Bone Turnover Markers For Monitoring Treatment of Osteoporosis

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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 Anti-resorptive
  o Anabolic drugs
• Use in the individual for identifying response
• Use in monitoring the offset of therapy
  o Oral bisphosphonate
  o Denosumab
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
  - Baseline CTX 500 ng/L, 6 months 120 ng/L
  - Baseline PINP 60 ug/L, 6 months 20 ug/L
- At review after 6 months, is she responding or not?
Bone Turnover Markers (BTM)

Matrix protein
- Osteocalcin (OC)
- Propeptides of type I procollagen
  - C- and N-terminal (PICP, PINP)

Enzyme
- Bone alkaline phosphatase (Bone ALP)

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

Enzyme
- Tartrate-resistant acid phosphatase (TRACP)

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
Anabolic drugs
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
  - 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
  - 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

![Graph showing the effect of Alendronate therapy on bone resorption markers over 96 weeks. The graph compares the percentage change from baseline for CTX and NTX groups.](image-url)
Effect of Alendronate Therapy in Osteoporosis: Bone Formation Markers, TRIO Study

Naylor...Eastell. Osteoporos Int. 2016 Jan;27(1):21-31
Zoledronic Acid: The Horizon Study

Antiresorptive treatments reduce the level of both bone resorption (CTX) and bone formation (PINP) markers (coupling)

Vertebral fracture risk reduction is related to reduction in BTM: FNIH Bone Quality Study
Teriparatide: DATA Extension Study

B  P1NP

\[
\begin{align*}
\text{% change} & \quad \text{Month} \\
0 & \quad 0 \\
50 & \quad 6 \\
100 & \quad 12 \\
150 & \quad 18 \\
200 & \quad 24
\end{align*}
\]

C  CTX

\[
\begin{align*}
\text{% change} & \quad \text{Month} \\
0 & \quad 0 \\
50 & \quad 6 \\
100 & \quad 12 \\
150 & \quad 18 \\
200 & \quad 24
\end{align*}
\]

Abaloparatide: ACTIVE Study

Use in the individual for identifying response
A responder is someone whose result exceeds the least significant change.

$LSC = \text{least significant change (also, RCV, reference change value)}$
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%

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

Action at 6-month monitoring

6 month PINP

PINP $< 35 \, \mu g/L$ and/or decrease by $> 10 \, \mu g/L$

- **Good response**
  - Continue treatment and encourage continued compliance

PINP $> 35 \, \mu g/L$ (CTX$> 280$) and decrease by $< 10 \, \mu g/L$ (CTX 100)

- **Suboptimal response**
  - Evaluate & either correct reason for poor response or change treatment
Target for Treatment: Bone Turnover Marker in the Lower Half of the Reference Interval

Alendronate Therapy for Osteoporosis

PINC:µg/L

- 12
- 48

Responders
96% 96%

CTX:µg/L

- 12
- 48

Responders
82% 94%

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
Sheffield PINP monitoring algorithm

Baseline
- Decision to treat
- Baseline PINP

1 month
- Compliance check

6 months
- PINP to check response

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

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 µg/L

Case Report

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- Bone turnover markers
  - Baseline CTX 500 ng/L, 6 months 120 ng/L
  - Baseline PINP 60 ug/L, 6 months 20 ug/L
- At review after 6 months, is she responding or not?
  - YES, she is responding and she met her target
Teriparatide monitoring algorithm

PINP response defined by:
- Increase ≥10 µg/L
- Increase to ≥69 µg/L
PINP change with teriparatide in clinical practice

Response defined by:
- Increase $\geq 10$ µg/L (LSC)
- Increase to $\geq 69$ µg/L (target)

Response
- LSC and target
- LSC, not target
- Neither LSC nor target

Use in monitoring the offset of therapy

Oral bisphosphonate
Denosumab
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 Alendronic Acid on Hip BMD over 10 Years: FIT and FLEX

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

When do we re-start bisphosphonates after a drug holiday?

An increase, greater than the least significant change

- Statistical approach
- Example: increase in PINP of 10 ug/L

Above the mean value for healthy young women

- Low bone turnover is associated with low fracture risk
- Example: consider re-treatment when PINP increases above 35 ug/L

These approaches need further research
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
Effects of Denosumab Treatment and Discontinuation on Bone Turnover

Bone HG et al, J Clin Endocrinol Metab. 2011;96(4):972-980
Recent reviews

Osteoporosis 2

Use of bone turnover markers in postmenopausal osteoporosis

Richard Eastell, Pawel Szulc

Bone turnover comprises two processes: the removal of old bone (resorption) and the laying down of new bone (formation). N-terminal propeptide of type I procollagen (PINP) and C-telopeptide of type I collagen (CTX-I) are markers of bone formation and resorption, respectively, that are recommended for clinical use. Bone turnover

DIAGNOSIS OF ENDOCRINE DISEASE

Bone turnover markers: are they clinically useful?

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Summary

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

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