EDITORIAL

Where's the break? Critique of radiographic vertebral fracture diagnostic methods

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Vertebrall fractures are the most common osteoporotic fractures and are associated with the highest risk of subsequent incident fractures [1]. The majority of vertebral fractures do not come to medical attention and thus remain undiagnosed [2]. In most osteoporosis guidelines [3, 4], vertebral fracture, unrelated to trauma and on its own, represents an intervention threshold for pharmacological treatment and may need no further risk assessment, including bone mineral density (BMD) measurement. Furthermore, the Endocrine Society has recently published a clinical practice guideline related to therapy of osteoporosis in menopausal women who are a year or more past their final menstruation, [5] in which they recommended treatment with bone-forming agents in these women with osteoporosis at very high risk of fracture, such as those with severe (Grade 3) or multiple vertebral fractures. Anabolic therapy has recently proven to be superior to antiresorptives for incident vertebral fracture prevention in randomized, controlled clinical trial data of teriparatide versus risedronate [6].

Although vertebral fractures are common and important in osteoporosis diagnosis and management, the definition of osteoporotic vertebral fracture remains controversial [7–10]. Our purpose is to clear confusion for clinicians.

In 2000, 21.5% of men and 23.5% of women in a population-based national cohort of 6433 persons aged ≥ 50 years showed a Grade 1 or higher vertebral fracture (VF) or deformity that were systematically assessed by lateral vertebral radiography [11]. This prevalence was based on technologist triage followed by determination of 20–25% anterior wedging or three standard deviations (3 SD) greater height deviation than unaffected vertebrae at the same anatomical level in the same cohort [12]. On spine radiographs, the method identified the anterior, posterior, and middle vertebral heights of the superior and inferior endplates and compared the morphometry with the same, unaffected vertebral body in the population, as had Eastell in Rochester data [13]. Further refinements of the morpho*metric* approach to vertebral fractures were developed by the late Professor Harry Genant at the University of California, San Francisco

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[14] who further clarified vertebral deformities by grades of height loss—Grade 1 loss of 20–25%, Grade 2 of 26–40%, and Grade 3 of > 40% [14] that remain in common use. Although this now-classical text also mentions "endplate deformities and buckling of cortices" and "loss of vertical continuity of vertebral morphology" (page 1145), the persuasive powers of its diagram of *changed vertebral shapes* has since taken precedence [14].

> *However, not every vertebral deformity represents an osteoporotic vertebral fracture.*

Cross-sectional Canadian Multicentre Osteoporosis Study (CaM*os*) data on vertebral deformities or VF from randomly sampled women (2/3) and men (1/3) around nine urban centers from coast to coast across Canada, published in 2000, were similar to results previously documented in large USA, British, and European cohorts [12]. (Note that these *radiographic* VF, no matter how evaluated, are distinct from *clinical* VF in which a person has focal, usually acute, back pain and an investigating spine radiograph shows evidence of fracture.)

At about the same time, one of us (JCP), an academic working in the Vancouver, Canada, osteoporosis clinic was referred a healthy 60-year old Chinese man for osteoporosis evaluation and treatment because his CaM*os* spine radiographs had been interpreted as revealing a Grade 1 "vertebral fracture" at T-8. He was healthy, of normal weight and height, and his bone mineral density (BMD) was normal. He had no family history of fragility fracture, no clinical risk factors, no major trauma, and no previous fracture. (*Note that this was pre-FRAX but we estimate his major osteoporotic fracture risk would have been less*
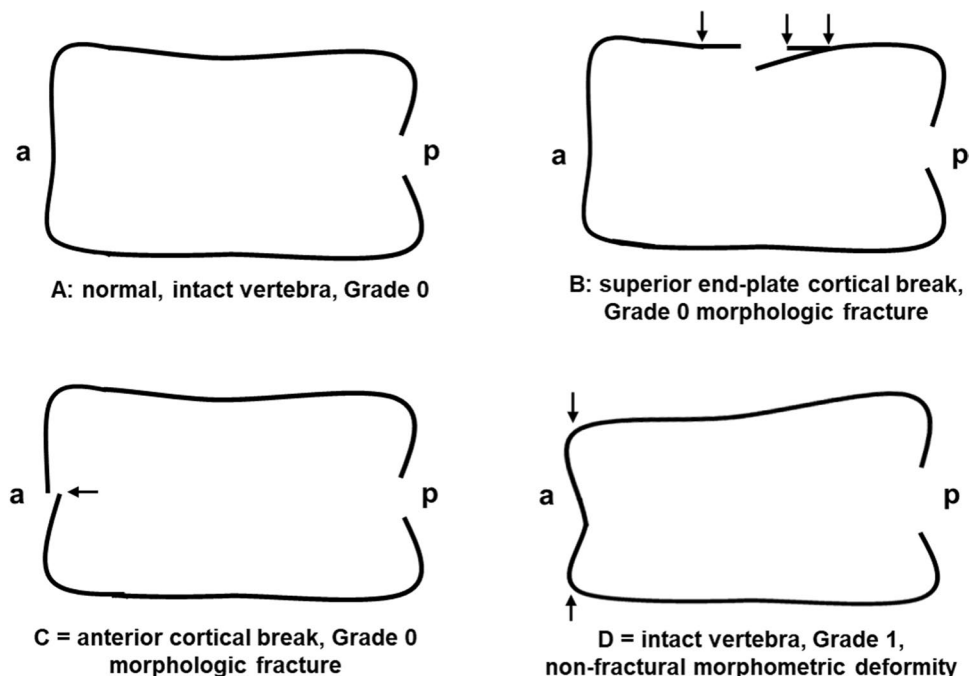
than 3%.) Should this man be prescribed an osteoporosis therapy (etidronate, the bisphosphonate then available in Canada)? Said another way: *Did this healthy fellow with a Grade 1 vertebral deformity have osteoporosis that required treatment?*

The diagnosis of "vertebral fracture" is controversial. It is often remarked that there is no "gold standard" for diagnosis of osteoporotic vertebral fracture [15]. Two primary assessment methods currently compete: the morpho*metric* method of Genant (called Genant Semiquantitative analysis, GSQ) [14] that relies on assessment of vertebral height, and the morpho*logic* (or "structural") method which depends on informed recognition of breaks in superior and inferior endplates as proposed by the Sheffield group (called Algorithm-Based Qualitative, ABQ) [16], and modified by Lentle et. al. to also include cortical breaks (mABQ) [7]. Others have questioned "short anterior height" vertebrae as part of systemic osteoporosis [17].

Figure 1 illustrates the fundamental issue in radiographic vertebral fracture/deformity diagnosis. It shows that vertebrae may have the same shape and dimensions as normal (called Grade 0), yet have morpho*logic* vertebral endplate or anterior cortical breaks. In addition, an *intact* vertebra may have a shortened anterior height and be considered a Grade 1 morpho*metric* "vertebral fracture" but have little relationship with what we know of clinical osteoporosis. Previous cross-sectional data have examined the frequency of morpho*metric* versus morpho*logic* fractures and shown that Grade 1 morpho*metric* "VF" are a lot more prevalent than are morpho*logic* VF [7, 8].

To decide which of the two competing methods (barring a gold standard) is the more specific and accurate for

Fig. 1 This diagram shows four vertebrae to illustrate the issues involved in differentiating Grade I morpho*metric* "vertebral fractures" (assessed by the Genant Semiquantitative, GSQ method) from morpho*logic or structural* vertebral fractures (by the modified Algorithm-Based Qualitative, ABQ method). (**A**) Grade 0, intact, normal-shaped vertebral body without a vertebral fracture; (**B**) Grade 0 morpho*logic* fracture of the superior endplate (ABQ); (**C**) Grade 0 morpho*logic* fracture of the anterior cortex (modified ABQ); (**D**) Grade 1 intact vertebral body with decreased anterior height that is a (GSQ) vertebral deformity. "a" = anterior and "p" = posterior (drawn by JCP and BCL with refinements by Dharani Kalidasan MSc)

A: normal, intact vertebra, Grade 0

B: superior end-plate cortical break, Grade 0 morphologic fracture

C = anterior cortical break, Grade 0 morphologic fracture

D = intact vertebra, Grade 1, non-fractural morphometric deformity

radiographic vertebral fracture (VF) assessment (morpho-*metric* versus morpho*logic*), we need to answer several questions:

1. Do morpho*metric* or morpho*logic* vertebral fractures similarly correlate with low or "osteoporotic" BMD levels (T-scores ≤ 2.5)?
2. Do morpho*metric* or morpho*logic* vertebral fractures better predict incident vertebral and non-vertebral fragility fractures?
3. Are morpho*metric* and morpho*logic* vertebral fractures of similar spine segmental (anatomical) distribution and gender prevalence as that expected given what is now known of the natural history of osteoporosis?

Using recently published, *population-based data*, primarily from the CaM*os* and the Rotterdam Study research, we seek to answer these key questions.

Relationship of vertebral fractures with low BMD

Using BMD in participants without a radiographic VF as the comparator, both morpho*metric* and morpho*logic* VF of all grades (Gr 0–3) are associated with lower BMD values. This was true for the femoral neck (FN) BMD measured in the Rotterdam Study [8] and for lumbar spine (L1–4), FN, and total hip (TH) BMD [7] data in CaM*os*. Regression assessment of BMD differences between Grade 1 morpho*metric* and morpho*logic* deformities in the entire CaM*os* baseline cohort (adjusted for age, height, BMI, and sex) documented significantly lower BMD values in those with Grade 1 morpho*logic* than Grade 1 morpho*metric* deformities: L1–4 (−0.073 [95% CI −0.122; −0.024]), FN (−0.047 [−0.078; −0.016]), and TH (−0.052 [−0.089; −0.015]) [7]. However, in USA cross-sectional assessment of individuals selected to represent national data (NHANES), 26% of those with osteoporosis by BMD T-scores of ≤ 2.5 had prevalent morphometric vertebral fractures [18]. Thus, morpho*logic* vertebral deformities and fractures are more strongly associated with the lower BMD values of osteoporosis than are morpho*metric* vertebral deformities and fractures.

Vertebral fractures as predictors of *incident* fractures

Remarkably fewer *incident* morpho*metric* than morpho*logic* vertebral fractures are documented in prospective cohort data [7, 8, 19, 20]; reasons for this observation remain unclear.

Using a modified morpho*logic* method that included anterior cortical breaks as well as endplate fractures (Fig. 1C), CaM*os* and the Rotterdam Study data documented that both morpho*metric* and morpho*logic* vertebral deformities/VF (of all grades) appear to predict *incident VF* [7, 8]. When prospectively examining all sites of incident osteoporotic fracture, however, vertebral deformities/VF by morpho*metric* criteria were less consistently related to fractures at other sites. In the prospective Rotterdam Study, prevalent morpho*logic* fractures predicted non-vertebral, hip, and clinical vertebral fractures but morpho*metric* deformities/VF did not predict incident hip fractures [8]. In the CaM*os* prospective data, morpho*logic* deformities/VF predicted all incident fractures but morpho*metric* deformities/VF did not predict incident non-vertebral fractures. Thus, morpho*logic* VF are more consistent and comprehensive predictors of osteoporotic incident fractures than are morpho*metric* VF and deformities.

Vertebral fracture spinal anatomy and sex/gender distribution

Multiple studies have shown that prevalent or baseline morpho*metric* deformities/VF are more likely to be diagnosed in the mid-thoracic spine (T7–9) compared with morpho*logic* deformities/VF that predominate in T11-L1 [7, 8, 19] (Fig. 2). This anatomical/segmental difference in prevalent vertebral Grade 1 deformities and VF is striking between the two methods of vertebral fracture assessment.

As CaM*os* initial, cross-sectional radiographic data so clearly showed, men are nearly equally likely to have morpho*metric* VF and deformities as women [12]. This observation differs from the gendered natural history of other fractures that occur predominantly in women [14, 15, 21] (even when accounting for men's competing risk of mortality and average higher BMD) [19, 22]. Furthermore, at baseline, examining percentage of VF by sex/gender, there were 2.1 times the proportion of women than men in CaM*os* with a prevalent morpho*logic* VF although men slightly predominated in baseline morpho*metric* ones (Fig. 3). In the same cohort over 10 years, the rate of incident morpho*metric* and morpho*logic* VF and deformities were similar in men and women [19].

It is interesting that the loss of a gender difference in incident morpho*metric* VF 10 years later in CaM*os* is similar across the two VF assessment methods. This likely reflects the trend over time documented by CaM*os* related to incident hip fractures (both community-dwelling men and women aged ≥ 75 at baseline had a 7.0% 10-year likelihood of an incident hip fracture [22]) and in population-based data from Finland [23]. Given the importance of gender differences and their documentation in research [24], if a method

Fig. 2 This diagram, reprinted from [7] with permission, contrasts the prevalent (baseline) anatomical/segmental distribution along the entire vertebral length, of Grade 1 and higher morpho*metric* vertebral deformities and fractures versus similar grades of morpho*logic* vertebral fractures. The morpho*metric* assessment shows much more common prevalent fractures and a peak at T8 of Grade 1 vertebral deformities and a lesser one at T12. The morpho*logic* method shows fewer baseline vertebral fractures of all grades with a Grade 1 maximum VF prevalence at L1
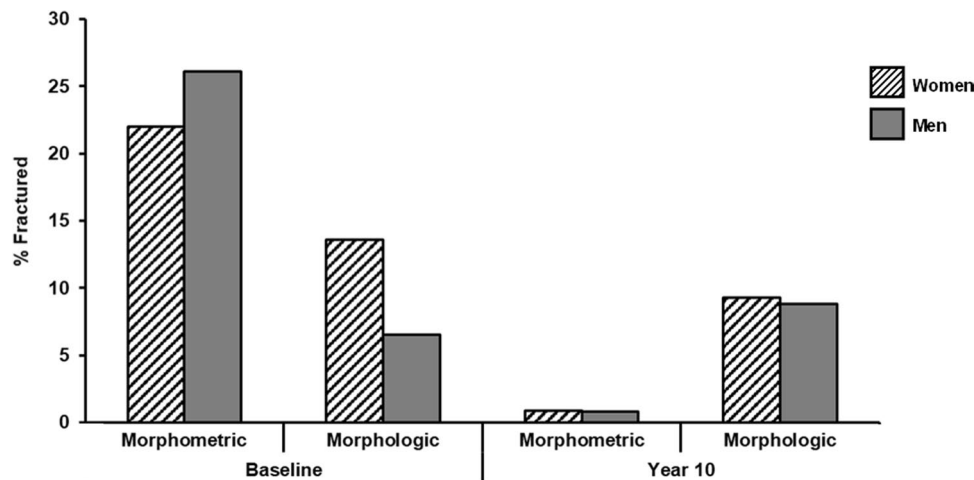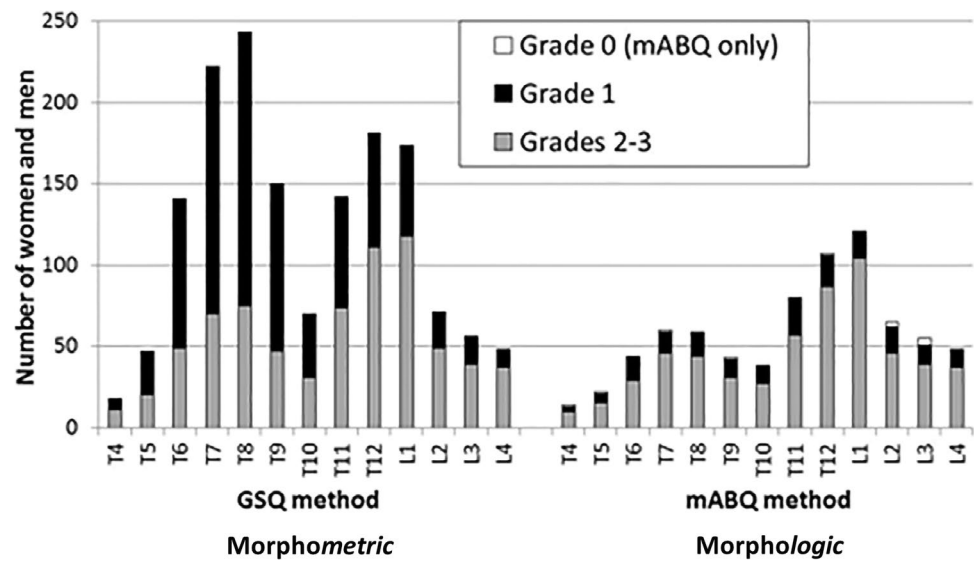
Fig. 3 This bar graph contrasts the baseline sex/gender distribution of vertebral deformities and fractures in the Canadian Multicentre Osteoporosis Study cohort of 828 individuals whose spine radiographs were systematically assessed at baseline and after 10 years using both morpho*metric* (GSQ) and morpho*logic* (mABQ) methods [7]. Morpho*metric* methods showed a higher prevalence of VF and deformities as well as that vertebral deformities were more frequent in men than women. The morpho*logic* assessment documented fewer prevalent VF and a more typical osteoporosis-related predominance in women. There were no sex/gender differences in *incident* VF and deformities by either assessment method (drawn by Dharani Kalidasan MSc)

of measurement does not reflect the gender/sex distribution that is known to occur in a disease entity, that method needs to be questioned.

In summary, in every carefully studied instance, vertebral fractures diagnosed by morpho*logic* criteria (even when of Grades 0 and 1) are more specific (and accurate) for the diagnosis of osteoporosis by BMD criteria, and the prediction of incident osteoporotic fragility fractures than are morpho*metric* deformities and VF. It seems likely that prevalent Grade 1 morpho*metric* deformities may be the end result of a number of diverse processes yet are rarely or never related to osteoporosis.

What are the implications of answers to these three key vertebral fracture questions? We should stop referring to "wedge fractures" and vertebral "deformities" and measuring (or eye-balling) vertebral heights. It is also time to revisit the issue of a missing gold standard for osteoporotic vertebral fracture. We now understand, that a *vertebral endplate or cortex* break, or *discontinuity,* with or without a change in vertebral height, *is a bona fide* vertebral *fracture*. Thus, the vertebral fracture gold standard is the same as we use for diagnosing any bone fracture at any site. To put it simply—*we should generally ignore prevalent Grade*

1 morphometric vertebral deformities. If there is no break*, there is no vertebral* fracture.

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