J Musculoskel Neuron Interact 2004; 4(2):184-186

Perspective Article

Hylonome

Bone quality: Understanding what matters

D.B. Burr

Dept. of Anatomy and Cell Biology and Dept. of Orthopaedic Surgery, Indiana University School of Medicine, Indianapolis, IN, USA

Keywords: Osteoporosis, Bone Quality, Mineralization, Microdamage, Architecture

Introduction

Although bone strength and fracture risk are generally assessed by measuring bone mineral density (BMD), the mechanical properties of bone are in fact determined not only by bone mass, but also by the architecture/geometry of the bone and by the intrinsic material properties of the tissue.

Fracture risk increases with age, partly as a function of changes in BMD. However, the risk of fracture in a 75-year-old woman is 4-7 times that in a 45-year-old woman with an identical bone mass[1]. This demonstrates that there is a component to bone fragility that is independent of bone mass, and determined by bone quality. This has been emphasized recently by the observation that anti-resorptive treatments for osteoporosis all have about the same fracture efficacy, though there is a seven-fold difference in their effect on BMD.

Bone quality is defined by at least four factors: (1) the rate of bone turnover; (2) properties of the collagen/mineral matrix; (3) microdamage accumulation; (4) architecture/geometry of cancellous and cortical bone.

Bone turnover

Vertebral fracture risk is determined by both BMD and turnover rate[2]. Rapid turnover accelerates osteoclastic resorption on trabecular surfaces that can reduce their resistance to buckling and make failure more likely[3]. Resorption lacunae on trabecular surfaces are responsible for larger decreases in bone stiffness than in trabecular thinning[4]. Additionally, the resorption bays create stress concentrations that may promote the initiation of microcracks. More rapid turnover also increases the probability for perforation and elimination of trabecular struts. A 50% reduction in turnover can result in a 4-fold reduction in trabecular perforation[5]. However, agents such as teriparatide that increase turnover also may lower fracture risk by increasing net bone formation on trabecular surfaces.

Matrix mineralization

The amount of energy that can be absorbed before fracture is reduced by either hypo- or hypermineralization of the bone tissue[6,7]. Suppression of remodeling increases tissue mineralization by lengthening the period of time over which secondary mineralization can occur[8-12]. This may increase the tendency for microcracks to initiate. As importantly, remodeling suppression increases tissue homogeneity, possibly making crack growth easier as well. However, the magnitude of the effect is probably determined by the amount of suppression. On the other hand, teriparatide stimulates increased bone turnover and increases the heterogeneity of the tissue matrix.

Collagen

The collagen matrix has a profound effect on bone's mechanical properties[13]. The risk of vertebral fracture is significantly increased in subjects with the Sp1 polymorphism of the COL1A1 gene[14]. Changes in collagen with aging are known to affect the amount of energy required to cause fracture[15]. This may have to do either with the amount of collagen in the matrix, or with the extent or nature of its cross-linking. Anti-resorptive treatments probably increase the amount of cross-linking, but whether this is a positive or a negative change is unclear at this time.

Microdamage

Microdamage accumulation reduces bone's strength, stiffness and toughness[16]. Bone from older women is more susceptible to the initiation of microcracks[17] and must be inherently more fragile than bone from younger women. This may

The author is a consultant for Elli Lilly Co. and Procter & Gamble Pharmaceuticals and holds stock in Elli Lilly Co.

Corresponding author: David B. Burr, Ph.D., Department of Anatomy & Cell Biology, MS 5053, Indiana University School of Medicine, Indianapolis, IN, USA 46202
E-mail: dburr@iupui.edu

Accepted 28 May 2004

be why there is a significant accumulation of microdamage at several anatomical sites with age[18-21]. Suppression of remodeling pharmaceutically also increases damage accumulation[22,23]; the extent of this increase is probably dependent on the magnitude of the suppression[24].

Architecture/Geometry

Cancellous bone that is more plate-like, with thicker and more trabeculae, enhances strength. Trabecular architecture that is more isotropic, having similar mechanical properties in all directions, may lower fracture risk further. This could provide a rationale for the clinical observation that fracture risk decreases by 50-60% in the first year of bisphosphonate therapy with only a 5% increase in bone mineral density. Teriparatide increases trabecular number and connectivity via longitudinal tunneling, converting thickened trabeculae to multiple struts of normal thickness[25]. Although it increases cortical porosity, the porosity is located close to the marrow cavity where its mechanical effect is small[26,27]. Simultaneously, teriparatide allows periosteal apposition, which maintains or improves cortical bone strength[28].

Conclusion

It is quite clear that the assessment of bone quality as defined here, in addition to BMD measurement, is important to determine fracture risk, but techniques to measure these properties are nascent. Development of new non-invasive techniques will be necessary to provide better pre-fracture evaluations of tissue quality. These will need to be made accessible and convenient for the health practitioner.

References

1. Hui S, Slemenda CW, Johnston CC. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest 1988; 81:1804-1809.
2. Riggs BL, Melton LJ III. Bone turnover matters: the raloxifene treatment paradox of dramatic decreases in vertebral fractures without commensurate increases in bone density. J Bone Miner Res 2002; 17:11-14.
3. Parfitt AM. High bone turnover is intrinsically harmful: two paths to a similar conclusion. J Bone Miner Res 2002; 17:1558-1559.
4. Van der Linden JC, Verhaar JAN, Weinans H. A 3-D simulation of age-related remodeling in cancellous bone. J Bone Miner Res 2001; 16:688-696.
5. Weinans H. Architectural changes independent of bone mineral in osteoporosis. Presented at the 32nd International Sun Valley Hard Tissue Workshop; 2002.
6. Currey JD. The effect of strain rate, reconstruction and mineral content on some mechanical properties of bovine bone. J Biomech 1975; 8:81-86.
7. Currey JD, Brear K, Zioupos P. The effects of aging and changes in mineral content in degrading the toughness of human femora. J Biomech 1996; 29:257-260.
8. Meunier PJ, Boivin G. Bone mineral density reflects bone mass but also the degree of mineralization of bone: therapeutic implications. Bone 1997; 21:373-377.
9. Boivin G, Chavassieux PM, Santora AC, Yates, J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. Bone 2000; 27:687-694.
10. Roschger P, Rinnerhtaler S, Yates J, Rodan GA, Fratzl P, Klaushofer K. Alendronate increases degree and uniformity of mineralization in cancellous bone and decreases the porosity in cortical bone of osteoporotic women. Bone 2001; 29:185-191.
11. Nuzzo S, Lafage-Proust MH, Martin-Badosa E, Boivin G, Thomas T, Alexandre C, Peyrin F. Synchrotron radiation microtomography allows the analysis of three-dimensional microarchitecture and degree of mineralization of human iliac crest biopsy specimens: effects of etidronate treatment. J Bone Miner Res 2002; 17:1372-1382.
12. Boivin G, Lips P, Ott SM, Harper KD, Sarkar S, Pinette KV, Meunier PJ. Contribution of raloxifene and calcium and vitamin D_3 supplementation to the increase of the degree of mineralization of bone in postmenopausal women. J Clin Endocrinol Metab 2003; 88:4199-4205.
13. Burr DB. The contribution of the organic matrix to bone's mechanical properties. Bone 2002; 31:8-11.
14. Mann V, Ralston SH. Meta-analysis of COL1A1 Sp1 polymorphism in relation to bone mineral density and osteoporotic fracture. Bone 2003; 32:711-717.
15. Burr DB, Turner CH. Biomechanical measurements in age-related bone loss. In: Rosen CJ, Glowacki J, Bilezikian JP (eds) The Aging Skeleton. Academic Press, San Diego; 1999:301-311.
16. Burr DB, Forwood MR, Fyhrie DP, Martin RB, Schaffler MB, Turner CH. Bone microdamage and skeletal fragility in osteoporotic and stress fractures. J Bone Miner Res 1997; 12:6-15.
17. Courtney AC, Hayes WC, Gibson LJ. Age-related differences in post-yield damage in human cortical bone. Experiment and model. J Biomech. 1996; 29:1463-1471.
18. Schaffler MB, Choi K, Milgrom C. Aging and matrix microdamage accumulation in human compact bone. Bone 1995; 17:521-525.
19. Mori S, Harruff R, Ambrosius W, Burr DB. Trabecular bone volume and microdamage accumulation in the femoral heads of women with and without femoral neck fractures. Bone 1997; 21:521-526.
20. Fazzalari NL, Forwood MR, Smith K, Manthey BA, Herreen P. Assessment of cancellous bone quality in severe osteoarthrosis: bone mineral density, mechanics, and microdamage. Bone 1998; 22:381-388.
21. Zioupos P. Accumulation of *in vivo* fatigue microdamage and its relation to biomechanical properties in ageing human cortical bone. J Microsc 2001; 201:270-278.

22. Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB. The effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites of beagles. Bone 2001; 28:524-531.
23. Komatsubara S, Mori S, Mashiba T, Ito M, Li J, Kaji Y, Akiyama T, Miyamoto, K, Cao Y, Kawanishi J, Norimatsu H. Long-term treatment of incadronate disodium accumulates microdamage but improves the trabecular bone microarchitecture in dog vertebra. J Bone Miner Res 2003; 18:512-520.
24. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res 2000; 15:613-620.
25. Jerome CP, Burr DB, van Bibber T, Hock JM, Brommage R. Treatment with human parathyroid hormone (1-34) for 18 months increases cancellous bone volume and improves trabecular architecture in ovariectomized cynomolgus monkeys (*Macaca fascicularis*). Bone 2001; 28:150-159.
26. Hirano T, Burr DB, Turner CH, Sato M, Cain RL, Hock JM. Anabolic effects of human biosynthetic parathyroid hormone fragment (1-34), LY333334, on remodeling and mechanical properties of cortical bone in rabbits. J Bone Miner Res 1999; 14:536-545.
27. Burr DB, Hirano T, Turner CH, Hotchkiss C, Brommage R, Hock JM. Intermittently administered human parathyroid hormone (1-34) treatment increases intracortical bone turnover and porosity without reducing bone strength in the humerus of ovariectomized cynomolgus monkeys. J Bone Miner Res 2001; 16:157-165.
28. Zanchetta JR, Bogado CE, Ferretti JL, Wang O, Wilson MG, Sato M, Gaich GA, Dalsky GP, Myers SL. Effects of teriparatide (recombinant human parathyroid hormone (1-34)) on cortical bone in postmenopausal women with osteoporosis. J Bone Miner Res 2003; 18:539-543.