

**ECTS**  
**35th European Symposium**  
**on Calcified Tissues**  
 24-28 May 2008 BARCELONA SPAIN

**Markers of bone formation**  
 Núria Guañabens

**Osteoblast differentiation and maturation**

|   |   |   |                |
|---|---|---|----------------|
| Osteopontin<br>Fibronectin<br>Collagen<br>Histone | Alkaline phosphatase<br>Bone sialoprotein<br>Collagen | Osteocalcin<br>Osteopontin<br>Collagenase | <b>markers</b> |
|---|---|---|----------------|

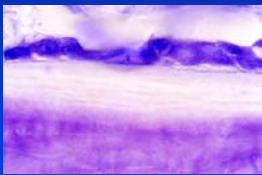
proliferation      matrix maturation      matrix mineralization      apoptosis

growth      differentiation

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**Markers of bone formation**  
**Alkaline phosphatase**

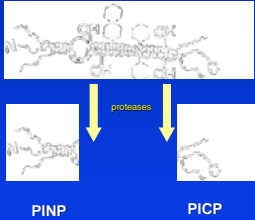
- Ubiquitous, membrane-bound enzyme
- **Total ALP**: serum pool originated from bone, liver, intestine, spleen, kidney and placenta.
- **Bone ALP**: specific product of osteoblasts



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**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

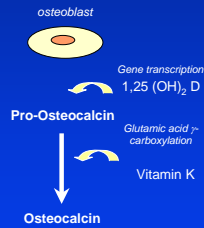


PINP      PICP

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## Markers of bone formation Osteocalcin

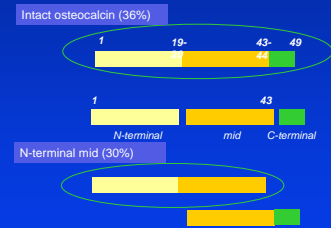
- 15 % of non-collagenous protein fraction of bone matrix
- Contains 3 residues of  $\gamma$ -carboxy-glutamic acid
- Circulating osteocalcin: neosynthesized by OB and released from matrix by OC



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## 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.

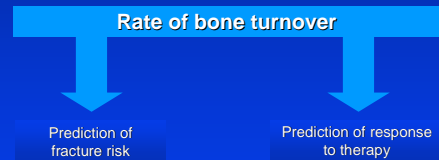


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## Evaluation of assays of bone formation markers

|                 | pros  | cons  |
|-----------------|---|---|
| <b>BALP</b>     | Specific product of osteoblasts.<br>Small circadian variability       | 10-20% cross-reactivity with liver isoenzyme  |
| <b>OC</b>       | Bone specific protein   | Some may be derived from resorption<br>Different immunoreactive forms<br>Unstable assay<br>Limited value in renal failure and Paget's |
| <b>PINP</b>     | Robust to sample conditions<br>Measures monomeric and trimeric forms. | Other tissues synthesize type I collagen  |
| <b>PICP</b>     |   | Disappointing results in osteoporosis   |
| <b>Under-OC</b> | Bone matrix properties?   | Little experience<br>Changes of unclear significance  |

## Clinical uses of bone formation markers



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## Bone markers in the identification of high risk of fracture

### Why measure?

- 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

### Goal

- To identify women at high risk of fracture

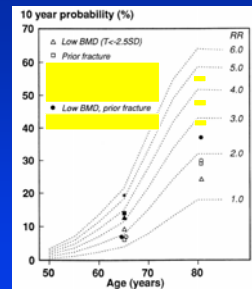
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## Bone markers and high risk of fracture

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

Cauffman et al. *JAMA* 2005  
Cummings et al. *Ann Intern Med* 2002  
Lee et al. *Journal of Bone and Mineral Research* 2006

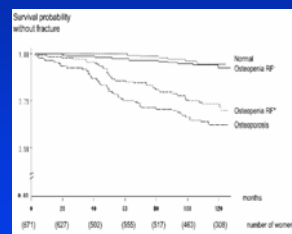
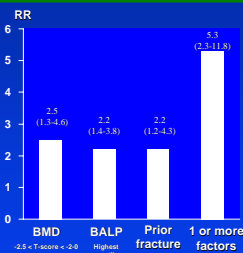


Johann et al. *Osteoporosis Int* 2002

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## Bone formation markers and risk of fracture in osteopenic women

OFELY study



Strawderman et al. *JAMA* 2005

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## 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

<http://www.sciencedirect.com/science/article/pii/S1473214905000000>

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## 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 > 3-5%
- 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 remodelling

### Anti-catabolic drugs

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



### Anabolic drugs

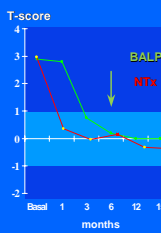
- Teriparatide
- PTH 1-84



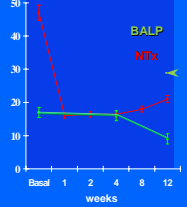
Strontium ranelate

## Response of bone markers to treatment

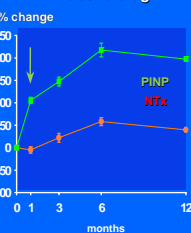
### Anti-catabolic drug



Mean (±SE)



### Anabolic drug



Cauley et al. J Clin Endocrinol Metab 1999

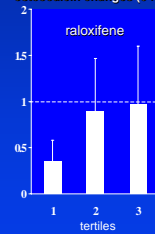
Singh et al. Bone 2007

Stachura et al. Bone 2007

## Prediction of therapeutic efficacy by formation markers

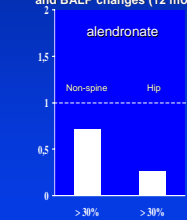
### Anti-catabolic drugs

RR of vertebral fracture and osteocalcin changes (6 mo)



Sturchler-Pierrat et al. Osteoporos Int 2001

HR of non-spine and hip fractures and BALP changes (12 mo)



Reinisch et al. J Bone Miner Res 2004

## Prediction of therapeutic efficacy by formation markers

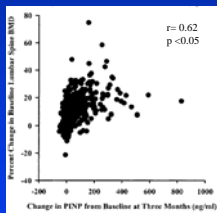
### Anabolic drugs (Teriparatide)

Signal-to-noise ratio of bone formation markers



Essell et al. Cur Med Res Opin 2006

Relationship between PINP and BMD changes (18 mo)



Chen et al. J Bone Miner Res 2005

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## Monitoring individual patients by bone formation markers

### Control of variability

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

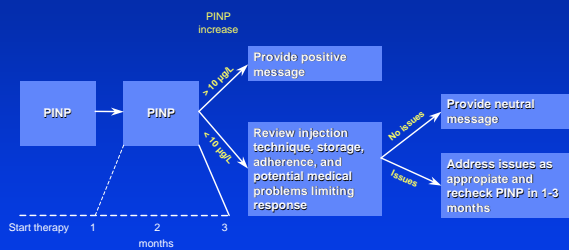
### Interpreting results

- 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: 0-3 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

Boyan, Bone 2008; Gevers, Clin Chim Acta; Alvarez, Bone 2010; Harris, JBM 2008

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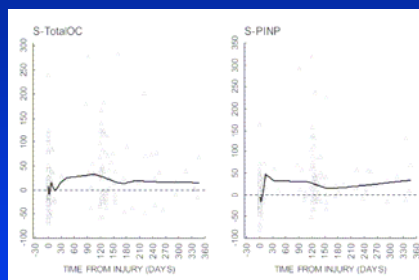
## Algorithm for using PINP to monitor treatment with teriparatide



Essell et al. Cur Med Res Opin 2006

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## Effect of fracture on bone formation markers



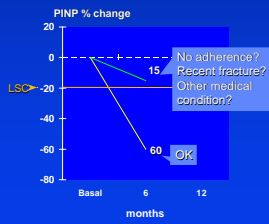
Wada et al. JBM 2007

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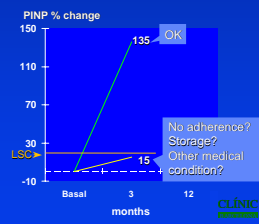
## Using bone formation markers in monitoring therapy in an individual patient

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

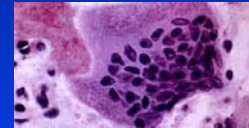
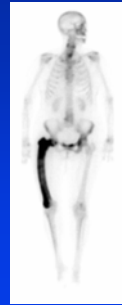
### Alendronate



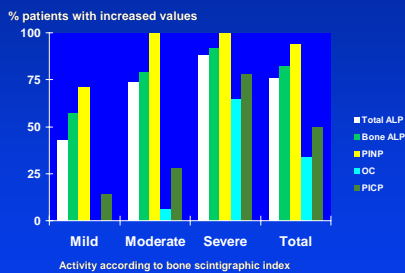
### Teriparatide



## Paget's disease



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



Alvarez et al. *Arthritis & Rheum* 1997

## 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.

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