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Bone Turnover Markers For Monitoring Treatment of Osteoporosis

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30<sup>th</sup> Annual Metabolic Bone Disease Society, Denver, October 12, 2018

## **Conflicts of Interest**

#### Consultant and research grants

- Immunodiagnostic Systems
- Roche Diagnostics
- o Nittobo
- $\circ$  Amgen

## Outline

- Introduction to bone turnover markers
- Use for monitoring treatment
  - Anti-resorptive
  - Anabolic drugs
- Use in the individual for identifying response
- Use in monitoring the offset of therapy
  - 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)





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

#### Szulc P, et al. Osteoporos Int. 2017 Sep;28(9):2541-2556

## **Clinical Uses of BTM**

**Risk assessment** 

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

#### Treatment

- Selection of treatment
- Monitoring of response
  Identification of poor adherence
- Monitoring of offset of effect

#### Eastell R, et al. Eur J Endocrinol. 2018 Jan;178(1):R19-R31





# 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

Paggiosi et al Osteoporos Int 2014;25(12):2729-41, Naylor KE, et al Osteoporos Int. 2016 Jan;27(1):21-31

#### BTM is Usually 'Normal' in Osteoporosis TRIO Study, n=172



sCTX, µg/L



Only 20% have high bone turnover at baseline

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

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



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

# 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**







#### Black DM, et al. N Engl J Med. 2007 May 3;356(18):1809-22

#### **Denosumab: the FREEDOM Trial**



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

Eastell R, et al. J Bone Miner Res. 2011 Mar;26(3):530-7

#### Raloxifene



Naylor KE, et al. Osteoporos Int. 2016 Aug;27(8):2585-92

#### Vertebral fracture risk reduction is related to reduction in BTM: **FNIH Bone Quality Study**



Raloxifene

Lasofoxifene

Bauer DC...Eastell R. J Bone Miner Res. 2018 Apr;33(4):634-642

Risedronate

 $\bigcirc$ 

Zoledronic acid

#### **Teriparatide: DATA Extension Study**



Leder BZ, et al. J Clin Endocrinol Metab. 2014 May;99(5):1694-700

### Abaloparatide: ACTIVE Study



Miller PD, et al. JAMA. 2016 Aug 16;316(7):722-33





# 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)

Paggiosi et al Osteoporos Int 2014;25(12):2729-41, Naylor KE, et al Osteoporos Int. 2016 Jan;27(1):21-31

#### Least significant change for CTX, 56% Change at 12 weeks



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

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



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

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



Diez Perez,...Eastell. Osteoporos Int. 2017 Mar;28(3):767-774



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

#### Alendronate Therapy for Osteoporosis



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

#### Sheffield PINP monitoring algorithm



Eastell et al. European Journal of Endocrinology (2018) 178, R19–R31

## Types of BTM response observed in general practice



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

Eastell R, et al. Eur J Endocrinol. 2018 Jan;178(1):R19-R31.

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  - 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



Eastell et al. European Journal of Endocrinology (2018) 178, R19–R31

### PINP change with teriparatide in clinical practice



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



#### Eastell et al. European Journal of Endocrinology (2018) 178, R19–R31





# 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



Shane E, et al. *J Bone Miner Res.* 2014;29(1):1-23 Neviaser AS, et al. *J Orthop Trauma*. 2008 May-Jun;22(5):346-50.

# Effect of Alendronic Acid on Hip BMD over 10 Years: FIT and FLEX



Black DM, et al. JAMA. 2006;296:2927-2938.

## 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 postmenopausa l osteoporosis
- Treatments stopped for two years



Naylor...Eastell. Osteoporos Int. 2018 Jun;29(6):1407-1417

#### 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

## **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
  - Baseline CTX 500 ng/L, 60 months 120 ng/L, 72 months 400 ng/L
  - 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 Lancet Diabetes Endocrinol 2017 (formation). N-terminal propeptide of type I procollagen (PINP) and C-telopeptide of type I collagen (CTX-I) are Published Online markers of bone formation and resorption, respectively, that are recommended for clinical use. Bone turnover July 6, 2017



#### 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