Bone Turnover Markers For Monitoring Treatment of Osteoporosis

Richard Eastell
Director,
The Mellanby Centre for Bone Research, Department of Oncology and Metabolism
Faculty of Medicine, Dentistry and Health, University of Sheffield, UK

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Conflicts of Interest

• Consultant and research grants
  o Immunodiagnostic Systems
  o Roche Diagnostics
  o Nittobo
  o Amgen
Outline

• Introduction to bone turnover markers
• Use for monitoring treatment
  o Bisphosphonates
• Use in the individual for identifying response
• Use in monitoring the offset of therapy
  o Oral bisphosphonates
Case Report

• 70 year old woman
• Osteopenia noted on spinal radiographs
• Treated with alendronate 70 mg once a week, calcium and vitamin D
• BMD T-score at the total hip and lumbar spine -3
• Bone turnover markers
  o Baseline CTX 500 ng/L, 6 months 120 ng/L
  o Baseline PINP 60 ug/L, 6 months 20 ug/L
• At review after 6 months, is she responding or not?
Bone Turnover Markers (BTM)

**Resorption**
- Collagen degradation products
  - Pyridinium cross-links of collagen
    - Deoxypyridinoline (DPD)
    - C- and N-telopeptides (CTX, CTX-MMP, NTX)
- Enzyme
  - Tartrate-resistant acid phosphatase (TRACP)

**Formation**
- Matrix protein
  - Osteocalcin (OC)
  - Propeptides of type I procollagen
    - C- and N-terminal (PICP, PINP)
- Enzyme
  - Bone alkaline phosphatase (Bone ALP)

IOF/IFCC proposed CTX and PINP as reference markers
Sources of Variability in BTM (NBHA)

Controllable
- Circadian variation
- Food intake
- Menstrual
- Seasonal
- Exercise
- Lifestyle

Uncontrollable
- Age
- Gender
- Menopausal status
- Pregnancy and lactation
- Renal failure
- Geography
- Ethnicity
- Diseases and drugs
- Fracture

Clinical Uses of BTM

Risk assessment

• Prediction of bone loss
• Prediction of fracture
• Identification of secondary osteoporosis

Treatment

• Selection of treatment
• Monitoring of response
  o Identification of poor adherence
• Monitoring of offset of effect
Use for monitoring treatment

Anti-resorptive
The TRIO Study

• 2-year, open-label, parallel randomised control trial of oral ibandronate, alendronate and risedronate, at their licensed dose

• Aim: to examine and compare their effects on bone turnover and BMD

• 172 postmenopausal women (53–84 years) with osteoporosis
  
  o Measurements on treatment (12 and 13 weeks) allow study of variability of 5 BTMs on treatment, least significant change

• Premenopausal women (33–40 years, n=226) were concurrent controls
  
  o Allows calculation of reference intervals

BTM is Usually ‘Normal’ in Osteoporosis
TRIO Study, n=172

• Only 20% have high bone turnover at baseline.

Effect of Alendronate Therapy in Osteoporosis: Bone Resorption Markers, TRIO Study

Effect of Alendronate Therapy in Osteoporosis: Bone Formation Markers, TRIO Study

% change from baseline

Week

Bone ALP
OC
PINP
Vertebral fracture risk reduction is related to reduction in BTM: FNIH Bone Quality Study
Use in the individual for identifying response
A responder is someone whose result exceeds the least significant change

LSC = least significant change (also, RCV, reference change value)
Least significant change for CTX, 56%
Change at 12 weeks

Responders
84% 98% 78%

Least significant change for PINP, 38%
Change at 12 weeks

Responders
94% 82% 75%

Target for Treatment: Bone Turnover Marker in the Lower Half of the Reference Interval

Alendronate Therapy for Osteoporosis

Responders

96% 96%

82% 94%

Naylor...Eastell. Osteoporos Int. 2016 Jan;27(1):21-31
Targets for Therapy

Greater than the least significant change

- Statistical approach
- Large reductions in BTM are associated with low fracture risk
- Requires BTM before and during treatment
  - Initial value may be useful
- Example: PINP reduced by 10 ug/L, or more

Below the mean value for healthy young women

- BTM level associated with minimal bone loss
- Low bone turnover is associated with low fracture risk
- Only requires a BTM on treatment
- Example: reduce PINP to below 35 ug/L
The problem of adherence

- Bisphosphonates (BPs) are considered a first-line treatment of osteoporosis
- Adherence to BPs has been reported at 50% or below after one year\(^1\text{-}^3\)
- Low adherence results in lack of efficacy (no or limited decrease in fracture risk) and reduced cost effectiveness\(^4\)

Algorithm for adherence screening: International Osteoporosis Foundation and European Calcified Tissue Society

Baseline BTM (PINP, CTX) → 3-months BTM (PINP, CTX)

- BTM Decrease > LSC → Continue Treatment
- BTM Decrease < LSC → Reassess Treatment

Treatment initiation

Oral bisphosphonate monitoring algorithm

**Baseline**
- Decision to treat
- Baseline PINP or CTX

**1 month**
- Compliance check

**6 months**
- PINP or CTX to check response

**5 years**
- Reassess fracture risk using DXA
- Consider “pause” in treatment

**PINP response defined by:**
- Decrease $\geq 10$ µg/L
- Decrease to $\leq 35$ µg/L

**CTX response defined by:**
- Decrease $\geq 100$ ng/L
- Decrease to $\leq 280$ pg/L

Approach to non-response

3-6 month BTM

Bone turnover suppressed
Continue treatment

Bone turnover not suppressed
Reassess treatment
?compliance
?other issues

Types of BTM response observed in general practice

Response, and target
Response, not target
No response, target
No response, not target
Increase

Response is decrease more than 10, target is below 35 ug/L

Case Report

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• Osteopenia noted on spinal radiographs
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• BMD T-score at the total hip and lumbar spine -3
• Bone turnover markers
  o Baseline CTX 500 ng/L, 6 months 120 ng/L
  o Baseline PINP 60 ug/L, 6 months 20 ug/L
• At review after 6 months, is she responding or not?
  o YES, she is responding and she met her target
BTM to assist management decision

BMD decrease or fracture on alendronate

Bone turnover not suppressed

?adherence ?absorption
Consider parenteral treatment

Bone turnover suppressed

Consider anabolic treatment
Use in monitoring the offset of therapy

Oral bisphosphonate
Atypical Fractures of the Femur Have Been Associated with Long-term Bisphosphonate Therapy

- Fracture of the subtrochanteric region or femoral shaft
- Transverse of short oblique orientation
- Minimal trauma
- Medial spike
- No comminution

Can we limit the risk by using ‘Drug Holidays’?

Effect of alendronate on hip BMD over 10 years: FIT and FLEX

![Graph showing the effect of alendronate on hip BMD over 10 years: FIT and FLEX](image)

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BISPHOSPHONATES
Changes in Bone Resorption (NTX/Cr) after Alendronate for 0, 2, 4 and 6 Years (EPIC)

McClung MR. Osteoporos Int. 2015 May;26(5):1455-7
How Quickly Does Anti-resorptive Effect Wear off after Stopping Oral Bisphosphonates?

• 57 women with postmenopausal osteoporosis
• Treatments stopped for two years
BTM to monitor offset of bisphosphonate treatment

Baseline BTM when decision made to stop treatment
Repeat BTM at 12 months

- BTM $\geq$ threshold or increase by $>\text{LSC}$
  - *Reversal of treatment*
  - Exclude other causes for increased BTM
  - Consider restarting treatment

- BTM $<\text{threshold and increase by } <\text{LSC}$
  - *Continued response*
  - Continue to monitor off treatment
  - BTM every 12 months
Case Report

• 70 year old woman
• Osteopenia noted on spinal radiographs
• Treated with alendronate 70 mg once a week, calcium and vitamin D
• BMD T-score at the total hip and lumbar spine -3
• Bone turnover markers; treatment stopped at 60 months
  o Baseline CTX 500 ng/L, 60 months 120 ng/L, 72 months 400 ng/L
  o Baseline PINP 60 ug/L, 60 months 20 ug/L, 72 months 40 ug/L
• She is showing signs of offset of effect with PINP increasing by more than 10, to above 35 ug/L
Case examples
Female, 87 years old, clinic follow up

- Osteoporosis
- Previous fractures: left femur, left shoulder, right wrist, vertebral L3, L4
- Treatment: alendronate for 10 years, stopped 2017. Now on calcium and vitamin D

- Vertebral fracture assessment performed, suspicion for new fracture at L2, confirmed by radiographs
- Investigations normal

- How would you treat?
Female, 87 years old, clinic follow up (cont.)

- Treatment options: teriparatide, denosumab, bisphosphonate
- PINP 140μg/L

- What treatment would you give?

- Decision
  - Treat with zoledronate
Female 78y, clinic follow up

- Osteoporosis, no fractures
- PMH: AF, Parkinson’s disease

- Treatment:
  - alendronate, 2004-2008
  - zoledronate, six annual infusions 2008-2013

- BMD:
  - T score spine -2.9, hip -2.3.
  - 5% loss since 2017

What would you do?
Female 78y, clinic follow up (cont.)

- PINP 36µg/L

- Would you treat?

- Previous result PINP 8µg/L in 2013
  - >10 µg/L increase, above 35 µg/L

- Decision: One more infusion of zoledronic acid
Summary

• Bone turnover markers show large and early response to anti-resorptive or anabolic therapy
  o Response is indicated by a decrease beyond the least significant change
  o Target is reached if beyond the mean value for young women
  o Response relates to fracture risk reduction

• Bone turnover markers are partially suppressed for several years after stopping bisphosphonate therapy, but not other therapies
  o Offset of effect may be detected earliest by bone turnover markers
Q & A
THANK YOU

On behalf of IOF, we thank you for your participation in this webinar.

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