

Bone Quality: What is it and How is it Measured?

review article

ABSTRACT

Juliet Compston

Bone quality describes aspects of bone composition and structure that contribute to bone strength independently of bone mineral density. These include bone turnover, microarchitecture, mineralisation, micro-damage and the composition of bone matrix and mineral. New techniques to assess these components of bone quality are being developed and should produce important insights into determinants of fracture risk in untreated and treated disease. (**Arq Bras Endocrinol Metab 2006;50/4:579-585**)

Keywords: Bone quality; Turnover; Mineralisation; Microarchitecture; Fracture; Bone strength

RESUMO

Qualidade Óssea: O Que Significa e Como Mensurá-la?

A qualidade do osso compreende os aspectos da composição e estrutura óssea que contribuem para sua força, independentemente da densidade mineral óssea, as quais incluem: *turnover* ósseo, microarquitetura, mineralização, microdanos e a composição da matriz óssea e mineral. Novas técnicas para avaliar estes componentes da qualidade óssea têm sido desenvolvidas e devem proporcionar importantes avanços para determinação do risco de fraturas nas doenças tratadas e não tratadas. (**Arq Bras Endocrinol Metab 2006;50/4:579-585**)

Descritores: Qualidade óssea; *Turnover*; Mineralização; Microarquitetura; Fratura; Força óssea

*University of Cambridge School of
Clinical Medicine, Cambridge
CB2 2QQ, UK.*

WHAT IS BONE QUALITY?

BONE STRENGTH IS DETERMINED by bone mass, geometry and quality. The latter includes several aspects of bone structure and composition, including bone turnover, microarchitecture, the degree and distribution of mineralisation, the extent of microdamage and its repair and, finally, the composition of bone matrix and mineral (figure 1). These components are largely interdependent, so that a primary abnormality in one will often lead to changes in others. In particular, bone turnover is a major determinant of other components of bone quality and hence its measurement in clinical practice is of key importance.

The recent interest in bone quality has arisen from observations that the traditional measure of bone strength in clinical practice, namely bone densitometry, does not always reliably predict fracture risk (1). This has stimulated the search for other aspects of bone composition and structure that contribute to bone fragility. This review describes some disease states in which abnormal bone quality is associated with increased fracture risk, sometimes despite increased bone mineral density. Techniques for the measurement of bone quality will be discussed together with how these

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Determinants of bone quality

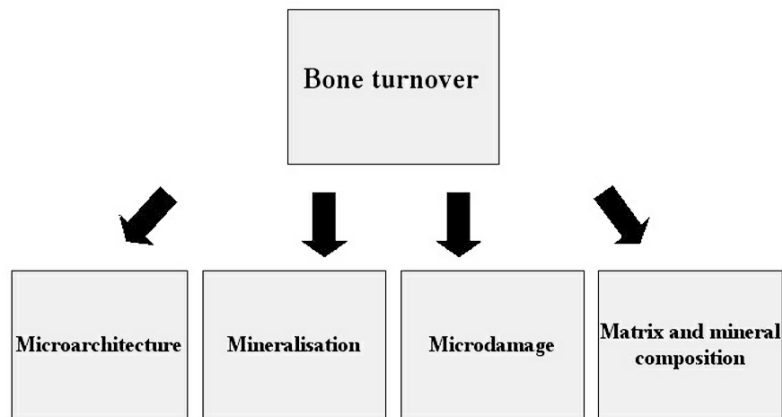


Figure 1. Determinants of bone quality.

have advanced our understanding of the mechanisms by which bone strength may be improved by therapeutic intervention.

ASSESSMENT OF BONE QUALITY

In vivo assessment of bone quality is limited to measurement of bone turnover and of some aspects of bone geometry and architecture. However, using bone biopsy or autopsy specimens, a number of approaches have been developed that have increased our understanding of how bone quality contributes to bone strength in untreated and treated disease (table 1).

Bone turnover

Bone turnover is most commonly assessed in clinical practice by measurement of biochemical markers of resorption and formation (table 2). The markers, which are mainly serum based, reflect whole body turnover and thus provide assessment predominantly of cortical bone, which constitutes 80–90% of the skeleton. They show considerable variability, both within and between individuals, and may be affected by diet, so blood or urine specimens should ideally be obtained in the fasting state and at a standard time of the day.

Bone turnover can also be assessed by histomorphometric assessment of bone, using tetracycline labelling prior to the biopsy (2). The extent of tetracycline-labelled surfaces indicates bone turnover, provided that bone remodelling is in a steady state and that bone resorption and formation are coupled.

However, bone turnover in iliac crest biopsies may not reflect turnover at other sites, since there are considerable intra-individual variations in bone turnover throughout the skeleton (3). Thus it is not surprising that there may be differences between biochemical markers and histomorphometry in their assessment of bone turnover; in particular, the degree of suppression of bone turnover by anti-resorptive agents is generally greater when assessed by the latter technique. Techniques such as ^{18}F -fluoride positron electron tomography and single photon emission computed tomography gamma camera imaging using technetium labelled bisphosphonate provide new approaches to the assessment of regional bone turnover at sites of clinical relevance, for example the spine.

Assessment of bone microarchitecture

Alterations in bone microarchitecture make an important contribution to bone strength that may not always be captured by bone mineral density measurements. Cortical and cancellous architecture are both important in this respect. In cancellous bone, the size and shape of trabeculae and their connectivity and orientation (anisotropy) contribute to bone strength whilst in cortical bone cortical width, cortical porosity and bone size are the main determinants. Although some of these architectural features can be assessed in histological sections of bone biopsy specimens using 2-dimensional approaches (4), more sophisticated methods have now been developed that enable 3-dimensional visualisation and quantification. These include high-resolution magnetic resonance imaging (HR-MRI), high resolution peripheral quantitative computed tomography (HR-

Table 1. Assessment of bone quality.

Variable	Technique
Bone turnover	Biochemical markers, histomorphometry
Bone microarchitecture	Histomorphometry, μ CT, SR- μ CT, HR-MRI, pQCT
Bone mineralisation	Microradiography, qBSEI, SAXS, spectroscopy
Microdamage	Histology, confocal microscopy
Matrix/mineral composite	FTIR, TEM, SAXS, Raman spectroscopy, biochemistry

μ CT – micro computed tomography; SR – synchrotron radiation; HR-MRI – magnetic resonance imaging; pQCT – peripheral computed tomography; qBSEI – quantitative backscattered electron imaging; FTIR – Fourier Transform Infrared; TEM – transmission electron microscopy; SAXS – small angle X-ray scattering

Table 2. Biochemical markers of bone turnover.

Bone formation	Bone resorption
Osteocalcin	Collagen type 1 telopeptides (Ctx, Ntx)
Bone specific alkaline phosphatase	Deoxypyridinoline
Procollagen type 1 N propeptide (P1NP)	Tartate-resistant acid phosphatase type 5b

pQCT), micro-CT (μ CT) and synchrotron radiation μ CT (5). These are currently research tools and, in vivo, can only be applied to the peripheral skeleton although technological advances may eventually extend their use to the central skeleton.

Changes in bone microarchitecture in untreated and treated disease states result from the underlying alterations in bone remodelling. High turnover states and increased osteoclast activity predispose to trabecular penetration, loss of connectivity, cortical thinning and increased cortical porosity, whereas low bone turnover states and reduced bone formation are associated with trabecular thinning and relative preservation of bone microarchitecture.

Assessment of bone mineralisation

Mineralisation of bone matrix occurs in two phases. Primary mineralisation occurs when the bone mineral is deposited during the bone remodelling cycle, whereas secondary mineralisation describes the process of further mineralisation after the remodelling cycle has been completed. The degree of secondary mineralisation is critically dependent on bone turnover; when this is low, there is more time for mineralisation to proceed whereas in high turnover states, recently formed bone is removed before there is time for prolonged secondary mineralisation (6). The degree of mineralisation and its distribution throughout bone can be measured ex vivo by several methods including microradiography, quantitative back-scattered electron imaging and spectroscopic techniques. The degree of mineralisation is captured by bone mineral density measurements, but its contribution relative to other factors influencing bone mineral density cannot be directly deduced.

Assessment of bone matrix and mineral composition

Relatively little is known about how bone matrix and mineral composition contribute to bone strength. Changes in the cross-linking of type I collagen (7) and post-translational modifications such as lysyl-hydroxylation, glycosylation and beta-isomerisation of aspartate residues in carboxyterminal telopeptides may have significant biomechanical implications (8,9), as may alterations in the size and structure of bone mineral. Since collagen structure and mineralisation are so closely associated it is likely that when changes occur in one, both are affected (10).

New approaches to studying bone matrix and composition include Raman and Fourier transform infrared spectroscopy, transmission electron microscopy, and small angle X-ray scattering (SAXS). These techniques can only be applied ex vivo to bone specimens; however, assays for the measurement of beta-isomerisation of CTX have recently been developed and this approach, together with the development of other biochemical measurements of changes in collagen composition in serum or urine, is an important area for research in the future.

Assessment of microdamage

Microdamage in bone consists of microcracks and microfractures. The relationship between these, if any, is unknown and although both forms of microdamage increase with age their effects on bone strength are unclear (11). Assessment of microdamage can currently be made only by histological techniques.

CHANGES IN BONE QUALITY IN BONE DISEASES

Reduced bone strength and increased fracture risk may be caused by a number of abnormalities in bone quality and may occur despite increased bone mineral density. Examination of these disease states emphasises the interdependence of the different components of bone quality and the importance of normal bone quality in the maintenance of bone health.

Changes in bone mineralisation

Both decreased and increased mineralisation may be associated with increased bone fragility. Osteomalacia is associated with reduced mineralisation of bone, leading to accumulation of osteoid. Osteomalacic bones are soft and bend easily, resulting in the characteristic skeletal deformities that are seen in rickets and in severe cases of adult osteomalacia. Pseudofractures and pathological fractures may also occur. In contrast, the condition of osteopetrosis is characterised by increased mineralisation as a result of absent or greatly reduced osteoclastic activity (figure 2). Osteopetrotic bones are stiff and brittle and can absorb little energy before breaking; thus despite greatly increased bone mineral density, fracture risk is increased.

Bone exposed to fluoride provides an example of a qualitative abnormality of bone mineral that is associated with reduced bone strength. The size and composition of hydroxyapatite crystals is changed as a result of substitution of the hydroxyl group of hydroxyapatite by fluoride; in addition, there may be accumulation of osteoid and the formation of woven bone (12).



Figure 2. X-ray of pelvis in a patient with osteopetrosis. Note the increased radiodensity of bone and disordered microarchitecture of cortical and cancellous bone.

Abnormalities of type 1 collagen

Osteogenesis imperfecta is a disease in which there is production of abnormal type 1 collagen. Depending on the genotype, there may be alterations in the bone matrix/mineral composite, decreased mineralisation of bone and abnormal bone modelling and architecture; these changes are associated with increased fracture risk (13).

Even subtle abnormalities in the structure of type 1 collagen may adversely affect bone strength and fracture risk. For example, a polymorphism affecting a binding site of the transcription factor Sp1 in the promoter region of the collagen type 1A1 gene is associated with reduced spine bone mineral density and increased fracture risk (14). The increase in fracture risk cannot be explained solely on the basis of the decrease in bone mineral density, indicating that the abnormal collagen structure contributes independently to reduced bone strength.

High bone turnover

Several high turnover states are associated with increased fracture risk including postmenopausal osteoporosis, Paget's disease of bone, immobilisation-induced bone loss, post-transplantation bone disease and secondary hyperparathyroidism. High bone turnover reduces bone strength both through reduction in bone mass and disruption of bone microarchitecture, an effect that is largely independent of the changes in bone mass. The degree of mineralisation of bone is also reduced in high turnover states. Cortical porosity and endosteal resorption increase, resulting in reduced cortical thickness and strength.

In Paget's disease of bone, increased bone turnover and osteoclastic activity are associated with multiple alterations in bone quality. Bone matrix may have a mosaic structure due to the presence of both woven and lamellar bone, and mineralisation, architecture and geometry may also be abnormal. Post-transplantation bone loss affects both cortical and cancellous bone (15), whilst in secondary hyperparathyroidism bone loss is predominantly cortical. Increased bone turnover is also likely to contribute to bone loss in the early stages of glucocorticoid therapy, although in the longer-term reduced bone turnover and formation predominate. There is evidence that the increase in fracture risk associated with glucocorticoid therapy is to some extent independent of bone mineral density (16), consistent with a role for altered bone quality.

Low bone turnover

The effects of low bone turnover on bone strength have not been established. In theory, low bone

turnover might be expected to increase bone fragility as a result of hypermineralisation, reduced osteocyte viability and accumulation of microdamage (17). However, whilst over-suppression of bone turnover in dogs causes significant accumulation of microdamage, adverse effects on bone strength have not been shown. In humans, adynamic renal bone disease (18,19) is associated with histological evidence of very low bone turnover, but robust evidence for increased fracture risk in this condition is lacking. Biochemical markers of bone turnover do not always reflect the suppression of bone turnover seen histologically and bone mineral density may be normal.

Concerns have been expressed about whether long-term treatment with potent anti-resorptive agents for osteoporosis might cause over-suppression of bone turnover and increased bone fragility. Clinical trials indicate that anti-fracture efficacy is maintained for up to five years of treatment; subsequently, the data are less robust but studies for up to 7 years of treatment with risedronate (20) and 10 years with alendronate (21) are consistent with continued efficacy and have not demonstrated an increase in fracture risk above that expected.

Odvina et al. (22) recently reported the presence of spontaneous fractures, often with evidence of impaired healing, in 9 patients treated with alendronate. Three were also taking hormone replacement therapy and two prednisolone. Bone biopsy in all cases showed complete absence of double tetracycline labelling, although biochemical markers of bone turnover were normal in many cases and only two patients had osteoporosis as defined by densitometric criteria. Although firm conclusions cannot be drawn from these observational data, these cases raise the possibility that very low bone turnover may be associated with increased bone fragility despite normal bone mineral density values.

A possible association between osteonecrosis of the jaw and bisphosphonate therapy has recently been reported (23). This condition often presents with a non-healing tooth extraction socket or painful exposed bone in the mandible or maxilla and is seen most commonly in individuals with malignant disease. Although not exclusively associated with bisphosphonate therapy, the increased numbers of cases reported in such patients has raised the possibility that bisphosphonates may contribute to osteonecrosis by several mechanisms including immunosuppression, inhibition of angiogenesis and suppression of bone turnover. It should be emphasised that the majority of cases have been described in association with malignant diseases for which high doses of intravenous bisphosphonates have been used.

EFFECTS OF PHARMACOLOGICAL INTERVENTIONS ON BONE QUALITY

Bone turnover

The degree of suppression of bone turnover induced by anti-resorptive drugs varies, whether measured by biochemical markers or bone histomorphometry. The most potent effects are seen with alendronate, zoledronate and ibandronate, which reduce activation frequency in iliac crest bone biopsies by around 75–90% (24–26). Risedronate and hormone replacement therapy are of intermediate potency, with a reduction of around 50% (27,28) and the smallest effect is seen with raloxifene (approximately 20%) (29). These differences do not appear to be reflected by variations in anti-fracture efficacy, at least in the spine. However, different degrees of suppression of bone turnover may be relevant to anti-fracture efficacy at non-vertebral sites. Thus for weaker anti-resorptive agents such as raloxifene, whilst the modest reduction in bone turnover is sufficient to reduce fractures at cancellous bone sites where high bone turnover has a marked effect on bone strength, this may not be the case at cortical bone sites where the effects of bone turnover on bone microarchitecture are less prominent, and where larger increases in bone mineral density are required to provide protection against fracture (30).

The reduction in bone turnover induced by anti-resorptive agents has been shown to be a major and independent determinant of fracture reduction, at least at vertebral sites (31,32). This is attributable to the major role of high bone turnover in the pathogenesis of vertebral fracture, which again is independent of bone mineral density (33) and the consequent prevention of microarchitectural changes by anti-resorptive drugs.

In the case of teriparatide (recombinant human parathyroid hormone peptide 1–34) activation frequency is increased in cancellous bone, but this is associated with a positive remodelling balance and thus bone mass increases.

Microarchitecture

Both anti-resorptive and anabolic interventions affect bone microarchitecture, the changes induced reflecting the associated alterations in bone turnover. Anti-resorptive agents preserve existing bone architecture, as demonstrated in iliac crest biopsies using 2-dimensional histological techniques in women treated with hormone replacement therapy (34), raloxifene (29) or ibandronate (26) and μ CT in women treated with risedronate (35,36). Decreased cortical porosity (37) and

unchanged cortical thickness (35) have also been reported in iliac crest bone obtained from women undergoing treatment with anti-resorptive therapy.

In contrast, teriparatide improves bone microarchitecture in both cancellous and cortical bone. Increased connectivity density of cancellous bone and increased cortical thickness have been demonstrated using μ CT of iliac crest biopsy specimens (38,39). There is also some evidence for increased periosteal bone apposition, leading to an increase in bone size.

Mineralisation

Anti-resorptive therapy increases the degree of mineralisation of bone as a result of the reduction in bone turnover. Three years alendronate therapy in postmenopausal women with osteoporosis increased the mean degree of mineralisation in iliac bone by around 11%, an effect that was seen both in cancellous and cortical bone (40). Similar, although smaller, changes have been reported in women treated with risedronate (35), hormone replacement therapy (41), and raloxifene (44). These changes are associated with increased homogeneity of mineralisation.

In postmenopausal women with osteoporosis treated with teriparatide, a small reduction in the degree of mineralisation of bone has been reported, reflecting the increased bone turnover that results from this treatment (42).

Bone matrix and mineral composition

Little is known about the effects of anti-resorptive and anabolic interventions on the bone matrix/mineral composite. There is some evidence that age-related changes in the ratio of non-reducible to reducible collagen cross-links and in bone mineral crystallinity are prevented by anti-resorptive therapy; however, the implications of these effects, if any, on bone strength are unclear.

The effects of strontium ranelate on bone mineral structure are of particular interest since strontium is a bone-seeking element that is taken up mainly by adsorption onto bone mineral, exchanging with a maximum of one in ten calcium ions in hydroxyapatite (43). These changes in mineral composition do not result in any change in the degree of mineralisation of bone.

SUMMARY AND CONCLUSIONS

Bone quality comprises a number of components that contribute to bone strength but are only partially captured by measurements of bone mineral. Advances in

the assessment of bone quality in recent years have provided new insights into bone fragility in both untreated and treated bone disease. The translation of these into clinical practice is an important priority for future research and may eventually lead to better prediction of fracture risk and an improved understanding of the mechanisms by which pharmacological interventions affect bone strength.

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Address for correspondence:

JE Compston
Box 157, Dept of Medicine
Addenbrooke's Hospital
Cambridge CB2 2QQ, UK
Fax: +44 1223 336846
E-mail: jec1001@cam.ac.uk