



## Perspective Article

# Introduction – Bone turnover and fracture risk

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At its Consensus Development Panel on Osteoporosis in 2001, the National Institutes of Health defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality"<sup>1</sup>. The issue of bone quality as a factor in osteoporotic fracture has received increasing attention in recent years because the reduction in vertebral fracture risk subsequent to treatment with anti-resorptive agents appears to have little relationship to the percentage increase in bone mineral density (BMD). Moreover, the increase in fracture risk with age in untreated patients is only partly a function of changes in BMD. The risk of fracture in a 75-year-old woman is 4-7 times that of a 45-year-old woman with an identical bone mass, demonstrating a bone quality component to fragility that is independent of bone mass. This shows that there is a component to bone fragility that is independent of bone mass, and determined by bone quality.

Bone quality is defined by four characteristics of the bone tissue matrix and skeletal physiology: (1) the rate of bone turnover; (2) the properties of the collagen/mineral matrix; (3) microdamage accumulation and (4) skeletal architecture and geometry.

Rapid turnover accelerates osteoclastic resorption on trabecular surfaces that can reduce their resistance to buckling and make failure more likely<sup>2</sup>. Ultimately, increased resorption will increase the probability for perforation and elimination of trabecular struts<sup>3,4</sup>. Reduced turnover by anti-resorptive treatments may reduce fracture risk by more than expected given the magnitude of BMD increases by preventing this weakening of trabecular struts and increasing tra-

becular thickness. A computational model developed by Weinans<sup>5</sup> shows that there is a nonlinear relationship between the rate of bone turnover and the number of complete trabecular perforations that will result over time. Reducing the remodeling space by 50% (from 5.2% to 2.6%) reduces the number of perforations by 75% over 200 remodeling cycles, suggesting that a suppression of bone turnover may have a larger effect on bone strength than one would expect from the amount of suppression alone.

Using data from a one-year clinical trial with transdermal estrogen administered by Lufkin et al.<sup>6</sup>, Riggs and Melton show that vertebral fracture rate is determined by both BMD and bone turnover rate<sup>7</sup>. This analysis shows that vertebral fracture rate per 1,000 person years is increased at both low BMD ( $< 0.8 \text{ g/cm}^2$ ) and at a high bone formation rates ( $> 4.0\%/yr$ ) in placebo treated individuals. In those patients in which remodeling was suppressed using transdermal estrogen, vertebral fracture rate was determined only by low BMD.

An increased rate of bone turnover does not always weaken bone. In some cases, increased turnover can also be associated with increased strength and reduced fracture risk. PTH increases bone turnover on trabecular surfaces and in cortical bone near the endocortical surface, but the increase in net bone formation and positive architectural changes created by increased turnover are associated with increased strength<sup>8,9</sup>. In cortical bone, the increased turnover occurs close to the marrow cavity, and is more than offset by increased periosteal apposition<sup>10</sup>, which maintains or increases the cross-sectional moment of inertia.

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