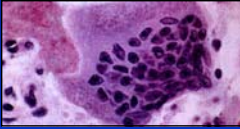




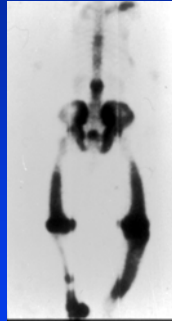
### Paget's bone disease

Disorder characterized by a marked increase in bone turnover in localized parts of the skeleton

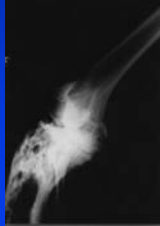
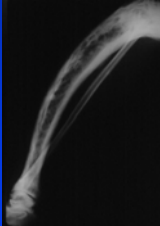
The primary event is an intense focal bone resorption rapidly followed by disordered bone formation

### Paget's bone disease

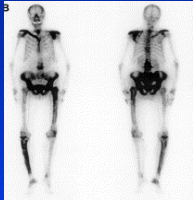


Bone scintigraphy is the most reliable method for evaluating the extent and the activity of the disease

The diagnosis is based on radiological study





### Paget's bone disease




Biochemical markers of bone turnover have proven to be of value in assessing the activity of the disease

There is a good correlation between bone markers and scintigraphic indices of disease activity



**FORMATION:** Total alkaline phosphatase (Total ALP)



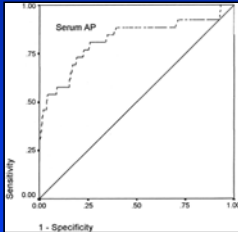
**RESORPTION:** Hydroxyproline (HYP)

### Usefulness of bone makers in Paget's disease

- Diagnosis of Paget's disease
- Evaluation of disease activity
- Monitoring treatment
- Evaluation of qualitative bone changes

## Diagnosis of Paget's bone disease

Serum Total ALP is a good indicator of Paget's disease in Dutch population



The relative risk for Paget's disease in the presence of increased Total ALP was 10.9 (95% CI, 4.8, 24.9) (in absence of associated liver disease)

20.5 % of subjects with elevated Total ALP had Paget's disease

However most pagetic population from this study (86%) had normal Total ALP

Tekampol / J Bone Miner Res 2003

## Usefulness of bone markers in Paget's disease

- Diagnosis of Paget's disease
- Evaluation of disease activity
- Monitoring treatment
- Evaluation of qualitative bone changes

## Evaluation of Paget's disease activity



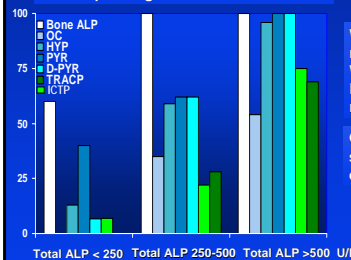
There is a good correlation between bone markers and scintigraphic indices of disease activity

	Total ALP	Bone ALP	PINP	HYP	NTX
SAI	0.686 (0.0004)	0.772 (0.0001)	0.886 (0.0001)	0.705 (0.0003)	0.863 (0.0001)

Alvarez L, Parfitt P et al. Bone 2001

## Evaluation of Paget's disease activity

% increased values in bone markers depending on serum Total AP



When disease activity is high most bone markers are increased. When disease activity is low, Bone ALP is the most sensitive marker.



Other markers: OC, ICTP, TRACP show a low sensitivity in Paget's disease.

Alvarez L, Ceballos N, Parfitt P et al. JBMR 1995

### Evaluation of Paget's disease activity

When additional markers of bone turnover were analyzed:

Bone markers determined:

- **FORMATION:** 
- **RESORPTION:** 

Total ALP, Bone ALP, PINP, PICP, OC

HYP, PYR, D-PYR, NTX,  $\beta$ -CTX, TRACP, ICTP

PINP, Bone ALP and NTX were more sensitive than Total ALP in mild disease

From ROC plots PINP, Bone ALP and NTX were the most sensitive markers


Whereas OC, PICP, ICTP and TRACP were the least sensitive markers

Advances in Paediatric Rheumatology 1997

### Evaluation of Paget's disease activity

Bone markers recommended for the evaluation of disease activity

- Total ALP
- Bone ALP (when Total ALP is normal)





- There is little clinical benefit to be obtained from routine clinical use of resorption markers

Sokal PJ. Guidelines on the management of Paget's disease. Bone 2002

### Evaluation of Paget's disease activity

Bone markers not recommended in the evaluation of Paget's disease activity

- Osteocalcin
- PICP
- TRACP (Hillman method)
- ICTP

### Usefulness of bone makers in Paget's disease

- Diagnosis of Paget's disease
- Evaluation of disease activity
- **Monitoring treatment**
- Evaluation of qualitative bone changes

## Monitoring treatment

The aim of treatment is to relieve symptoms and prevent complications and the primary treatment is with bisphosphonates



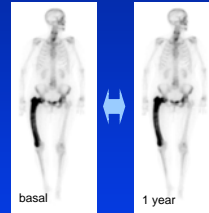
The evaluation of bone markers is easily measured and provides a rapid indication of treatment effects

It has been indicated that the measurement of bone markers should be carried out every 3 months (first 6 months of therapy) and then at 6 month intervals. A change > 25% in Total ALP is considered significant.

*Guidelines on the management of Paget's disease, Bone 2002*

## Monitoring Paget's disease activity

Variability of bone markers in patients with Paget's disease



15 pagetic patients with stable disease

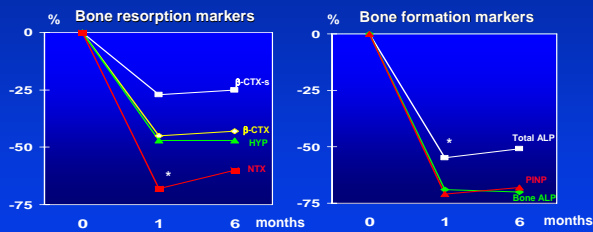
Bone marker	Critical difference (%)
Total ALP	35
Bone ALP	25
PINP	35
HYP	53
β-CTX	70
NTX	47

Variations > 35% for serum Total ALP and > 25% for serum Bone ALP seem to be more appropriate in representing a significant change in disease activity

*Alvarez L, Pariz P et al. Bone 2000*

## Monitoring treatment

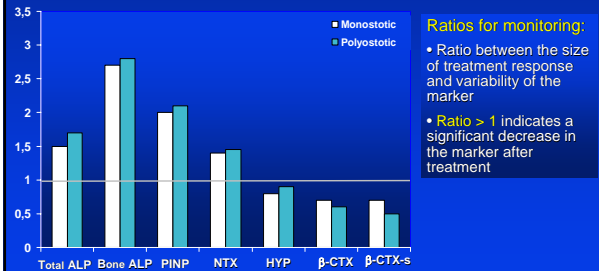
Evolution of bone markers after treatment with tiludronate (3 months)



*Alvarez L, Granados J, Pariz P et al. Bone 2001*

## Monitoring treatment

Ratios of bone markers for monitoring changes



Ratios for monitoring:

- Ratio between the size of treatment response and variability of the marker
- Ratio > 1 indicates a significant decrease in the marker after treatment

*Alvarez L, Granados J, Pariz P et al. Bone 2001*

## Long-term evolution after tiludronate therapy

32 pagetic patients treated with tiludronate (400 mg/d x 3 months)

### METHODS:

Biochemical determinations:

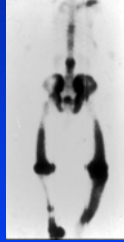
- Total ALP
- Bone ALP
- PINP

Urinary determination:

- NTX

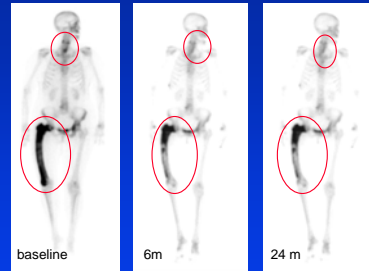
Baseline, 1, 6, 12 y 24 m.  
After discontinuation of therapy

Quantitative bone scintigraphy: obtaining the scintigraphic activity index (SAI) at baseline, 6, 24 m.



Alvarez L, Peris P et al. Rheumatology 2004

## Long-term assessment of disease activity



Patients were classified in 2 groups depending on response to therapy:

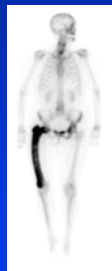
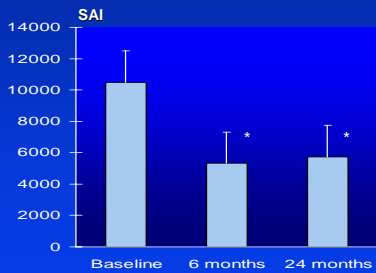
- G-I: patients with persistent decrease in the activity of the disease at 24 months
- G-II: patients with a relapse in the activity of the disease at 24 months

Response to therapy: decrease of SAI >13% (baseline-6m)

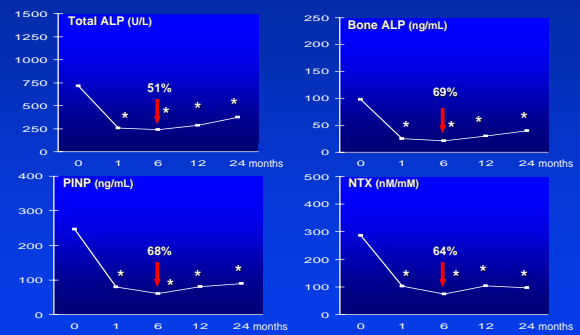
Relapse of disease activity: increase of SAI >13% (6-24m)

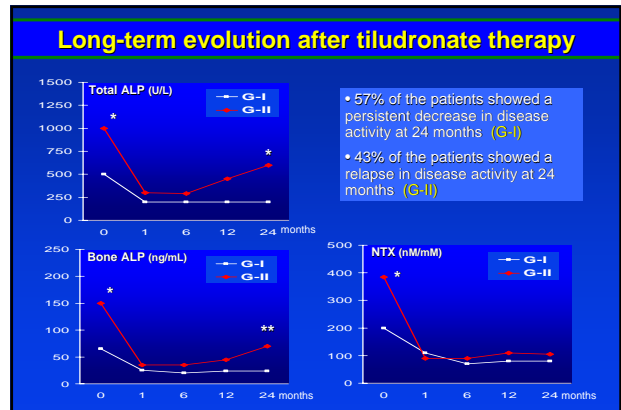
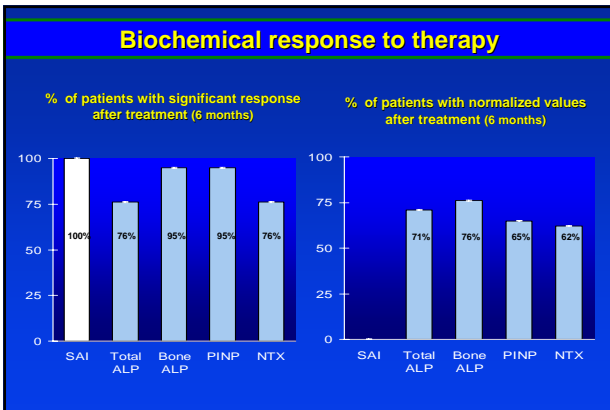
## Long-term assessment of disease activity

Evolution of the scintigraphic activity index



## Long-term evolution after tiludronate therapy





### Long-term evolution after tiludronate therapy

Percentage of patients with biochemical relapse at 12 and 24 months

	Group I		Group II	
	12 months	24 months	12 months	24 months
Total ALP	0%	0%	13%	33%
Bone ALP	33%	45%	57%	100%
PINP	0%	50%	29%	78%
NTX	10%	20%	25%	22%

**Factors related to long-term relapse**

Baseline Total ALP > 600 U/L (OR 6(0.89;40.3)) or Bone ALP > 60 ng/L (OR 10.5 [1.3;81.05])

Alvarez L, Pons F et al. Rheumatology 2009

- ### Recommendations
- The relapse of disease activity depended on baseline activity of the disease and the marker used in the evaluation
  - It seems appropriate to monitor treatment at 6 months after the end of therapy and thereafter at 6-month intervals in more active patients at baseline (Total ALP > 600 U/L) and on a yearly basis in the remaining patients if serum Total ALP is analysed
  - If a more sensitive marker such as Bone ALP is used we recommend monitoring treatment at 6-month intervals, independently of baseline disease activity

### Other determinants of response to therapy

- Magnitude of response to therapy
- Doses and duration of therapy
- Skull involvement
- Number of affected bones
- Type of therapy and previous therapy

### Type of therapy and previous therapy

Patients achieving biochemical remission at 1 year of treatment

Evolution after treatment with Risedronate vs Zoledronic acid

Therapy	All patients	Previously untreated	Previously treated
Alendronate	~85%	~90%	~75%
Pamidronate	~55%	~85%	~15%

Days	Zoledronic acid	Risedronate
10	~10%	~10%
28	~65%	~25%
63	~75%	~45%
91	~80%	~60%
182	~90%	~65%

### Evaluation of Paget's disease activity

For unknown reasons skull involvement has been associated with markedly high serum Total ALP values

Monostotic patients with skull involvement show higher serum values of Total ALP per unit of affected area than monostotic patients with other locations

*Peiris P et al. Calcif Tissue Int 2006*

### Skull involvement

Biochemical normalization 6 months after the end of treatment with tiludronate in pagetic patients depending on skull involvement

Marker	Skull involvement	No skull involvement
TAP	~75%	~25%
BAP	~70%	~15%
PINP	~65%	~10%
NTX	~55%	~30%

Pagetic patients with skull involvement have a lower response to therapy

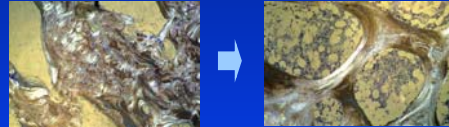
*Peiris P et al. Calcif Tissue Int 2006*

## Usefulness of bone makers in Paget's disease

- Diagnosis of Paget's disease
- Evaluation of disease activity
- Monitoring treatment
- Evaluation of qualitative bone changes

## Qualitative changes in Paget's disease

The decrease of bone turnover is associated with a resumption of formation of lamellar bone



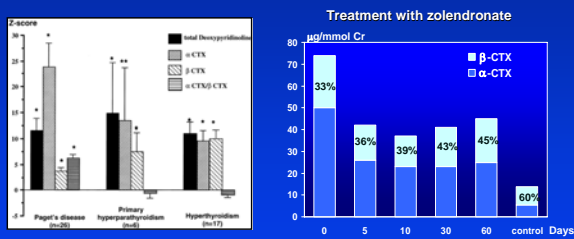
A site of the collagen type I C telopeptide can be spontaneously isomerized ( $\beta$ -CTX)

EKAHD- $\alpha$ -GGR  
( $\alpha$ -CTX)

EKAHD- $\beta$ -GGR  
( $\beta$ -CTX)

## Qualitative changes in Paget's disease

In Paget's disease there is an increase of the  $\alpha$ -CTX and the  $\alpha$ -CTX/ $\beta$ -CTX ratio (related to the woven pagetic bone)



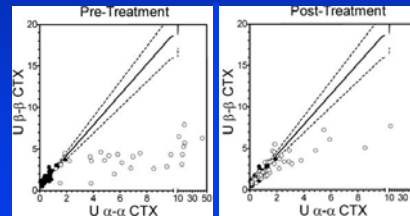
Diwanji, J Bone Miner Res 1997

Samaro, Arthritis Rheum 1998

## Qualitative changes in Paget's disease

32 pagetic patients treated with TLD (400 mg/d x 3 m.), evaluated at baseline, 1 and 6 months after therapy with biochemical markers (U  $\alpha$ -CTX, U  $\beta$ -CTX, NTx, U  $\alpha$  CTX, DPD, HYP, BoneALP, Total ALP, PINP, TRACP) and SAI

Correlation between U  $\alpha$ - $\alpha$  and  $\beta$ - $\beta$  CTX in patients (O) and in controls (●)



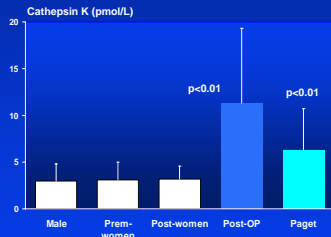
U  $\alpha$ - $\alpha$  CTX showed a marked reduction (-82%) after therapy and provided the highest correlation with SAI ( $r=0.89$ )

Alexanderson P, Poels P et al. J Bone Miner Res 2005



## Other bone markers

### Serum Cathepsin K in Paget's disease and postmenopausal osteoporosis



No significant correlation was observed between cathepsin K and bone markers (BALP or  $\beta$ -CTX)

Treatment with bisphosphonates was associated with a significant decrease in cathepsin K (-33%) only in postmenopausal OP

Walter O et al. J Clin Lab 2016

## Summary (1)

- Bone markers are useful tools for evaluating Paget's disease activity.
- Serum Total ALP is a good marker for evaluating moderate and severe active pagetic patients.
- In patients with monostotic or mild active disease, Bone ALP or PINP are the most sensitive bone formation markers, whereas  $\alpha$ - $\alpha$  CTX is the most sensitive bone resorption marker.

## Summary (2)

- Bone markers are useful for disease monitoring.
- Monitoring intervals depend on baseline disease activity, the marker used in monitoring and the type of therapy.
- Serum Bone ALP is the most sensitive marker for monitoring disease activity.
- $\alpha$ - $\alpha$  CTX seems to be a sensitive bone resorption marker for disease monitoring.
- Further studies are necessary to indicate the evaluation of qualitative changes in pagetic bone.