Bone Markers in Osteoporosis: Prediction of Fractures & Treatment Monitoring

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<table>
<thead>
<tr>
<th>Usefulness of Markers in the Individual Patient</th>
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<tbody>
<tr>
<td><strong>Outline</strong></td>
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<tr>
<td>• <strong>Bone turnover</strong></td>
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<td>– Changes at the menopause and with osteoporosis</td>
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<td>• <strong>High bone turnover markers</strong></td>
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<tr>
<td>– Association with bone loss and fracture</td>
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<tr>
<td>• <strong>Effects of treatment on bone turnover</strong></td>
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<tr>
<td>• <strong>Treatment monitoring</strong></td>
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<td>• <strong>Example</strong></td>
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The Effects of Age and Estrogen Status on Bone Remodeling

Activation frequency (#/yr)

- A 2-fold increase across the menopause
- A 3-fold increase by age 65 yr.

BTMs Reflect Resorption and Formation

Matrix proteins
- osteocalcin (OC)
- procollagen type I propeptides
  - C-terminal (PICP)
  - N-terminal (PINP)

Enzyme
- bone isoform of alkaline phosphatase (bone ALP)

Collagen degradation products
- pyridinium cross-links of collagen
  - C- and N-telopeptides (CTX, NTX)
  - Deoxypyridinoline (DPD)

Enzyme
- tartrate-resistant acid phosphatase (TRACP), type 5b
- Cathepsin K

Related factors
- OPG, RANK-L

Formation

Commercially available assays
Serum: OC, PICP, PINP, bone ALP, NTX, CTX, TRACP 5b
Urinary: CTX, NTX, free DPD

Resorption
Levels of Serum $\beta$CTX in Women
Community-based study, OPUS (n=2780)

Data from Blumsohn A et al, *J Bone Miner Res* 2003;18:1274-81
High Bone Turnover Markers
Bone Turnover Markers in Relation to Bone Loss and Fracture Risk

- A high bone remodelling rate is associated with
  - More rapid bone loss in postmenopausal women\(^1\)
  - Increased risk of fractures\(^2\)
- The association with fracture is variable\(^2\)
  - Hazard ratios of between 1 and 2
  - More consistently observed for bone resorption than bone formation markers

1. Stepan JJ. Osteoporos Int. 2000; 11 Suppl.6:S45-54;

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Bone Turnover and Bone Loss from the Spine


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High Bone Resorption Markers May Predict Hip Fracture Risk in Elderly Women – the EPIDOS Study

EPIDOS = Epidemiologie de l'Osteoporose

BMD = bone mineral density; U = urinary.

10-year Risk of Hip Fracture

- This approach has now been implemented as the WHO FRAX™ score
  - Doesn’t include bone markers

Postmenopausal Osteoporosis
Effects of Treatments

**Quiescence**

- **Activation**
- **Anti-catabolic Drugs**
  - Decrease activation frequency
  - Restore remodelling balance

**Remodelling Balance**

- **Resorption**

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Changes in Bone Resorption Marker NTX With Alendronate Therapy in Osteoporosis – Mean Decrease 75%

ALP = alkaline phosphatase; iFDPD = free deoxypyridinoline; OC = osteocalcin; NTX = N-terminal telopeptide.

Treatment Effects on Telopeptide Markers

CTX and NTX

- Different responses to treatments
  - Strontium, calcium, 10 to 20%
  - Raloxifene, 30 to 40%
  - HRT and risedronate, 50 to 60%
  - Zoledronic acid, ibandronate, alendronate, 70 to 80%

- All reduce vertebral fractures
  - Mechanism may involve effects other than a decrease in bone resorption

- The telopeptide response helpful for any particular treatment

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Postmenopausal Osteoporosis  
Effects of Treatments

Quiescence

Activation

Resorption

Positive Remodelling Imbalance

Anabolic Drugs
- Increase activation frequency
- Induce positive remodelling balance

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Randomized, Controlled Trial of Alendronate or Teriparatide in Postmenopausal Osteoporosis

% Change from baseline (Mean ± SE)

Teriparatide

- PINP (Formation)
- NTX (Resorption)

Alendronate

P<0.001 between-group difference teriparatide vs. alendronate

Strontium increases bone formation markers and decreases bone resorption markers, but the effects are small (<10%).

Bone ALP (ng/mL) +8%

S-CTX (pmol/L) -12%

E = Estimate of difference between strontium group and placebo group, covariance analysis, baseline adjusted *** p<0.001; ** p<0.01; * p<0.05

Treatment Monitoring
The average response to risedronate 5 mg exceeds LSC earlier for BTM (3 months) than BMD (18 months).

Spine BMD, %△ from baseline

- Risedronate 5mg
- Control

LSC, least significant change

NTX, %△ from baseline

- Risedronate 5mg
- Control

LSC, least significant change

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Using BMD and Bone Turnover Markers in Clinical Practice: Anti-Catabolic Therapies

LSC, least significant change
BMD, bone mineral density

Urinary NTX, % change at 6 months

Spine BMD, % change
Fracture Incidence Over 3.6 Years of Alendronate, vs 12-Month Bone ALP: % Change From Baseline

- One year change in bone ALP in alendronate-treated women

- FIT study
  - 3105 in alendronate arm
  - One-year change in bone ALP (insufficient samples for PINP or CTX)
  - 3.6 years of follow-up for fracture

OR=Odds ratio.
### Surrogates for Fracture Risk Reduction

Proportion of 3 year fragility fracture treatment effect explained by surrogates

<table>
<thead>
<tr>
<th>Surrogate</th>
<th>Proportion explained</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral neck BMD</td>
<td>14%</td>
<td>7, 21%</td>
</tr>
<tr>
<td>Urinary NTX</td>
<td>52%</td>
<td>29, 75%</td>
</tr>
<tr>
<td>NTX and FNBMD</td>
<td>67%</td>
<td>39, 100%</td>
</tr>
</tbody>
</table>

Delmas PD, et al. *ECCEO 2005; abstract P360*
We Would Like to Suppress Bone Turnover to Levels Found in Healthy Young Women (Who Have an Average T-Score of 0)

Treatment:
- Calcium
- Calcium and risedronate 5 mg

Reduce absolute vertebral fracture risk by 10%
Reduce bone resorption by 2 SD


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Vertebral Fractures over 3 years and Bone Resorption Complied Treated and Placebo Groups

Decile Analysis, about 66/decile

No. women with vertebral fractures

Urinary CTX (T-score) at 3 to 6 months, decile

Threshold is at mean for young women (T=0)


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Develop Reference Range for Women Based on at least 150 Healthy Young Women

### NTx/Cr Premenopausal Reference Range (Healthy drug-free subset)

<table>
<thead>
<tr>
<th>Reference Range</th>
<th>Graphical Display of the Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>47.066</td>
</tr>
<tr>
<td>Median</td>
<td>42.4079</td>
</tr>
<tr>
<td>Mode</td>
<td>No Mode</td>
</tr>
<tr>
<td><strong>Spread</strong></td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>24.4041</td>
</tr>
<tr>
<td>Variance</td>
<td>595.5589</td>
</tr>
<tr>
<td>Parametric 95% LRL</td>
<td>-1.7422</td>
</tr>
<tr>
<td>Parametric 95% URL</td>
<td>95.8742</td>
</tr>
<tr>
<td>Non Parametric 2.5th centile</td>
<td>16.3759</td>
</tr>
<tr>
<td>Non Parametric 97.5th centile</td>
<td>103.5667</td>
</tr>
<tr>
<td>Minimum</td>
<td>8.03217427</td>
</tr>
<tr>
<td>Maximum</td>
<td>211.0338478</td>
</tr>
<tr>
<td>Interquartile Range</td>
<td>25.2433</td>
</tr>
<tr>
<td>Range</td>
<td>203.0016735</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Miscellaneous</th>
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<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>CV</td>
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Effect of Risedronate Therapy on Bone Resorption

- **Lower half of reference interval**
- **Upper half of reference interval**

**Osteoporosis, Untreated**
- 0
- 11
- 62 (27%)

**Osteoporosis, Risedronate**
- 7
- 63
- 28 (2%)

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Eastell R and Delmas PD. *J Bone Miner Res.* 2005;20:1261-2

[www.shef.ac.uk/bmg](http://www.shef.ac.uk/bmg)
Does monitoring affect adherence?
Does Monitoring affect Adherence?

- 75 women with osteopenia
- Treated with Raloxifene and randomised
  - Repeat prescriptions (no medical contact)
  - Visit nurse every 3 months
  - Visit nurse and monitor BTM every 3 months
- Measured compliance using MEMS caps

Clowes JA et al, *J Clin Endocrinol Metab* 2004;89:1117-23
Monitoring improves adherence to treatment with Raloxifene

Proportion of patients who remained adherent

Cumulative adherence >75%

- Proportion of adherent subjects increased by 57% in those monitored
- P = 0.04

Clowes JA et al, J Clin Endocrinol Metab 2004;89:1117-23
Greater adherence is associated with greater biological response

% Change Hip BMD

% Change uNTX

r = 0.34
P = 0.003

r = -0.46
P = 0.0001

Clowes JA et al, J Clin Endocrinol Metab 2004;89:1117-23

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Case Presentation

- Woman (71) develops acute onset back pain
- There are no clear risk factors for osteoporosis from the questionnaire or the biochemical workup
- Bone turnover marker
  - NTX T-score +4 (150 nmol BCE/mmol Cr)
  - Bone alkaline phosphatase T-score +3 (90 ug/L)
<table>
<thead>
<tr>
<th>Question</th>
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<tbody>
<tr>
<td>Could it just be a spurious result?</td>
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<tr>
<td>How can we use the information?</td>
</tr>
<tr>
<td>Is the patient more likely than average to have rapid bone loss or an increased risk of fracture?</td>
</tr>
<tr>
<td>Does this high result mean she might have secondary osteoporosis?</td>
</tr>
<tr>
<td>What do we expect to happen to the result when we treat her? What is the goal of our treatment?</td>
</tr>
</tbody>
</table>
Could it just be a spurious result?
Bone resorption markers do vary from day to day, but it is very likely that she is in a high turnover state.

If we know why bone turnover markers vary, we can allow for it

<table>
<thead>
<tr>
<th>Controllable source</th>
<th>Uncontrollable source</th>
</tr>
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<tbody>
<tr>
<td>Circadian</td>
<td>Growth</td>
</tr>
<tr>
<td>Day to day</td>
<td>Age and gender</td>
</tr>
<tr>
<td>Diet</td>
<td>Fractures</td>
</tr>
<tr>
<td>Exercise</td>
<td>Diseases and drugs</td>
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<table>
<thead>
<tr>
<th>Consequence</th>
<th>Consequence</th>
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<tr>
<td>Morning, fasting samples</td>
<td>Establish age and gender-specific reference range</td>
</tr>
<tr>
<td>Take average of more than one measurement</td>
<td></td>
</tr>
</tbody>
</table>

Hannon RA, Eastell R. Osteoporosis Int. 2000;11 (Suppl.6):S30-44.

Arrows indicate meal times
- Untreated osteoporosis, n = 15
- Osteoporosis treated with risedronate for 3 months, n = 15
Biochemical Markers following Ankle Fracture

Is the patients more likely than average to have rapid bone loss or an increased risk of fracture?
She is likely to be a ‘fast bone loser’
Would she really lose 5% per year?

10-year Risk of Hip Fracture

With low BMD, prior fracture and high bone turnover marker she has a 30% 10-year risk of fracturing, better do something soon!


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Use in Decision-Making

• Does this help us diagnose osteoporosis?
• Does this help us select the best treatment?
• Does the result make us suspect secondary osteoporosis?
The high turnover doesn’t allow us to diagnose osteoporosis, or choose the best treatment; it might point us to secondary osteoporosis.

- Bone turnover markers are increased in about 25% of women with primary osteoporosis.
- Bone turnover markers have not yet proven useful in the selection of treatment:
  - Bisphosphonates are effective at all levels of bone turnover\(^1\) or only with high turnover\(^2\)
  - Teriparatide most effective if bone turnover is high\(^3\)
- A high level of bone turnover may indicate the presence of secondary osteoporosis.

What are the causes of high bone turnover? Watch out particularly for endocrine or other bone diseases

<table>
<thead>
<tr>
<th>HIGH</th>
<th>LOW</th>
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<tr>
<td><strong>Metabolic bone diseases</strong></td>
<td><strong>Cushing’s syndrome</strong></td>
</tr>
<tr>
<td>– Paget’s disease</td>
<td>– low osteocalcin</td>
</tr>
<tr>
<td>– Secondary hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>– osteomalacia</td>
<td>– low PICP</td>
</tr>
<tr>
<td>– renal osteodystrophy</td>
<td>– Hypophosphatasia</td>
</tr>
<tr>
<td>– malabsorption syndrome</td>
<td>– low alkaline phosphatase</td>
</tr>
<tr>
<td><strong>Endocrine diseases</strong></td>
<td><strong>Osteogenesis imperfecta</strong></td>
</tr>
<tr>
<td>– Primary hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>– Thyrotoxicosis</td>
<td>– low PICP</td>
</tr>
<tr>
<td>– Hypogonadism</td>
<td>– Hypophosphatasia</td>
</tr>
<tr>
<td><strong>Malignancy, e.g. myeloma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Recent fracture</strong></td>
<td><strong>Endocrine diseases</strong></td>
</tr>
<tr>
<td></td>
<td>– Primary hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>– Thyrotoxicosis</td>
</tr>
<tr>
<td></td>
<td>– Hypogonadism</td>
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What do we expect to happen to the result when we treat her? What is the goal of our treatment?
After starting antiresorptive therapy, should we make follow-up measurements of bone turnover?

- **Identify poor response that can be caused by**
  - Poor compliance
  - Secondary osteoporosis
  - Ineffective therapies

- **Take action to improve response**
  - Advise on correct dosing instructions
  - Investigate for secondary osteoporosis
  - Consider larger dose or different treatment

- **Encourage compliance**
  - No immediate symptomatic benefit to patient
Our patient was treated with alendronate 70 mg once a week, and met both of our targets.

**Goals**

- Decrease to levels in the lower half of the reference range for young women, <35 nmol/mmol Cr
- Decrease by more than the least significant change, 50%

**NTX/Cr, nmol BCE/mmol**

**NTX, % change**

BMD increase of 5.3% at lumbar spine at 1 year
Usefulness of Markers in the Individual Patient

Summary

• **Bone turnover**
  – Increases at the menopause and increases further in osteoporosis

• **High bone turnover markers**
  – Associated with higher risk of bone loss and fractures

• **Treatments for osteoporosis**
  – Result in changes in bone turnover markers

• **Treatment monitoring**
  – Goal is to decrease bone turnover markers beyond least significant change and into pre-menopausal range