatment. This study assessed whether MBBF in the femoral neck (FN) is preserved in the context of inhibited remodeling in subjects receiving denosumab. This open-label study enrolled postmenopausal women with osteoporosis who had received two or more doses of denosumab (60 mg subcutaneously every 6 months [Q6M]) per standard of care and were planning elective total hip replacement (THR) owing to osteoarthritis of the hip. Transverse sections of the FN were obtained after THR and analyzed histomorphometrically. MBBF, based on fluorochrome labeling and presence of smooth cement lines, was evaluated in cancellous, endocortical, and periosteal envelopes of the FN. Histomorphometric parameters were used to assess MBBF and remodeling-based bone formation (RBBF) in denosumab-treated subjects \((n = 4); \text{mean age} = 73.5 \text{ years; range, 70 to 78 years}) and historical female controls \((n = 11); \text{mean age} = 67.8 \text{ years; range, 62 to 80 years}) obtained from the placebo group of a prior study and not treated with denosumab. All analyses were descriptive. All subjects in both groups exhibited MBBF in the periosteal envelope; in cancellous and endocortical envelopes, all denosumab-treated subjects and 81.8% of controls showed evidence of MBBF. Compared with controls, denosumab-treated subjects showed 9.4-fold and 2.0-fold higher mean values of MBBF in cancellous and endocortical envelopes, respectively, whereas RBBF mean values were 5.0-fold and 5.3-fold lower. In the periosteal envelope, MBBF and RBBF rates were similar between subjects and controls. These results demonstrate the occurrence of MBBF in the human FN and suggest that denosumab preserves MBBF while inhibiting remodeling, which may contribute to the observed continued gains in BMD over time after remodeling is maximally inhibited. © 2020 The Authors. Journal of Bone and Mineral Research published by American Society for Bone and Mineral Research.

KEY WORDS: ANTIRESORPTIVES; BONE HISTOMORPHOMETRY; BONE MODELING AND REMODELING; OSTEOPOROSIS

Dempster et al, J Bone Miner Res. 2020;35:1282-1288
Modeling-based Bone Formation with DMAb in Human Femur Neck

Dempster et al, J Bone Miner Res. 2020;35:1282-1288
Upregulation of Wnt16 in DMAb-treated subjects; Wnt16 inhibits resorption and stimulates differentiation of osteogenic cells
Early Effects of Abaloparatide on Bone Formation and Resorption Indices in Postmenopausal Women With Osteoporosis

David W. Dempster, Hua Zhou, Sudhaker D. Rao, Chris Recknor, Paul D. Miller, Benjamin Z. Leder

Abstract
Anabolic osteoporosis drugs improve bone mineral density by increasing bone formation. The objective of this study was to evaluate the early effects of abaloparatide on indices of bone formation and to assess the effect of abaloparatide on modeling-based formation (MBF), remodeling-based formation (RBF), and overflow MBF (oMBF) in transiliac bone biopsies. In this open-label, single-arm study, 19 postmenopausal women with osteoporosis were treated with 80 μg abaloparatide daily. Subjects received dual fluorescence labels before treatment and before biopsy collection at 3 months. Changes in cancellous and cortical histomorphometry indices in four bone envelopes were assessed. Median mineralizing surface per unit of bone surface (MS/BS) increased to 24.7%, 48.7%, 21.4%, and 16.3% of total surface after 3 months of abaloparatide treatment, representing 5.5-, 5.2-, 2.8-, and 1.2-fold changes, on cancellous, endocortical, intracortical, and periosteal surfaces (p < 0.01 versus baseline for all). Mineral apposition rate (MAR) was significantly increased only on intracortical surfaces. Bone formation rate (BFR/BS) was significantly increased on all four bone envelopes. Significant increases versus baseline were observed in MBF on cancellous, endocortical, and periosteal surfaces, for oMBF on cancellous and endocortical surfaces, and for RBF on cancellous, endocortical, and intracortical surfaces. Overall, modeling-based formation (MBF + oMBF) accounted for 37% and 23% of the increase in bone-forming surface on the endocortical and cancellous surfaces, respectively. Changes from baseline in serum biomarkers of bone turnover at either month 1 or month 3 were generally good surrogates for changes in histomorphometric endpoints. In conclusion, treatment with abaloparatide for 3 months stimulated bone formation on cancellous, endocortical, intracortical, and periosteal envelopes in transiliac bone biopsies obtained from postmenopausal women with osteoporosis. These increases reflect stimulated of both remodeling- and modeling-based bone formation, further elucidating the mechanisms by which abaloparatide improves bone mass and lowers fracture risk. © 2021 The Authors, Journal of Bone and Mineral Research published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: ABALOPARATIDE; BONE HISTOMORPHOMETRY; BONE MODELING AND REMODELING; CLINICAL TRIAL; OSTEOPOROSIS

Study Design

- Single-arm study of 23 postmenopausal women with osteoporosis
- Treatment with open-label, 80 μg abaloparatide-SC for 3 months
- Trans-iliac bone biopsy after quadruple fluorochrome labeling taken at 3 months

SC, subcutaneous.
Median Mineralizing Surface/Bone Surface (MS/BS) at Baseline and 3 Months for the 4 Bone Envelopes

#P<0.001 within envelope changes from baseline to 3 months by paired t test.

Dempster DW et al, J Bone Miner Res. 2021 Apr;36(4):644-653
Abaloparatide

Cross-Study Comparison: Changes in Mineralizing Surface (Median)

Percent Bone Formation at Baseline and 3 Months (Median)

BS, bone surface; ES, eroded surface; MBF, modeling-based formation; oMBF, overflow modeling-based formation; QS, quiescent surface; RBF, remodeling-based formation.

Dempster DW et al, J Bone Miner Res. 2021 Apr;36(4):644-653
Activation of MS/BS and MBF with Abaloparatide

MBF, modeling-based formation; MS/BS, mineralizing surface/bone surface.
Romosozumab Treatment in Postmenopausal Women with Osteoporosis


BACKGROUND
Romosozumab, a monoclonal antibody that binds sclerostin, increases bone formation and decreases bone resorption.

Romozosumab - Histomorphometry

Table 3. Static and Dynamic Bone Formation Parameters After 2 and 12 Months of Romozosumab

<table>
<thead>
<tr>
<th></th>
<th>Month 2</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=14</td>
<td>Romosozumab 210 mg QM N=15</td>
</tr>
<tr>
<td>Cancellous bone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cn-W.Th</td>
<td>31.6±2b (30.4, 33.9)</td>
<td>31.6</td>
</tr>
<tr>
<td>μm</td>
<td></td>
<td>1.2±1 (1.1, 1.5)</td>
</tr>
<tr>
<td>Cn-OS/BS</td>
<td>1.2±1 (1.1, 1.5)</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>1.2±1 (1.1, 1.5)</td>
<td></td>
</tr>
<tr>
<td>Cn-ON/BS</td>
<td>0.6±1 (0.5, 0.7)</td>
<td></td>
</tr>
<tr>
<td>μm/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cn-MAR3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>μm/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cn-ON/BS</td>
<td>2.3±1 (1.2, 2.5)</td>
<td></td>
</tr>
<tr>
<td>μm²/m²/year</td>
<td>2.99±1 (2.165, 4.713)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Schema of the bone biopsy substudy. ( one set of double fluorescent labeling, transiliac bone biopsy)

Fig. 3. Effects of romosozumab at month 12 on bone mass and microarchitecture assessed by μCT. Tb.BV/TV = trabecular bone volume per tissue volume

Chavassieux et al, J Bone Miner Res. 2019 Sep;34(9):1597-1608
Romosozumab – Biochemical Markers

Lewiecki EM, et al J Clin Endocrinol Metab. 2018 Sep 1;103(9):3183-3193.
Bone Modeling and Remodeling After 2 Months of Romosozumab vs Placebo

Fig 3. Bone modeling and remodeling after 2 months of romosozumab versus placebo: referent to total bone surface. Box plots show 25th and 75th percentiles (lower and upper edges of the box), median (horizontal bar inside the box), mean values (x), outliers (*), and minimum to maximum ranges excluding any outliers (error bars). Outliers are defined as values either greater than 1.5 IQR above 75th percentile or less than 1.5 IQR below 25th percentile. n = number of patients with evaluable histomorphometry data at the time point of interest. Nominal p values are the treatment difference (romosozumab versus placebo) and are based on the Wilcoxon rank-sum test without multiplicity adjustment. BS = bone surface; IQR = interquartile range; LS = labeled surface.

Eriksen et al, J Bone Miner Res 2021
Bone Modeling and Remodeling After 2 Months of Romosozumab vs Placebo

Fig 4. Bone modeling and remodeling after 2 months of romosozumab versus placebo: referent to labeled surface. Box plots show 25th and 75th percentiles (lower and upper edges of the box), median (horizontal bar inside the box), mean values (x), outliers (‘), and minimum to maximum ranges excluding any outliers (error bars). Outliers are defined as values either greater than 1.5 IQR above 75th percentile or less than 1.5 IQR below 25th percentile. n = number of patients with evaluable histomorphometry data at the time point of interest. Nominal p values are the treatment difference (romosozumab versus placebo) and are based on the Wilcoxon rank-sum test without multiplicity adjustment. IQR = interquartile range; LS = labeled surface.

Eriksen et al, J Bone Miner Res 2021
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 are now being 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, possibly stimulate it. Coupled with a low rate of remodeling, this may contribute to prolonged gains in bone mass with such agents.

• Anabolic agents (e.g., Teriparatide, Abaloparatide, Romosozumab) stimulate modeling in both cancellous and cortical bone.
Thank You!

Vagelos College of Physicians and Surgeons of Columbia University, New York

ddempster9@aol.com