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Hindsight

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Better tools for assessing osteoporosis

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Some 30 years ago, we applied the newly described method of dual photon absorptiometry (DPA) to demonstrate that osteoporotic women with vertebral fractures had lost substantially more bone from the vertebrae than controls. This opened a whole new field of research into the determinants of bone loss and fractures in the axial skeleton and set the stage for subsequent development of dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (QCT), which are now the standard methods for assessing osteoporosis severity and treatment efficacy.

Although it had long been recognized that vertebral fractures due to osteoporosis were associated with excessive bone loss, this was not initially studied because bone density could not be measured noninvasively. However, in the early 1970s, it became possible to measure 2D areal bone mineral density (aBMD in g/cm²) in the appendicular skeleton using single photon absorptiometry (SPA), which is based on bone attenuation of photons emitted from a ¹²⁵I-isotope source. Unfortunately, these results were disappointing because of poor discrimination between osteoporotic patients and controls. In 1981, the *JCI* published a paper from our group that introduced a new technique to assess bone density in the axial skeleton (1). This has been one of the most highly cited articles in the Journal's history (964 times as of this writing), and it highlights the contribution of methodologic advances to progress in research.

In that 1981 paper (1), we assessed bone loss in 187 normal subjects (105 women and 82 men, age 20 to 89 years) and in 76 women and 9 men with vertebral fractures, the sine qua non of osteoporosis. We measured aBMD of the lumbar spine (LS) using our modification of the then newly developed method of dual photon absorptiometry (DPA); aBMD at the mid-radius (MR) and distal radius (DR) was measured using SPA. DPA differentiates bone from soft tissue by differential absorption coefficients of two photon energies emitted from a ¹⁵³Gd-isotope source. Between ages 20 and 90 years, aBMD at the LS declined in women by a mean of 47% compared with

only 30% at the MR and 39% at the DR. The age-related decline in men was about one-third of this. The decrease in LS aBMD with aging was linear and began in young adulthood in both sexes, but did not start until later in life at the radius sites. Of the women with vertebral fractures, almost all had LS aBMD values below the 50th percentile of normal (about half below the 10th percentile), whereas aBMD values at the MR and DR were more widely distributed throughout the normal range.

The study made several novel observations. First, it demonstrated that bone loss appears to begin in young adulthood in the predominantly trabecular ("spongy") bone of the vertebrae in both sexes, thus challenging the prevailing belief that bone loss from the central skeleton in women only begins at menopause. This finding raised the important question of what causes early bone loss. In contrast, significant bone loss in the predominantly cortical bone of the appendicular skeleton seemed to begin in mid-life. Second, age-related bone loss was greater in the axial than in the appendicular skeleton. Finally, women with vertebral fractures lost even more bone, with the greatest loss in the axial skeleton.

In a subsequent *JCI* paper (2), we assessed rates of bone loss prospectively at various skeletal sites and confirmed that, prior to menopause, women had minimal loss from the appendicular skeleton but substantial bone loss from the axial skeleton. Since neither DPA nor its successor, dual-energy x-ray absorptiometry (DXA), differentiated cortical from trabecular bone, we incorporated quantitative computed tomography (QCT) into our population-based studies and showed that 3D trabecular volumetric BMD (vBMD in mg/cm³) declined by over 50% in both spine and hip among women

between ages 20 and 90 years, with a somewhat lesser decline in men (3). Changes in cortical vBMD at those sites were only half as great but equalled those in the DR by peripheral QCT (pQCT). We are now using high-resolution pQCT (HRpQCT) to evaluate bone microstructure at the DR ("noninvasive bone biopsy") and show, for example, that sex-specific patterns of change in trabecular microstructure (trabecular thinning in men, trabecular loss in women) help account for the lower fracture rates seen in aging men (4). We have reviewed potential mechanistic explanations for such changes elsewhere (5).

Long-term follow-up revealed that the aBMD measurements by DPA could also predict future fractures (6). This observation supported the commercialization of bone densitometry as a clinical test and is important in practice because bone loss can be prevented, but lost bone cannot readily be restored. DPA was subsequently replaced by DXA, which is the more precise (e.g., coefficient of variation [CV], 0.6% vs. 2.3% for LS aBMD) instrument most used in current clinical practice. Our group and others have demonstrated that aBMD by DXA provides a useful but imperfect assessment of future fracture likelihood (7), and this has become a key to personalizing the use of treatments for preserving bone and preventing fractures.

Although the association of aBMD with fracture risk depends on its high correlation with bone strength *ex vivo*, bone failure also depends on bone macro- and microstructure. Consequently, we have evaluated more direct determinations of bone strength that incorporate these other factors. For example, we combined data on bone geometry (e.g., cross-sectional area) with bone material properties estimated from vBMD data to quantify absolute vertebral compressive strength in women and men in a population-based study (8). The greater spatial resolution of bone tissue available from QCT further facilitates the creation of detailed biomechanical models for strength of specific bones. Thus, we used finite element analysis (FEA) to develop individual models of bone strength for

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hindsight

lumbar vertebrae in 283 postmenopausal women (9). When these models were virtually compressed to failure, vertebral strength and load-to-strength ratio were better discriminators of vertebral fractures than was LS aBMD. Moreover, voxel-by-voxel heterogeneity in trabecular vBMD, a surrogate for disruption of trabecular microstructure (bone “quality”) in the vertebral body, accounted for a substantial portion of the reduced bone strength of women with vertebral fractures (9).

In retrospect, one of the major features of our original *JCI* paper was the collaboration it reflected among researchers in clinical investigation, epidemiology, and nuclear medicine/radiology. Thus, while that early work has had a considerable impact on both research and clinical practice in osteoporosis, it also presaged the current emphasis on “team science” to optimize

innovation and, ultimately, to improve patient care.

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