Update on the Use of Bone Turnover Markers

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No Disclosures

Outline

• Potential clinical uses and limitations of current BTMs
  – Other considerations in clinical practice
• Six criteria for BTM monitoring
  – Clinical cutpoints
  – Reproducibility
• A path forward...

Bone Remodeling Sequence

Currently Available Biochemical Markers of Bone Turnover

• Resorption (urine and serum)
  – Pyridinoline and deoxypyridinoline
  – N-telopeptides of type 1 collagen (NTX)
  – C-telopeptides of type 1 collagen (CTX)*

*Recommended by IOF-IFCC Working Group
Markers of Bone Resorption: Type I Collagen Crosslinks

- Bone matrix
- Osteoclastic bone resorption
- C-telopeptides
- N-telopeptides

Free PYD and DPD (40%)
Crosslinked C and N-telopeptides (60%)

PYD = pyridinoline; CTX = C-telopeptides of type I collagen
DPD = deoxypyridinoline; NTX = N-telopeptides of type I collagen

Currently Available Biochemical Markers of Bone Turnover

- Formation (serum)
  - Osteocalcin (OC)
  - Bone alkaline phosphatase (Bone ALP)
  - N-terminal propeptide of type I procollagen (PINP)*

Markers of Bone Formation: PINP

- Procollagen type I
- C-Terminal pro-peptide (PICP)
- N-Terminal pro-peptide (PINP)
- Intact PINP (trimer - liver)

Clinical Utility of BTMs in the Near Future

- Unlikely use
  - Diagnose osteoporosis
  - Improve compliance with treatments
- Possible use
  - Predict treatment benefit before initiation of therapy
  - Predict fracture risk after discontinuation of therapy
  - Predict fracture risk in untreated individuals

IOD-FCC Bone Marker Standards Working Group, Osteoporosis Int, 2011
Fracture Prediction In Untreated Individuals

- Elevated urine resorption markers associated with fracture in most studies
- Less consistent data for serum or formation markers
  - Meta analysis of PINP or sCTX: RR=1.2 per SD increase (weaker than BMD)
- Value of combining markers + BMD unclear
- Markers are an alternative when BMD unavailable

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- Likely use
  - Predict treatment efficacy among treated individuals

FLEX Placebo Group

- Received 5 yrs of ALN then 5 yrs of PBO. Blinded
- BMD and BTMs (BAP and NTX) when PBO begun and after 1-3 yrs.
- Do short-term changes in BTMs after discontinuation predict long-term fracture outcomes?

FLEX PBO: Proportion With Fracture by 1 Year Change in BTMs

Bauer et al. Jama Internal Med 2014

IOF-IFCC Bone Marker Standards Working Group, Osteoporosis Int, 2011
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IOF-IFCC Bone Marker Standards Working Group, Osteoporosis Int, 2011

Using BTMs to Predict Treatment Efficacy Among Treated Individuals

- Assess BTM changes with therapy; “monitoring”
- Goal is to identify those with suboptimal response and intervene
- Are there guiding principles?

Six Suggested Criteria for Routine BTM Monitoring of Treated Patients

1. Large treatment-related changes in BTMs
   - True for most available therapies

2. Significant between-person heterogeneity in BTM response to a therapy
   - True for alendronate, likely true for others

3. Short-term changes in BTM measurements associated with long-term fracture risk
   - True for several bisphosphonates, raloxifene

Schousboe et al, Curr Osteoporos Rep, 2012
Bell et al, JBMR, 2012

Reduction in uCTX and New Vertebral Fracture: Risedronate


n=358 risedronate-treated postmenopausal women
n=3105 alendronate-treated postmenopausal women

Bauer et al. J Bone Miner Res, 2004

**Reduction in Bone ALP and Non-spine Fracture: Alendronate**

- Probability of non-spine fracture
- 0–4 year non-spine fracture incidence
- 1-year change in bone ALP (%)

- Alendronate 5-10 mg

n=3105 alendronate-treated postmenopausal women

Bauer et al. J Bone Miner Res, 2004

**Six Suggested Criteria for Routine BTM Monitoring of Treated Patients**

4. Optimal BTM cutpoint that identifies patients at sufficiently high risk to change therapy
   - Clinicians need validated cutpoints
   - May differ for each BTM, treatment class
   - Ideal cutpoint: >LSC, identifies small group at high risk

Schousboe et al, Curr Osteoporos Rep, 2012

**FIT: Fracture Rate With and Without “Good” Marker Response**

<table>
<thead>
<tr>
<th>Fracture Rates (Mean F/U 3.6 Years)</th>
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<tbody>
<tr>
<td>Placebo Group</td>
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<tr>
<td>Non-spine</td>
</tr>
<tr>
<td>Hip</td>
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</table>

†44% of ALN-treated women  *p<0.001 compared to PBO group

Bauer et al. J Bone Miner Res. 2004

**IMPACT: Fracture Rate With and Without “Good” Marker Response**

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†17% of RIS-treated women  *p=0.002 compared to <30% group

Eastell et al. J Bone Miner Res. 2011
Six Suggested Criteria for Routine BTM Monitoring of Treated Patients

4. BTM cutpoint that identifies patients at sufficiently high risk to change therapy
5. Adequate test reproducibility

Schousboe et al, Curr Osteoporos Rep, 2012

Importance of Test Reproducibility

• Test reproducibility
  – Important when assessing a single measurement of bone turnover
  – Extremely important if assessing change in BTM
• Pre-analytic variability (from diurnal variation, fasting status, exercise, etc.)
  – Poorly addressed in early BTM studies

IOF-IFCC Bone Marker Standards Working Group, Osteoporosis Int, 2011

Importance of Laboratory Reproducibility

• Analytic reproducibility
  – Assay and laboratory variability
• Standardization of assays and performance
  – Automated platforms
• Document commercial laboratory proficiency
  – In US, assessed by College of American Pathologists and others
  – Data not easily available to clinicians...

Published Studies of BTM Lab Reproducibility: Europe

• Low and high serum and urine pools
• Identical aliquot from each pool sent to 73 laboratories in 5 countries
  – Labs agreed to participate, unblinded
• Between laboratory coefficient of variation (CV)
  – BALP (IRMA) 16-25%
  – Osteocalcin (EIA) 24-31%
  – Total PYD and DPD/Cr (HPLC) 27-28%
  – NTX/Cr (EIA) 39%

Siebel et al, Clin Chem 2001
Published Studies of BTM Lab Reproducibility: United States

- Pooled serum and urine from postmenopausal women
- Identical aliquots sent to 6 high volume commercial labs
  - 5 times over 8 mo. period, then 5 aliquots together the last time
  - Labs unaware, submitted as clinical specimens
- Serum BALP assays:
  - Ostase ECI (N=5) and Metra (N=1)
- Urine NTX/Cr assays:
  - Vitros ECI (N=4) and Osteomark ELISA (N=2)

Schafer et al, Osteoporos Int, 2010

Serum BALP Results Over 8 Months From 6 Commercial Labs

<table>
<thead>
<tr>
<th>Lab</th>
<th>Assay</th>
<th>Mean (SD)</th>
<th>CV% (CI)</th>
</tr>
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<tbody>
<tr>
<td>ARUP</td>
<td>Ostase</td>
<td>13.8 (1.3)</td>
<td>9 (6-27)</td>
</tr>
<tr>
<td>Esoterix</td>
<td>Ostase</td>
<td>14.2 (0.4)</td>
<td>3 (2-9)</td>
</tr>
<tr>
<td>LabCorp</td>
<td>Ostase</td>
<td>11.4 (2.7)</td>
<td>24 (14-77)</td>
</tr>
<tr>
<td>Mayo</td>
<td>Ostase</td>
<td>14.4 (0.9)</td>
<td>6 (4-18)</td>
</tr>
<tr>
<td>Quest</td>
<td>Ostase</td>
<td>14.4 (1.5)</td>
<td>10 (6-31)</td>
</tr>
<tr>
<td>Specialty</td>
<td>Metra</td>
<td>24.0 (1.4)</td>
<td>6 (3-16)</td>
</tr>
</tbody>
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Serum BALP: US Laboratory Longitudinal Reproducibility

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<tr>
<td>ARUP</td>
<td>Ostase</td>
<td>15.6 (0.6)</td>
<td>4 (2-11)</td>
</tr>
<tr>
<td>Esoterix</td>
<td>Ostase</td>
<td>14.0 (0.0)</td>
<td>0</td>
</tr>
<tr>
<td>LabCorp</td>
<td>Ostase</td>
<td>11.3 (1.8)</td>
<td>16 (9-47)</td>
</tr>
<tr>
<td>Mayo</td>
<td>Ostase</td>
<td>13.2 (1.1)</td>
<td>8 (5-24)</td>
</tr>
<tr>
<td>Quest</td>
<td>Ostase</td>
<td>14.2 (0.3)</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td>Specialty</td>
<td>Metra</td>
<td>25.8 (0.9)</td>
<td>4 (2-10)</td>
</tr>
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Serum BALP: US Laboratory Within Run Reproducibility
Urine NTX/Cr Results Over 8 Months From 6 Commercial Labs

Urine NTX/Cr: US Laboratory Longitudinal Reproducibility

<table>
<thead>
<tr>
<th>Lab</th>
<th>Assay</th>
<th>Mean (SD)</th>
<th>CV% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARUP</td>
<td>Vitros</td>
<td>35.8 (1.9)</td>
<td>5 (3, 16)</td>
</tr>
<tr>
<td>Esoterix</td>
<td>Vitros</td>
<td>35.8 (2.9)</td>
<td>8 (5, 30)</td>
</tr>
<tr>
<td>LabCorp</td>
<td>Osteomark</td>
<td>74.2 (19.3)</td>
<td>26 (15, 88)</td>
</tr>
<tr>
<td>Mayo</td>
<td>Vitros</td>
<td>35.0 (3.0)</td>
<td>9 (5, 25)</td>
</tr>
<tr>
<td>Quest</td>
<td>Vitros</td>
<td>34.0 (2.2)</td>
<td>7 (4, 19)</td>
</tr>
<tr>
<td>Specialty</td>
<td>Osteomark</td>
<td>42.8 (16.0)</td>
<td>38 (22, 168)</td>
</tr>
</tbody>
</table>

Urine NTX/Cr: US Laboratory Within Run Reproducibility

Does Lab Reproducibility Matter?

- Hypothetical estimate of the effects of observed lab variability on reporting of paired BTM measurements
- Example: if a clinician orders a baseline and follow-up BTM using the same lab, what are 95% CI for a known 50% reduction?
  - Plausible range of reported results for a true 50% decrease in BTM
Plausible Results For Known 50% Decrease in BALP or NTX/Cr

- Plausible results for -50% change in BALP
  - Esoterix (Ostase): -56% to -43%
  - Labcorp (Ostase): -89 to +7% (i.e. could be reported as a 89% decrease or a 7% increase)
- Plausible results for -50% change in NTX/Cr
  - ARUP (Vitros): -61% to -37%
  - Specialty (Osteomark): -143% to +100%

Note: even worse if baseline and follow-up measurements sent to different labs!

A Path Forward...

4. BTM cutpoint that identifies patients at sufficiently high risk to change therapy
   - Additional treatment and BTM-specific data from existing and future trials
   - Consistent approach: same BTMs (sCTX and PINP), outcomes, analysis
   - Pool individual level data across studies to determine optimal cutpoints

FNIH Bone Quality Biomarkers Consortium Project

A Path Forward...

5. Adequate test reproducibility
   - Better assays and better quality control...
   - Collaboration between manufacturers, commercial labs, and researchers
   - Reference standards, harmonize assays
   - Publish results

IOF-IFCC Bone Marker Standards Working Group, Osteoporosis Int, 2011
National Bone Health Alliance BTM Project, Osteoporosis Int, 2012

A Path Forward...

6. Ideally, evidence that use of BTMs improves clinical outcomes
   - Usually large, expensive studies (example: fracture rates in those randomized to BTM or no BTM monitoring)
   - More feasible study designs? Surrogates? (example: use change in FEA as outcome)
Summary: How to Improve the Clinical Utility of Bone Turnover Markers

- Continued advances and optimism!
- Most likely clinical use: monitoring therapy
  - Some believe data adequate now
- Several criteria clearly need additional work
  - Optimal BTM cutpoints
  - Improved laboratory reproducibility
- Can we show that use of BTM improves clinical outcomes?

Acknowledgements

- Investigators and staff at San Francisco CC
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