

Biochemical markers of Bone Turnover

Compiled by the Chemical Pathologists

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Bone is a metabolically active tissue characterised by two continuous counteractive processes – bone formation and bone resorption. The bone remodeling cycle is illustrated in Figure 1.

The biochemical markers of bone remodeling (bone turnover markers or BTMs) are useful tools in the assessment and management of patients with metabolic bone diseases at the cellular level. They are non-invasive, safe and easily performed on serum and urine. It must be stressed that the use of BTMs remains a challenge for the **diagnosis** of metabolic bone disease, their predominant role remains for the assessment of fracture risk and for monitoring response to treatment.

BTMs can be broadly divided into two categories – bone formation markers and bone resorption markers. The table below lists the most commonly utilised BTMs.

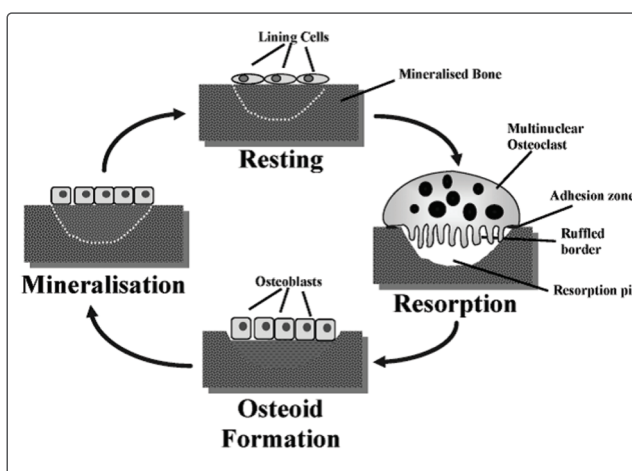


Figure 1. The bone remodeling cycle (Reference 4)

Bone formation markers (osteoblast activity)	Bone resorption markers (osteoclast activity)
N-terminal propeptide of Type 1 collagen (P1NP) *	C-telopeptide of collagen crosslinks (CTX) *
Bone-specific alkaline phosphatase (BAP) *	N-telopeptide of collagen crosslinks (NTx)
Osteocalcin *	Pyridinolines
Carboxy-terminal propeptide of Type 1 collagen (P1CP)	Deoxypyridinoline (DPD)*

* Tests available at Lancet Laboratories

BTMs should be measured in patients with suspected osteoporosis. Although it is not recommended to be used as a diagnostic tool, obtaining baseline values is useful for monitoring responses to treatment.

NOTE: levels of bone markers may vary significantly, especially in:

- Bedridden patients or significant immobility for any reason or following a fracture (up to 6 months)
- During pregnancy, lactation and in postmenopausal women
- The presence of co-morbid illnesses including hyperthyroidism, hyperparathyroidism, Paget's disease, auto-immune disease (e.g. scleroderma), multiple myeloma and metastatic malignancies
- Drug therapies e.g. gluco-corticosteroids, thyroid replacement therapy
- Severe diets including anorexia

N-terminal propeptide of type 1 collagen (P1NP)

This bone formation marker is secreted by the osteoblasts and exists as trimeric and monomeric forms in the circulation. The trimeric form is cleared by hepatic uptake and the monomeric form is cleared via the kidneys. Assays usually measure the total P1NP or the intact (trimeric) form. Levels therefore may be influenced by renal disease (total P1NP assays).

C-telopeptide of collagen crosslinks (CTX)

This resorption marker reflects osteoclast activity. CTx is also cleared by the kidney, hence its usefulness in chronic renal disease is limited. Highest levels are found between midnight and 8 am (circadian variation). An early morning sample is preferred for BTM testing to decrease variability associated with pre-analytical factors.

Both P1NP and CTx measurements are performed on serum using automated platforms and as such are the preferred markers for monitoring patients on treatment. Other BTMs include Bone-specific alkaline phosphatase (useful in Paget's disease), Osteocalcin, NTx and DPD. Both NTx and DPD are urine tests which are susceptible to pre-analytical variability.

The International Federation of Clinical Chemistry in collaboration with other international osteoporosis and bone health associations have designated P1NP and CTx in blood as reference standard BTMs.

Clinical use of BTMs

1. **Assessment of fracture risk.** At best, BTMs are used as an adjunct to Bone Density measurement to assess patients at higher risk for fractures. In this regard bone resorption markers probably have a higher association with fracture risk than bone formation markers. There is no clear evidence that BTMs are useful in population screening programmes for fracture risk.
2. **Selection of patients for therapy** i.e. choosing to use a bisphosphonate in a patient with evidence of accelerated bone resorption, or an anabolic agent (e.g. teriparatide, strontium ranelate) in a patient with evidence of reduced bone formation.
3. **Monitoring of effectiveness of therapeutic interventions,** and thus being able to determine whether to continue or change the therapeutic intervention. Follow-up repeat testing is probably only indicated after at least 6 months of therapy. In most instances a change of at least 20 – 40% from baseline values may indicate response to therapy.
4. **Prediction of bone loss and fracture risk.** Individuals with increased bone resorption markers lose bone at a faster rate than those with normal or low bone resorption markers. This may aid in the decision of whether to use a bisphosphonate to reduce further bone loss in a patient with osteomalacia, rather than to wait before osteoporosis is present.
5. Potential usefulness in the diagnosis and monitoring of **metastatic bone disease.**

Other clinical conditions that are directly or indirectly related to bone formation or resorption include:

- **Primary hyperparathyroidism:** Primary hyperparathyroidism is often an unrecognised underlying cause of osteoporosis.
- **Vitamin D deficiency:** Vitamin D deficiency is relatively common, even in our sunny climate, and often overlooked as a result.
- **Calcium, magnesium and phosphate abnormalities:** Interpretation of PTH levels should always be done in conjunction with serum calcium and phosphate concentrations, to determine whether there is an inappropriate elevation in PTH. Magnesium deficiency may result in low PTH secretion. An elevated PTH, in conjunction with a normal serum calcium level should prompt the investigation for vitamin D deficiency.
- **Liver disease:** As the liver is important in the first hydroxylation of vitamin D to 25(OH) vitamin D, significant liver disease may lead to vitamin D deficiency.
- **Renal failure:** Renal failure is a major cause of secondary hyperparathyroidism. Conversion of vitamin D to its active metabolite 1,25(OH)₂ vitamin D by 1 α -hydroxylase occurs in renal parenchyma.
- **Hyperthyroidism:** Hyperthyroidism is a well recognised cause of accelerated osteoclastic activity and osteoporosis.

Biochemical markers of bone turnover have numerous advantages over radiological measures of bone density (e.g. DEXA scans). DEXA scans can only be performed every 1½ - 2 years to reliably evaluate changes due to response to therapy. The biochemical markers can show a response to therapy much earlier, with the bone resorption markers showing a decrease within a few weeks, reaching a plateau after 3 – 6 months, and the bone formation markers responding a little more slowly, and reaching a plateau after 6 – 12 months. The disadvantages of the biochemical markers of bone turnover are that they show a large intra-individual variability. However, this can be overcome by measuring the marker on a sample taken at the same time of day for successive measurements and monitoring a trend in the concentrations rather than the absolute values.

References and additional reading

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