Markers of bone formation

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Markers of bone formation

Alkaline phosphatase

- Ubiquitous, membrane-bound enzyme
- Total ALP: serum pool originated from bone, liver, intestine, spleen, kidney and placenta.
- Bone ALP: specific product of osteoblasts

Markers of bone formation

Type I collagen propeptides

- Indices of type I collagen synthesis
- PINP & PICP are products of the extracellular processing of type I procollagen

Osteoblast differentiation and maturation

- Osteopontin
- Fibronectin
- Collagen
- Histone
- Alkaline phosphatase
- Bone sialoprotein
- Osteocalcin
- Collagenase

Markers of bone formation

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Markers of bone formation

Osteocalcin

- 15% of non-collagenous protein fraction of bone matrix.
- Contains 3 residues of γ-carboxy glutamic acid.
- Circulating osteocalcin: synthesized by OB and released from matrix by OC.

Osteocalcin

Circulating immunoreactive forms

- OC is present as the intact molecule and as fragments.
- The assay that measures both the intact molecule and the N-mid-fragment is the most robust and sensitive.

Evaluation of assays of bone formation markers

- **EALP**
  - **Pros**: Specific product of osteoblasts.
  - **Cons**: 10-20% cross-reactivity with liver isoenzymes.

- **OC**
  - **Pros**: Bone specific, precise.
  - **Cons**: Some may be dimer or tetramer, serum cross-reactivity.

- **PINP**
  - **Pros**: Robust in sample conditions, sensitive, specific to osteoblastic bone.
  - **Cons**: Other tissue synthesized type I collagen.

- **PICP**
  - **Pros**: Bone specific properties.
  - **Cons**: Disappointing results in osteoporosis.

Clinical uses of bone formation markers

- **Rate of bone turnover**
  - Prediction of fracture risk.
  - Prediction of response to therapy.
Only about one-half of women with incident fractures have BMD below a T-score < -2.5.

Not all women with osteoporosis (BMD criteria) will suffer fractures.

To identify women at high risk of fracture.

Why measure?

- Increased values of bone markers, particularly those of bone resorption, are associated with increased fracture risk, independently of BMD.
- Bone resorption markers have proved to be more useful than formation markers in the prediction of fracture risk.

Goal

Bone markers and FRAX model

World Health Organization Fracture Risk Assessment Tool

Bone markers have not been included in the FRAX algorithm because:
- No agreement on a reference analyte.
- Insufficient world-wide experience to know how they might be incorporated.

The manner in which the results of such tests are interpreted is a matter of clinical judgement.
Bone markers in monitoring the effectiveness of therapy

Why measure?
- Long-term treatment
- Poor compliance and persistence
- Other unidentified intercurrent diseases
- Problems with other markers of treatment efficacy:
  - Clinical endpoint: Low incidence of fractures (first year/s)
  - Surrogate endpoint: Long interval using BMD and a LSC > 2-5%
  - Change in BMD during therapy poorly reflects change in fracture risk

Goal
- To determine when anti-catabolic or anabolic therapy may be effective

Drugs used to treat osteoporosis

Classification based on their action on bone remodeling

Anti-catabolic drugs
- Estrogens
- SERM: raloxifene
- Bisphosphonates:
  - Etidronate
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronic acid
- Calcitonin

Anabolic drugs
- Teriparatide
- PTH 1-84

Response of bone markers to treatment

Anti-catabolic drug

Anabolic drug

Predicition of therapeutic efficacy by formation markers

Anti-catabolic drugs

Bisphosphonates
- Etidronate
- Alendronate
- Risedronate
- Ibandronate
- Zoledronic acid
- Calcitonin

Strontium ranelate

Bone markers

- Bone markers in monitoring the effectiveness of therapy
- Drug treatments
- Response of bone markers to treatment
- Prediction of therapeutic efficacy by formation markers

Clinical trial

Barcelona
Prediction of therapeutic efficacy by formation markers

Anabolic drugs (Teriparatide)

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r = 0.62
p < 0.05

Chen et al. J Bone Miner Res 2005

Relationship between PINP and BMD changes (18 mos)

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Signal-to-noise ratio of bone formation markers

Effect of fracture on bone formation markers

Ivaska et al. JBMR 2007

Monitoring individual patients by bone formation markers


Control of variability
- Adequate reference ranges (35 - 45 years)
- Timing of sample (fasting)

Interpreting results
- Awareness of selected bone marker (OC, BALP, PINP)
- Adequate intervals of measurement
  - anti-catabolic drugs: oral 0-6 mo; iv 0-3 mo
  - anabolic drugs: 3-9 mo
- Considering LSC for each marker
  - PINP: 20% - 10 µg/L; OC: 21%; BALP: 26%

Awareness of recent fractures
- Awareness of intercurrent or associated diseases

Algorithm for using PINP to monitor treatment with teriparatide

Start therapy

PINP

PINP increase

Provide neutral feedback

Provide positive feedback

Review injection technique, storage, adherence, and potential medical problems limiting response

Effect of fracture on bone formation markers

Start therapy

PINP increase

> 10 µg/L

< 10 µg/L

No issues

Issues

Effect of fracture on bone formation markers

Start therapy

PINP increase

> 10 µg/L

< 10 µg/L

No issues

Issues

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Using bone formation markers in monitoring therapy in an individual patient

A 64-year-old woman with 2 prior fragility fractures and low BMD who started treatment with:

- Alendronate

Markers of bone formation in assessing the activity of Paget's disease

Key points

- Bone formation markers, in combination with a variety of major risk factors, may contribute to identifying women at high risk of fracture. However, resorption markers appear to be more adequate.

- Bone formation markers are useful in the prediction of response to anti-catabolic drugs, but especially to anabolic drugs.

- Each bone formation marker must be used in the appropriate clinical setting and the clinician must know the main sources of variability.