MARKERS OF BONE TURNOVER – APPENDIX 5

The two primary roles of bone remodelling are, firstly to maintain the structural integrity of bone by repairing microdamage and responding to altered mechanical loading and, secondly, to maintain mineral homeostasis. 1

The Role of Bone Remodelling
· Structural integrity
  - Repair microdamage
  - Respond to altered mechanical loading
· Maintain mineral homeostasis

The process of bone remodelling starts when the lining cells reveal the bone surface upon activation. Osteoclast precursors arrive at the site and become active osteoclasts as they start to dig out a resorption pit. When the osteoclasts have finished the process of resorption, osteoblasts are attracted to the site. These osteoblasts lay down the organic matrix (mainly collagen type 1), which is subsequently mineralised. At the end of this process old bone has been replaced by new bone. Bone resorption and formation are coupled in this process.

Evidence suggests that in postmenopausal osteoporosis the rate of bone resorption increases leading to loss of bone. This increased bone resorption could weaken trabecular and cortical bone. With high turnover, there are many activation sites leading to an enhanced rate of bone loss and thus an increased probability of fracture.

The Remodelling Sequence: Bone Imbalance
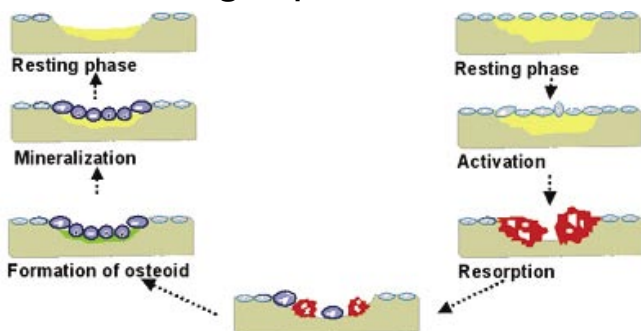
· Bone formation: markers of bone formation are products of active osteoblasts during different phases of osteoblast development. These markers may be measured in both serum or plasma.
  Alkaline phosphatase (ALP) is a ubiquitous enzyme involved in osteoid formation and mineralisation. Around half of ALP in adults is from bone and half from the liver. As such, bone-specific ALP is preferred in clinical practice for monitoring skeletal conditions. Osteocalcin (OC) in a hydroxyapatite-binding protein. It is rapidly degraded in serum, and the heterogeneity of fragments in serum limits its use in clinical practice. Procollagen type 1 (PINP) are derived from type 1 collagen and are measured to reflect newly formed type 1 collagen, and the trimer of PINP is believed to be a sensitive marker of bone formation in osteoporosis. 2

· Bone resorption: most markers of bone resorption are products of collagen degradation, though some non-collagenous proteins are also being investigated (e.g. bone sialoprotein, tartrate-resistant acid phosphatase). The hydroxypyridinium crosslinks of collagen are released when mature collagens are broken down. The type 1 collagen telopeptides (CTX and NTX) may be detected by sensitive immunoassay. 2

Markers of bone turnover	
Formation	Resorption
• Alkaline phosphatase (ALP)	•Hydroxypyridinium crosslinks of collagen (PYD, DPD)
• Osteocalcin (OC)	• C-terminal type 1 collagen telopeptide (CTX)
• Procollagen type 1 propeptides (PINP)	• N-terminal type 1 collagen telopeptide (NTX)

Accelerated or excessive turnover increases bone fragility because of the accumulation of osteoid matrix, decreased time for adequate mineralisation, and increased remodelling sites (erosion bays) that cause temporarily weakened focal lesions in the trabeculae, which are prone to load-bearing stress. 3

Monitoring osteoporosis treatment with bone resorption markers and providing adequate patient feedback may enhance compliance. A study comparing usual care with treatment follow-up by nursing staff or treatment follow-up by nursing staff plus feedback on urinary markers of bone resorption (urinary N-telopeptide of type 1 collagen, or untx) found that follow-up increased treatment adherence by 57% compared with no follow-up (usual care) (p=0.04). 4

Recommendations for the use of bone markers
· Biochemical markers are suitable for monitoring therapy
· Select a marker most relevant to the medication used
· Time sample appropriately
  - Serum measure in arm after overnight fast
  - Urine 1st or 2nd morning void (correcting for creatinine) after overnight fast
· Measurement interval
  - Baseline measure
  - Bone resorption markers should not be assessed before 3-6 months, bone formation markers not before months.

These are prospective data from the French EPIDOS study in elderly women from the general population. Women with Low hip BMD had a higher risk for hip fracture over a 2-year follow-up period. However, women with high rates of bone resorption, assessed by measurement of urinary CTX, had also an increased risk of hip fractures, which was independent of BMD. The highest risk for hip fracture was observed in women that had both low BMD and high bone resorption. In this study, high resorption is defined as the highest quartile, whereas low BMD is defined as the lowest quartile. These results indicate that markers of increased bone resorption, such as urine CTX, may be useful to predict hip fracture risk in elderly women in combination with hip BMD.

Clinical trial data have shown that increased levels of bone resorption markers are associated with fractures independently of BMD. Combining bone resorption markers with low BMD is a more powerful predictor of fragility fracture than either marker alone. It is currently not clear how to practically target women to identify individual women at risk. 2

Clinical applications
· Increased levels of markers of bone resorption predict the risk of fracture independent of BMD
· Combining bone resorption markers with BMD can improve risk assessment
· May be able to identify non-responders using appropriate cut offs
· Bone markers are correlated with fracture risk reduction with treatment

"References will be made available on request"
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