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.

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

The diagnosis is based on radiological study.

Usefulness of bone makers in Paget’s disease

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

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)
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.

Evaluation of disease activity

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

<table>
<thead>
<tr>
<th>Bone ALP</th>
<th>PINP</th>
<th>HYP</th>
<th>NTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAI</td>
<td>0.686</td>
<td>0.772</td>
<td>0.886</td>
</tr>
<tr>
<td>(0.0004)</td>
<td>(0.0001)</td>
<td>(0.0001)</td>
<td>(0.0003)</td>
</tr>
</tbody>
</table>

Usefulness of bone markers in Paget’s disease

- Diagnosis of Paget’s disease
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- Evaluation of qualitative bone changes

Evaluation of Paget’s disease activity

- 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.

<table>
<thead>
<tr>
<th>Bone ALP</th>
<th>D-PYR</th>
<th>TRACP</th>
<th>ICTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>% increased values in bone markers depending on serum Total ALP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ALP &lt; 250</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>250 - 500</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
When additional markers of bone turnover were analyzed:

Bone markers determined:
- **FORMATION**: Total ALP, Total ALP, PINP, ALP, PINP, PICP, OC
- **RESORPTION**: HYP, PYR, D-PYR, NTX, β-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.

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.

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

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.

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

Variability of bone markers in patients with Paget’s disease

<table>
<thead>
<tr>
<th>Bone marker</th>
<th>Critical difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ALP</td>
<td>35</td>
</tr>
<tr>
<td>Bone ALP</td>
<td>25</td>
</tr>
<tr>
<td>PINP</td>
<td>35</td>
</tr>
<tr>
<td>ICTA</td>
<td>72</td>
</tr>
<tr>
<td>NTX</td>
<td>47</td>
</tr>
</tbody>
</table>

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.

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

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.
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
- NTX

Urinary determination:
- NTX

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

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

Patients were classified in 2 groups depending on response to therapy:
- Group I: patients with persistent decrease in the activity of the disease at 24 months
- Group 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
Biochemical response to therapy

- % of patients with significant response after treatment (6 months)
- % of patients with normalized values after treatment (6 months)

Long-term evolution after tiludronate therapy

- 57% of patients showed a persistent decrease in disease activity at 24 months (G-I)
- 43% of patients showed a relapse in disease activity at 24 months (G-II)

Percentage of patients with biochemical relapse at 12 and 24 months

<table>
<thead>
<tr>
<th>Group</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-I</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td>G-II</td>
<td>20%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Factors related to long term relapse

- Baseline Total ALP > 600 U/L (OR 6.0 [0.89;40.3]) or Bone ALP > 60 ng/mL (OR 10.5 [1.3;81.05])

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

- Evolution after treatment with Risedronate vs Zoledronic acid

Patients achieving biochemical remission at 1 year of treatment

<table>
<thead>
<tr>
<th>Therapy</th>
<th>% Normalization of TAP</th>
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<tbody>
<tr>
<td>Risedronate</td>
<td>90%</td>
</tr>
<tr>
<td>Zoledronic</td>
<td>90%</td>
</tr>
</tbody>
</table>

Evolution after treatment with Risedronate vs Zoledronic acid

<table>
<thead>
<tr>
<th>Days</th>
<th>% Normalization of TAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10%</td>
</tr>
<tr>
<td>30</td>
<td>70%</td>
</tr>
<tr>
<td>60</td>
<td>90%</td>
</tr>
<tr>
<td>90</td>
<td>90%</td>
</tr>
<tr>
<td>120</td>
<td>90%</td>
</tr>
</tbody>
</table>

Type of therapy and previous therapy

- Evolution after treatment with Risedronate vs Zoledronic acid

Evaluation of Paget’s disease activity

- Monostotic patients with skull involvement show higher serum values of Total ALP per unit of affected area than monostotic patients with other locations
- Pagetic patients with skull involvement have a lower response to therapy

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

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<th>Treatment</th>
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For unknown reasons skull involvement has been associated with markedly high serum Total ALP values
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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 (β-CTX)

In Paget's disease there is an increase of the α-CTX and the α-CTX/β-CTX ratio (related to the woven pagetic bone)

Garnero J Bone Miner Res 1997
Garnero Arthritis Rheum 1998

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 α-CTX, U β-CTX, NTx, U α-CTX, OPC, HYP, BoneALP, Total ALP, PINP, TRACP) and SAI

Correlation between U α-CTX and β-CTX in patients (O) and in controls (I)

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

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

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.