Markers of bone turnover
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Mature bone is metabolically active and undergoes constant remodelling. Resorption of bone occurs via the osteoclasts, while replacement is undertaken by the osteoblasts. Bone remodelling is subject to regulation by a complex interaction of hormones, growth factors and cytokines and relies on adequate intake of phosphate and calcium. In health, the rate of resorption is matched by the rate of replacement.

Bone resorption Bone formation Quiescent bone

Osteoclast

Osteoblasts

Bone lining cells

Factors that alter the activity of the osteoclasts or osteoblasts can disrupt bone homeostasis and result in a decrease or increase in bone mass. Markers of the activity of these processes can be measured. This allows an assessment of the bone activity, independent of Bone Mineral Density (BMD).

Bone formation versus resorption

Bone turnover markers can be divided into those which reflect formation, and those which reflect resorption of bone.

<table>
<thead>
<tr>
<th>Bone formation markers</th>
<th>Bone resorption markers</th>
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<tbody>
<tr>
<td>P1NP (Serum)*</td>
<td>CTX or Crosslaps (Serum or Urine)*</td>
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<tr>
<td>P1CP (Serum)</td>
<td>NTX</td>
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<tr>
<td>ALP (Serum Total or bone specific isoenzyme)</td>
<td>DPD (Urine)</td>
</tr>
<tr>
<td>Osteocalcin (Serum)</td>
<td>PYD (Urine)</td>
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</table>

*Recommended preferred marker per IFCC and IOF

Markers reflecting formation of bone generally reflect the osteoblast secretion of precursor of type I collagen. This is cleaved at N and C terminal ends, resulting in circulating P1NP and P1CP. Alkaline phosphatase is secreted by osteoblasts during mineralisation but is non-specific unless measured as an isoenzyme. Osteocalcin is a protein that binds to hydroxypapatite in the bone matrix and serum levels also reflect formation.

Resorption markers reflect breakdown of type I collagen. Pyridinoline (PYD) or deoxypyridinoline (DPD) cross-links formed between collagen molecules, or their peptide bound forms (C-terminal and N-terminal cross-linked telopeptides) can be measured.
Clinical uses

It is important to note that these markers reflect activity, but, in general, are not specific for particular disease states. They can be useful in management of conditions, including rheumatoid arthritis, osteoporosis, Paget’s disease, thyrotoxicosis, bone cancer, renal bone disease and hyperparathyroidism. Some of these are summarised below.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical use</th>
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</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>BMD is required for diagnosis. Bone markers indicate rate of bone remodelling and may be used for monitoring treatment. Changes in CTX and P1NP are more rapid, larger and more closely related to reduction of fracture risk than BMD.</td>
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<tr>
<td>Predicting fracture risk</td>
<td>Risk depends on fracture site. There is an association between increased CTX and fracture risk at some fracture sites. In general, low BMD with elevated CTX provides the greatest risk.</td>
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<tr>
<td>Monitoring treatment</td>
<td>Turnover markers respond to treatment, usually from 2-3 weeks and plateau at 3-6 months.</td>
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<tr>
<td>Paget’s disease</td>
<td>Increased bone turnover results in elevated CTX and elevated P1NP.</td>
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<tr>
<td>Bone metastases</td>
<td>Bone markers may be of use to monitor anti-resorptive treatment. There is insufficient current data to suggest a role in diagnosis or prognosis of bony metastases.</td>
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</tbody>
</table>

Standardisation for bone marker analysis

Bone turnover markers have been the subject of significant research and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), as well as the International Osteoporosis Foundation (IOF), have been working to improve the standardisation of bone markers and their use.

The value of studies in the past, investigating the potential relationship between bone markers and fracture risk, is limited by heterogeneity of the markers assessed and the fracture outcomes at different sites. This has led to inconsistencies in the predictive value for fracture risk, for specific markers. Variation between analytical platforms/method used to measure specific markers has also contributed to these inconsistencies.

The IFCC-IOF group have recommended better standardisation of measurements for bone markers and have proposed that P1NP (Type I N telopeptide) and CTX (C-terminal telopeptide or Crosslapse) are preferred markers for formation and resorption of bone respectively.

Measurement variation

A variety of physiological factors will contribute to increased variation of measurement of bone markers. Some of these sources of variation are readily controlled and can be minimised prior to phlebotomy, to improve interpretation. However, when interpreting the results of bone marker measurements, due consideration should be given to factors summarised adjacent.
All the bone markers mentioned in this publication are available via Clinpath Laboratories. Serum Crosslaps and Serum Total ALP are analysed on site in our main laboratory, providing superior turnaround times.

**Serum Crosslaps Reference Interval**

Consensus reference intervals for serum Crosslaps have recently been proposed by the AACB Reference Interval Harmonisation Project group, which includes Endocrinologists and Chemical Pathologists with specific expertise in bone markers. These intervals now feature on our reports.

It is worth remembering that chronic renal failure increases serum Crosslaps levels and, when eGFR is <30 mL/min/1.73m², results should be interpreted with caution.

In patients receiving IV anti-resorptive treatments, a decrease in serum Crosslaps to the lower half of the premenopausal range is likely within 3 months, while for oral therapies, this may be between 3 and 6 months.

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**For further information or collection requirements of other tests, please contact our laboratory**

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