JBMR®

The Radiology of Osteoporotic Vertebral Fractures Revisited

Brian Lentle,[1] Fjorda Koromani,[2,3,4] Jacques P. Brown,[5] Ling Oei,[3,4] Leanne Ward,[6] David Goltzman,[7] Fernando Rivadeneira,[3,4] William D Leslie,[8] Linda Probyn,[9] Jerilynn Prior,[10] Ian Hammond,[11] Angela M. Cheung,[12] and Edwin H. Oei[2]; on behalf of the Vertebral Fracture Research Groups of the CaMos, STOPP, and Rotterdam Studies

[1]Department of Radiology, University of British Columbia, Vancouver, BC, Canada
[2]Department of Radiology and Nuclear Medicine, University Medical Center Rotterdam, Erasmus MC, Rotterdam, The Netherlands
[3]Department of Internal Medicine, University Medical Center Rotterdam, Erasmus MC, Rotterdam, The Netherlands
[4]Department of Epidemiology, University Medical Center Rotterdam, Erasmus MC, Rotterdam, The Netherlands
[5]Department of Medicine, Division of Rheumatology, CHU de Québec Research Centre, Laval University, Québec City, QC, Canada
[6]Division of Bone Health, Department of Pediatrics, University of Ottawa, Ottawa, ON, Canada
[7]Department of Medicine, McGill University and McGill University Health Centre, Montréal, QC, Canada
[8]Department of Medicine, University of Manitoba, Winnipeg, MB, Canada
[9]Department of Medical Imaging, University of Toronto and Sunnybrook Health Sciences Centre, Toronto, ON, Canada
[10]Division of Endocrinology, University of British Columbia, Vancouver, BC, Canada
[11]Department of Radiology, University of Ottawa, Ottawa, ON, Canada
[12]Department of Medicine and Joint Department of Medical Imaging, Centre of Excellence in Skeletal Health Assessment, University Health Network, University of Toronto, Toronto, ON, Canada

ABSTRACT

Until recently there has been little evidence available to validate any method by which to make an accurate diagnosis of an osteoporotic vertebral fractures (OVFs) from plain radiographs. In part this reflects a lack of a completely satisfactory "gold standard," but primarily it relates to the absence of well-designed prospective studies in this context. Historically, OVFs were recognized by evidence of macroscopic structural failure in vertebrae using the criteria applied elsewhere in the skeleton. This comprised altered alignment, fragmentation, cortical disruptions, and breaks, among other changes. However, these morphological criteria were replaced by vertebral morphometry, referring to the use of quantitative or quasi-quantitative measurement tools for fracture diagnosis. Vertebral morphometry emerged as an understanding of and treatment for osteoporosis evolved, mainly in response to the need for expeditious assessments of large numbers of spine images for epidemiological and pharmaceutical purposes. Although most of the descriptions of such morphometric tools have stressed that they were not to be applied to clinical diagnosis with respect to individual patients, this constraint has been widely disregarded. Here we review the major attempts to develop a diagnostic strategy for OVF and describe their characteristics in adults and children. Recent evidence suggests that morphometric (quantitative; ie, based on measurement of dimensions and shape description) criteria are inferior to morphologic (qualitative; ie, based on structural integrity) vertebral damage assessment in identifying people with low bone density and at an increased risk of future fracture. Thus there is now an evidentiary basis for suggesting that morphological assessment is the preferred strategy for use in diagnosing OVF from radiographs. © 2019 American Society for Bone and Mineral Research.

KEY WORDS: SPINE; VERTEBRAL FRACTURES; SPINAL FRACTURES; OSTEOPOROSIS; DIAGNOSIS; MORPHOMETRIC DEFORMITIES; MORPHOLOGIC VERTEBRAL FRACTURES; EPIDEMIOLOGY

Introduction

Osteoporotic vertebral fractures (OVFs) are important in the identification of those at risk of future osteoporotic fracturing for several reasons: OVFs are the most frequent type of osteoporotic fracture;[1] they are associated with considerable morbidity and mortality;[2] and OVFs predispose to both further fracturing[3] and to the fracture cascade.[4] Recognition of OVF is therefore important in risk estimation as exemplified by several published clinical guidelines.[5–7] However, OVFs may often be relatively asymptomatic[8] so that, in the absence of localizing symptoms, spinal fracture status is usually

Received in original form November 5, 2018; revised form December 17, 2018; accepted January 5, 2019. Accepted manuscript online January 05, 2019.
Address correspondence to: Brian Lentle MB, MD, DSc(hc), FRCPC, Department of Radiology, BC Women's Hospital and Health Centre, University of British Columbia, Vancouver, BC, Canada. E-mail: bclentle@gmail.com

Journal of Bone and Mineral Research, Vol. 34, No. 3, March 2019, pp 409–418
DOI: 10.1002/jbmr.3669

determined by obtaining lateral radiographs of the spine from T_4 to L_4 either by conventional methods or by dual-energy X-ray absorptiometry (DXA) devices operating in imaging mode.[9] However, an overriding limitation of the literature of OVF, including those quoted above, has been that of inconsistency in how vertebral fractures are defined.[10,11]

The aim of this review is to provide a critical overview of the evolution of the methods for vertebral fracture diagnosis; examine the current state-of-the-art in clinical practice; weigh the advantages and drawbacks of the most commonly used approaches; and finally suggest recommendations for clinical practice intended for radiologists, epidemiologists, and related professionals working in the "bone field." Although the article mostly relates to adult data, reference is also made to distinctive features of vertebral fractures in children.

The Evolving Diagnosis of OVF

The era of visual assessment

Historically, OVFs were diagnosed by applying the standard criteria for fracture diagnosis; ie, those used elsewhere in the skeleton, namely observing breaks or discontinuities in bony architecture and other evidence of bony disruption and altered alignment. That this might occasionally be difficult in the spine had been already recognized.[12]

At a time when OVFs were seen as little more than an unavoidable consequence of aging, their accurate recognition had limited clinical implications. Similarly, there was little incentive to provide a sound evidentiary basis for the imaging diagnosis of OVF. This changed with the recognition of osteoporosis as a treatable disease and the emergence of pivotal trials of effective treatments.[13,14] With their necessarily large enrollments, emphasis became focused on morphometry (quantitative; ie, based on measurement of dimensions and shape description) rather than on morphology (qualitative; ie, based on structural integrity).

Emergence of the morphometric paradigm

Faced with the enormous logistical hurdle of assessing repeated spinal radiographs of very many subjects, strategies that were less expert-dependent and (at the time) less labor-intensive became important in the design of such trials. This way, the necessary morphometric judgments progressed sometimes to become automated and/or delegated to "radiological assistants." Despite this evolution, these methods continued to lack an evidence-based foundation.[8,10,11]

Hurxthal[15] had made early observations about vertebral dimensions and Barnett and Nordin[16] in a seminal paper had earlier suggested a quantitative approach to OVF diagnosis that has come to be described generically as vertebral morphometry. It is particularly fascinating to realize that the latter two investigators were already concerned in 1960 with documenting vertebral biconcavity, ie, endplate deformation in osteoporosis, which they regarded as a crucial feature of the disease with no reference to "wedging" or other morphometric deformities. With endplate deformation and wedging being, respectively, central to the differences between the two distinctive diagnostic approaches (addressed here and described in detail in Table 1, this illustrates that to a large extent the following narrative traces a trajectory that takes the reader on a near 60-year circuitous journey, which might be described in the words of T.S. Eliot: "the end of all our exploring will be to arrive where we started and know the place for the first time."

Since those beginnings, numerous ingenious morphometric tools have been described that, if the basic premise that *fractures are the principal cause of vertebral deformity* is accepted, might potentially provide effective diagnosis. Although most have been accompanied by some proof of concept, none have addressed their validity against a gold standard on a scale that might amount to evidence of efficacy (Table 1), let alone involve prospective, multicenter, multiobserver methods with an explicit "gold standard." Briefly, some of the methods that have been proposed are described below:

- *Vertebral height difference of 4 mm*. Kleerekoper and colleagues[17] proposed using absolute differences in various dimensions between adjacent vertebrae be used for diagnosis, suggesting that a 4-mm or greater difference in the heights of adjacent adult vertebral bodies be used as a basic measure for OVF diagnosis and the grades summed as a spinal deformity score. This suggestion of a 4-mm threshold was repeated by Guglielmi and colleagues[18] in the radiological literature without reference to the limitations caused by magnification inherent in the divergent beam geometry of radiography.

Table 1. Comparison of Morphometric and Morphological Methods of Scoring OVFs

Morphometric criteria[a]	Morphologic criteria[b]
Modestly associated with BMD levels and low-trauma incident vertebral fractures, but not consistently across different studies, and with nonvertebral fractures	*More strongly* associated with BMD levels and incident vertebral and nonvertebral fractures compared to morphometric criteria
Prevalent Grade 1 deformities are weakly or not at all associated with incident nonvertebral fractures	Grade 1 ABQ ("mABQ") as defined in Lentle and colleagues,[40] lesions associated with incident OVF and non-OVF fractures
Lesser degrees of interobserver and intraobserver agreement	Higher degrees of interobserver and intraobserver agreement
Bimodal anatomical distribution of prevalent OVF with peaks in both the mid-thorax region and at the thoracolumbar junction	Principally a unimodal anatomical distribution with a peak in the thoracolumbar junction
Fractures are graded based on severity	Fractures might be graded using morphometric criteria
The default method in children prior to complete mineralization of the centrum as the spine matures	Cannot be applied prior to complete mineralization of the centrum as the spine matures

OVF = osteoporotic vertebral fracture.
[a]Defined by asymmetric vertebral dimensions; quantitative.
[b]Mainly defined by breaks in and distortions of vertebral endplates; qualitative.

- *Relative vertebral dimensions compared with those of the same or normal vertebrae.* Measurements of individual vertical vertebral dimensions may be compared with either reference to a normal data base or with other measurements of the same vertebra. For example, McCloskey and colleagues[19] determined normal ranges for vertebral dimensions from radiographs in 100 women aged 45 to 50 years. These included ranges for ratios to posterior vertebral heights (anterior/posterior, central/posterior, and posterior/predicted from T_4 to L_5 to be used as reference values in diagnosing disease. (Note: L_5 will always be contentious in this context and Genant and colleagues[20] properly suggested it be excluded from morphometry because of wide variations in its dimensions present from birth—typically Ha>>Hp (where Ha is anterior height, and Hp is posterior height).
- *Vertebral areal measurement.* Nelson and colleagues[21] have suggested that reductions in vertebral areal measurements are indicative of fracture occurrence, and that its estimation might improve morphometric fracture detection. Accepting that the sample size was small, they found that in 10 individuals the proposed method was a reliable index of vertebral relative size when comparisons were made between two centers.
- *Population-based normal values for vertebral shape.* Jackson and colleagues[22] developed a statistical model in which they extracted reference norms for vertebral shape from a subset of the CaM*os* population data, and then used such data to categorize any deformity in the remaining sample.
- *Anterior vertebral height summation and the Spine Deformity Index (SDI).* Diacinti and colleagues[23] proposed using a summation of the anterior heights of all vertebrae between T_4 and L_4 as an index of spinal fracture detriment, whereas Minne and colleagues[24] went further and compared vertebral heights to the orderly increase in size expected from T_4 downward, to determine an index of deviations that they described as the SDI.

The various morphometric tools have been compared with no clear superiority evident for any given tool, and, importantly, there has been no prospective determination of an optimum numerical threshold to be used for fracture diagnosis.[25] Rosol and colleagues[26] have further shown that the use of digitized images for morphometry is accurate and reproducible in comparison with the use of Vernier calipers on the original radiographs.

Thus morphometry became an entrenched approach to fracture recognition and, as a measure of its perceived importance, pedagogical programs in morphometric methodology were developed.[27] The topic has been reviewed by Jergas[28] and others.[29,30] Meanwhile, several constraints upon morphometric assessments have been identified including regional, ethnic, and gender-based differences in vertebral size, heights, and ratios.[31,32] Moreover, the reviews have largely been unequivocal in stressing that measurement-based vertebral assessment for OVF diagnosis is only to be used in population studies and not in the clinical evaluation of individual patients.[27,29,30] McCloskey and colleagues[19] illustrated this emphasis by specifying this contention in the title of their publication. At the same time it has often been stressed that morphometric "diagnosis" needs the intervention of an "expert" (radiologist or experienced clinician) to minimize false-positive readings,[25,28,29] another constraint that is often ignored. Vertebral morphometry remains widely used in diagnosing OVF often without recognition of these limitations so that equating morphometric deformities with fractures may potentially lead to high false-positive rates as described below.[33]

In the early 1990s, Genant and colleagues[20] proposed a diagnostic strategy, labeled the Genant Semi-Quantitative tool (GSQ). The method was based on a strictly visual of both quantitative and qualitative characteristics of the vertebral body; it was quasi-morphometric in specifically not requiring a measurement but a visual estimate resulting in a numerical grade (hence semiquantitative). The method became a form of structured reporting, then unusual but now more common. In more detail, one or other vertical dimension(s)—Ha, Hm, or Hp—(where a, m, and p are the anterior, middle, or posterior visually estimated vertebral heights of a given vertebra, respectively) are compared. Depending on which of the heights is reduced, deformities are classified based on shape (wedge, biconcave, and crush) and then graded visually: grade 0 (normal <20% difference); grade 1 (20% to 25% in height reduction and in area of 10% to 20%); grade 2 (25% to 40% height reduction and in area of 20% to 40%); and grade 3 (>40% in height and area) (Fig. 1). The original description of GSQ included both quantitative and qualitative elements in the analysis, also stressing the importance of recognizing end-plate fractures as characteristic of OVF; ie, it was intended to be a hybrid method. The GSQ method has been used in particular in epidemiological and pharmacoepidemiological studies.[13,14] Unfortunately, in its widespread application, the quantitative elements of the GSQ tool, not least the iconic diagram,[20,30] have tended to be applied in isolation. That diagram published by Genant and colleagues[20] has often been reproduced and was later embellished.

GSQ brought clarity to morphometry but its validity was not assessed except that it was found to be reproducible in the

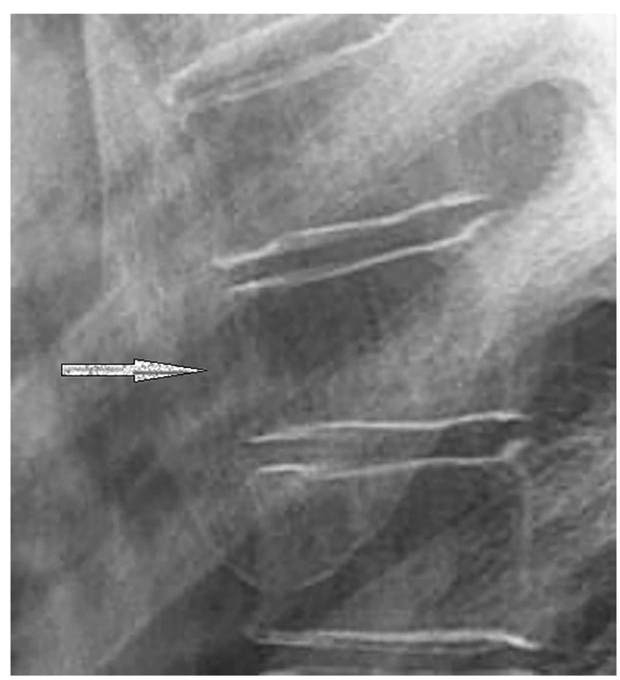

Fig. 1. A thoracic vertebra demonstrating abnormal morphometry (semiquantitative dimensions). The anterior vertical diameter measures less than the posterior by >25%. This vertebra is otherwise intact.

department in which it was conceived.[34] It has become so widely used as to be considered the default method for use in both epidemiological and clinical settings.[28]

As noted, the GSQ method relies on "measureless" measurements, ie, an eyeball estimate of vertebral dimensions, a potential source of observer error. This is compounded by the fact that the sagittal section of a normal vertebra cannot have equal heights anteriorly and posteriorly because, in the normal thoracic spine, for example, the typical kyphosis requires that each segment must be slightly wedge-shaped.

Recently, given digitized images and commercial scoring software, morphometry has been further modified without any substantive change in its purpose.[35] In the context of this review the challenge is now to design algorithms to also recognize qualitative evidence of OVF.

The qualitative or morphologic paradigm

An early attempt was made by Smith and colleagues[36] in the 1960s to standardize radiological practice in recognizing morphologic or qualitative signs of fracture. Meunier and colleagues,[37] in the late 1970s, used a hybrid qualitative/quantitative approach to diagnosing OVF. Later, Fabrequet and colleagues,[38] in a study of degenerative disease in men in France, used the GSQ tool but only accepted that a vertebra was fractured if it also betrayed evidence of structural damage; ie, qualitative evidence of fracturing. Their intent was not to examine the validity of the tool but use it to ask a different question of their data concerning degenerative disease. However, Fechtenbaum and colleagues[33] approached the problem differently in the clinical context of rheumatology (in which secondary osteoporosis is common) with their work directed at standardizing the definition of OVF. These workers were intent on observer issues and did not attempt to resolve the more fundamental question of veracity by assessing the relationship between radiological signs and biologically authentic parameters such as a relationship with lower bone mineral density (BMD) and fracture outcomes. First, they standardized the method of obtaining radiographs (developing a technical manual for the acquisition of images). This, however, is a frequently disregarded aspect, despite the importance of image quality as a component of an accurate diagnosis. Second, they developed a diagnostic algorithm, different from the Algorithm-Based Qualitative (ABQ) algorithm described in the next paragraph (although it shares some of its features). Last, they assessed intraobserver and interobserver agreement before and after attending a pedagogical session. They found that the number of patients having at least one fracture after the consensus-building exercise went from 13 to 26 patients out of 30. Eight of the 11 readers did particularly well. The agreement among these experts was, however, only 75% overall and 70% at first reading. The methods used by these investigators suggest the need for pedagogical programs to support scientific evidence related to vertebral fracture diagnosis.[38]

During extensive revision of incident vertebral fractures from radiographs of clinical trials at Sheffield University, Jiang and colleagues[39] noted that all such fractures involved endplate deformity and in 2004, proposed the use of a structured version of the morphologic (qualitative) approach to fracture diagnosis: the ABQ tool. This method was intended to bring some rigor to qualitative diagnosis and focuses on the recognition of vertebral endplate damage (Fig. 2) while excluding various confounders that also cause such damage, such as Schmorl nodes, Scheuermann disease, and the Cupid bow anomaly. The need to exclude these conditions does imply the need for qualified observers that are able to resolve the differential diagnosis. In the study reported by Jiang and colleagues,[39] the number of women with vertebral fractures according to the GSQ paradigm was twice the number identified by morphological (qualitative) criteria and more than three times the number of those identified by use of the ABQ protocol. In applying the ABQ method there is the option to obtain extra images in different projections to assess the integrity of the endplate. Newer technologies have progressively been shown to add diagnostic power if used with discrimination.[28]

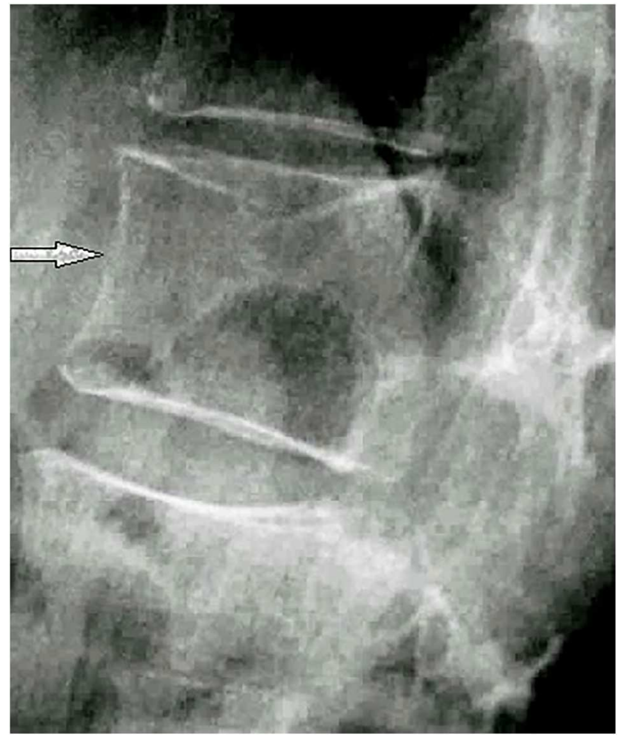

Fig. 2. Any measurable differences in the vertical diameters of this vertebra (L_1) are less than 25% but there is evidence of deformity and rupture of the superior end-plate, that is an abnormal morphological (structural) feature and evidence of fracture.

In the meantime, skepticism about low-grade morphometric deformities began to materialize.[40] Johansson and colleagues[41] had already reported that, although low-grade vertebral deformities were associated with incident vertebral abnormalities, they did not predict nonvertebral fractures. Moreover, there were an increasing number of prospective studies that ignored GSQ grade 1 deformities as a valid index of vertebral fracturing.[33,42]

The Present

Until very recently, there remained no satisfactory evidentiary basis to justify the preferential use of morphometric, morphologic, or mixed criteria in any one or other guise, for application in clinical practice.[11] However, Oei and colleagues,[43] Lentle and colleagues,[44] and Deng and colleagues[45] have all recently reported comparisons of the morphological (qualitative) and quasi-morphometric (quantitative) approaches to the diagnosis of OVF in large prospective studies in participants of both sexes. These studies' population sizes were 7582, 6236, and 3907 subjects, respectively. All three population-based studies with community-dwelling participants found that morphological fractures correlated inversely, and far better than morphometric ones, with BMD.[43–45] Grade 1 morphometric deformities (as defined by the GSQ method) were only weakly associated with incident OVFs and not at all with incident nonvertebral fractures as previously observed by Johansson and colleagues.[41] In the Rotterdam Study, fractures scored by quantitative morphometry, when including grade 1 in the definition, were weakly associated with incident nonvertebral fractures.[43] Contrastingly, prevalent grade 1 OVFs defined by a modified morphologic ABQ (mABQ) method were associated with a significant occurrence of both incident OVFs and incident nonvertebral fragility fractures[44] (Table 1). At the other end of the scale, grade 3 or severe OVFs *as defined by either method* were readily recognized as fractures because at that point the radiological signs converge as noted by Szulc.[46]

Observer Variables

A limitation of imaging research is that there are intrinsic subjective elements, meaning that any investigator is constrained in respect of both skill and vigilance. It has also been found that any innovation can be expected to perform better in the hands of its originators, as has occurred with OVF diagnosis. The GSQ tool was initially found to be highly reproducible within the department from which it originated,[20] but, subsequently, has performed less well.[34] The reasons are probably many, but likely include the commitment of those involved in the initial appraisals, as well as their better education in the precepts involved. No doubt reproducibility of the ABQ tool will also be prone in time to suffer a similar decline.

Ideally, imaging research comparing the diagnostic efficacy of techniques requires the involvement of multiple centers and observers with differing levels of experience and expertise. The CaM*os* study has approached such standards by involving clinicians, radiologists with differing backgrounds, and residents having completed their rotation in musculoskeletal radiology, calibrated by face-to-face interaction to ensure agreement about the basic criteria to be used.[44] During the comparison of the mABQ and GSQ methods, the GSQ imperative to visually judge the morphometric assessment was maintained, except that it was permissible to use a caliper to guide the assessment (it being found that otherwise the GSQ assessments would differ far more dramatically). The conclusions were unambiguous in that observer disagreements among all parties were significantly smaller with the use of the mABQ tool than the GSQ.[44]

In the study reported from Rotterdam, the ABQ assessment was performed by two teams each of seven research assistants and morphometric assessment was done with the assistance of the Spine Analyzer™ commercial software.[35,43] Definite or uncertain vertebral fractures observed using the ABQ method were then assessed by a musculoskeletal radiologist. There was little observer variation between techniques.

The Hong Kong (Deng and colleagues[45]) study used consensus in resolving the problem of observer disagreement and no information is provided on the scale of such disagreement. However, observer performance remains an issue and Jensen and colleagues[12] have pointed out that observer agreement may be a chance occurrence.

Coincidentally, these three publications[43–45] appeared nearly simultaneously. Had this been planned, identical diagnostic criteria might have been used across the studies. The differences in the relevant publications are tabulated in Table 2. It is evident that they are minor and potentially within the range of observer error. Consequently, it can reasonably be concluded that morphologic fracture criteria better reflect the generalized increase in skeletal fragility that characterizes osteoporosis than do morphometric or quasi-morphometric methods. However, the data from Jiang and colleagues[39] indicate that the two methods may perform differently, although in general, morphological (qualitative) criteria outperform morphometric (quantitative) ones in characterizing OVFs. Thus, in the study by Jiang and colleagues,[39] the prevalence of vertebral fracture was lowest when the ABQ paradigm was used; they attributed this to the more stringent criteria used in the ABQ paradigm to rule out deformation due to causes other than osteoporotic fracture. On the other hand, this may have led to false-negative results. This tension—the reciprocity between sensitivity and specificity—will be familiar to any investigator who has compared the relative power of diagnostic techniques.

Nevertheless, the main source of disagreement between methods as compared by Jiang and colleagues[39] was the large number of prevalent fractures identified by the purely morphometric application of the GSQ method but not by either the relatively loose qualitative morphological criteria or the more rigorous formalism of the ABQ method of diagnosis. They found "many of these were mild thoracic wedge fractures identified as non-fracture deformities or normal variants by the other two methods."[39] They go on to note that "bone density was lower in the women with fractures as designated consistently by all three methods [ie, qualitative, semiquantitative and ABQ], than in women with discrepant [G]SQ fractures." Differences in the way various methods of fracture definition are applied will inevitably lead to a certain amount of disagreement between methods, but the disproportionately large number of discrepant [G]SQ fractures identified in the Jiang and colleagues[39] study raises questions about the true nature of these "deformities." Notably, the prevalence of morphologic vertebral fractures was very similar in the three recent studies described here.[43–45] A comparison of the methods is summarized in Table 2, and some examples of radiographs illustrating the different diagnostic scenarios across methods are presented in Fig. 1.

Deng and colleagues[45] and others[8,17] have compared fracture rates among differing populations examined for vertebral fracture prevalence and incidence. It is at present difficult to draw any conclusions without some consensus on the taxonomy of vertebral lesions.

The problem of not having a reliable gold standard remains.[46] A case can be made for a set of reference teaching images agreed to by some investigators in this context, who will likely have benefitted from the feedback from their research. There is also a precedent in the fields of occupational medicine and radiology for using reference images in applying standardized chest radiographs for consistency in diagnosing and grading the industrial pneumoconioses,[47] a model which might be adopted in the osteoporosis field. Alternatively, pedagogical support might be offered in specialized national centers, and some international training courses are starting to be offered to the bone research community. For the future, it may be expected that machine learning and computer-aided diagnosis will be successfully applied to this problem.[48]

Table 2. Overview of Characteristics of Studies Referred to Across This Review and the Methods Used to Define OVF

Authors	Study aim and description of scoring method	Study population and findings	Conclusions
Genant and colleagues[20]	(a) Aim: compare an SQ method of defining OVF with a quantitative one. To estimate interobserver and intraobserver reproducibility of the SQ approach (b) OVF defined with (1) visual estimation of significant vertebral deformity (minimum 20% difference in vertical dimensions, etc.), namely the SQ method; and (2) direct measurement of vertebral dimensions, namely QM (c) Reference to endplate fractures but diagnosis not contingent on these	(a) $n = 57$ (women) (b) Excellent intrareader agreement and good interrater agreement (c) There were more OVFs located at the midthoracic region according to SQ compared to QM	(a) Excellent to good agreement for the intraobserver and interobserver variability of the SQ approach (b) Modest agreement between the morphometric and semimorphometric approach (c) Advice to use a combined approach incorporating both SQ and morphometric methods for clinical drug trials in osteoporosis
Jiang and colleagues[39]	(a) Aim: comparison of methods for the visual identification of OVF (b) OVF defined with (1) visual estimation on presence of endplate depression and differential diagnosis with a range of spine disorders; (2) visual estimation of significant vertebral deformity (minimum 20% difference in vertical dimensions, etc.), namely the SQ method; and (3) Qual. Reader 1 assessed the radiographs qualitatively with the aid of a radiological atlas of normal variants	(a) $n = 375$ (women) (b) Moderate agreement between Qual and ABQ, poor between SQ and Qual and between SQ and ABQ (c) Women with ABQ-defined OVF had lower BMD compared to those defined with SQ or Qual (d) ABQ OVFs were mostly located at the thoracolumbar junction whereas Qual and SQ OVFs were at the midthoracic region	(a) Poor agreement between methods arises mainly from difficulties in differentiating true fracture from nonfracture deformity (b) The ABQ approach attempts to address this (c) Need for further testing in a larger study population
Oei and colleagues[43]	(a) Aim: estimate statistical measures of agreement and prevalence of osteoporotic vertebral fractures across the two most commonly applied assessment methods (b) OVF defined by a team of seven trained research assistants applied readings using a commercial morphometric tool[35] (QM), a second team of another seven trained research assistants, applied the algorithm designed described above (ABQ), with definite or uncertain findings reviewed by a musculoskeletal radiologist) (*Morphologic*)	(a) $n = 7582$ (both sexes) (b) Interrater agreement was moderate for both methods and intramethod agreement was poor (c) The prevalence of ABQ-defined OVF was lower compared to QM-defined OVF (d) ABQ OVF were more strongly associated with BMD and future fracture risk compared to QM (e) ABQ-defined OVF were mostly located at the thoracolumbar junction whereas QM OVF were mostly located at the midthoracic region (f) Intermethod agreement increased when excluding mild deformities for the definition of QM or when reassessing mild QM for endplate depression	Mild deformities should be assessed for endplate depression, thereby decreasing false-positive QM fractures and reconciling the two methods
Lentle and colleagues[44]	(a) Aim: to compare the GSQ and an mABQ tool for radiologic (b) OVF defined by radiologists (including a musculoskeletal rad.) applying (1) GSQ method above and (2) same radiologists strictly applying an algorithm (modified after Jiang and colleagues[39]; mABQ) designed to exclude false positives	(a) $n = 6236$ (both sexes) (b) Observer agreement was higher for mABQ compared to GSQ (c) The prevalence of OVF was lower when defined with mABQ compared to GSQ (d) mABQ-defined OVFs were more strongly associated with low BMD compared to GSQ (e) Prevalent mABQ were more strongly associated with incident OVF and non-OVF fractures	Defining OVF by mABQ is preferred to the use of GSQ for clinical assessments
Deng and colleagues[45]	(a) Aim: to evaluate ECF-based method for detecting OVF in elderly Chinese population	(a) $n = 3907$ (both sexes) (b) ECF-defined OVFs are associated with lower BMD compared to GSQ-defined OVFs	ECF might be more specific to assess mild OVF

Table 2. (*Continued*)

Authors	Study aim and description of scoring method	Study population and findings	Conclusions
	(b) OVFs were defined by (1) presence of endplate/cortex fracture; and (2) applying GSQ method described above	(c) ECF-defined OVFs were mostly located at the thoracolumbar junction	

OVF = osteoporotic vertebral fracture; SQ = semiquantitative; QM = quantitative morphometry; Qual = qualitative visual assessment; ABQ = algorithm-based qualitative; mABQ = modified algorithm-based qualitative; GSQ = Genant Semiquantitative; ECF = endplate/cortex fracture.

The Segmental Distributions of Fractures

Jiang and colleagues,(39) Oei and colleagues,(43) and Lentle and colleagues(44) have examined the segmental distribution of OVF and all three studies have found it follows specific patterns, likely reflecting, in part, differing biomechanical stresses and structural properties across anatomical regions of the spine. All three reports note a distinct distribution of ABQ-diagnosed fractures with a principal peak at the thoracolumbar junction. Jiang and colleagues(39) distinguish morphometric, short vertebral height (SVH), a morphometric variant (see the SVH section below), and ABQ findings, whereas Oei and colleagues(43) and Lentle and colleagues(44) compare only quasi-morphometric and morphological findings. In all cases quasi-morphometric lesions have a different distribution of prevalent OVF with a principal peak in the mid-thorax. This again suggests that the difference between the two is more fundamental than simply that of two alternative means of describing the same phenomenon.

SVH

The diagnosis of OVF has been complemented by observations arising from the Osteoporosis and Ultrasound (OPUS) trial.(49) These investigators used the ABQ tool for diagnosis and developed the concept of SVH to explain their findings that prevalent morphometric (but non-ABQ) "fractures" (ie, vertebrae with abnormal morphometry but intact endplates) were common. They used a morphometric threshold of 15% and distinguished three groups of patients: normal ($n = 297$), those with fractures diagnosed using the ABQ tool ($n = 231$); and those with one or more SVH vertebrae ($n = 376$).(49) There was never more than a rudimentary basis for the use of 20% as a GSQ quasi-morphometric fracture threshold(25) so the use of a lower threshold enlarges the "morphometric" classification by use of a lower cut point. The BMD was significantly lower in the ABQ-diagnosed fracture group than in the SVH group and there was a significant association between the diagnosis of such fractures and a history of low-trauma nonvertebral and vertebral fractures ($p < 0.001$, odds ratios = 3.2 and 20.6, respectively).(49) However, there was also an association between a "diagnosis" of SVH and previous low-trauma nonvertebral fractures ($p < 0.05$, odds ratio = 1.7). The OPUS investigators concluded that SVH segments, without evidence of central endplate fracture and occurring in menopausal women, are by and large unrelated to osteoporosis and confirmed in a later publication that SVH did not correlate with BMD.(50) Further, a subsequent study in the same population showed that young women (20 to 40 years) were just as likely to have SVH as older women (55 to 85 years) in the OPUS study, suggesting that SVH was most likely to develop during childhood.(51) Morphometric deformities likely represent a continuous range of disease, if such it is, from minimal to severe. Perhaps a diagnostic label of SVH is less unwieldy than "morphometric deformity," pending the opportunity to clarify the exact implications of this finding.

Fracture Grading

Because the prognosis of OVF relates to both the number and severity of "fractures"(2) an innovative strength of the GSQ "morphometric" model of fracture diagnosis is that it grades fracture severity from grade 0 to grade 3. No such grading is implicit in the qualitative, morphological models described here, although in the CaMos study the mABQ tool was blended with the GSQ grading system.(44) In the Rotterdam Study(43) fractures scored by ABQ and quantitative morphometry grade 2 and 3 held stronger associations with fractures (both vertebral and nonvertebral), as well as with BMD, age, and sex. These data suggest the clinical utility of a grading system. Although potential criticisms of the GSQ grading system are that it is nonlinear (with thresholds of 20%, 25%, and 40% for grades 1 to 3) and that it has not been validated, it is hallowed by use and might be difficult to improve upon. However, as Jiang and colleagues(39) observed, morphologic fractures may occur in vertebrae that would be graded morphometrically as normal (grade 0), so that any grading system for future use has to provide for that contingency (scored as ABQ 0). In the Rotterdam Study, 35% of the ABQ fractures were observed in vertebrae without morphometric compromise.(43) We believe that fracture grading should be preserved, perhaps using the Genant tool but only when allied to recognition of the qualitative signs of fracturing.

It has become common to suggest that "low-grade fractures" be disregarded without reference to how these are defined. That view is only supported by the data noted here if there is no morphologic fracture in reference to purely "morphometric" lesions and may be open to debate.

Vertebral Fractures in Children

OVFs in children, usually due to glucocorticoid administration for serious diseases such as leukemia, chronic juvenile arthritis, renal disease, and Duchenne muscular dystrophy, among several others, require a separate understanding.(52–56) OVFs are a frequent manifestation of bone fragility in children, to the extent now that spine imaging for vertebral fracture detection is prioritized over BMD in the bone health assessment of at-risk children.(57,58) Routine monitoring in those at risk is paramount because OVFs in the young are frequently asymptomatic, similar to observations in at-risk adults. Care will be impacted across the lifespan as affected children increasingly live longer.(59,60)

In childhood, fractures often heal and the affected vertebrae may reshape and regain their original or near-original configuration, if the threat to bone health is transient *and* there remains sufficient residual growth potential to effect complete or partial reshaping (because reshaping appears to be a growth-dependent phenomenon). Pediatric radiologists may thus be afforded an advantage in that they are often provided with a retrospective "audit" of their diagnostic acumen.[52,57,61,62] For diagnosis the observer may have to rely on morphometric criteria because ossification of the centrum is centripetal from a central ossification center in the centrum with mineralization only reaching the vertebral endplates in adolescence.[57] As a result, the ABQ methodology is of uncertain effectiveness related to plain-film radiography in children. The long-term implications of fractures in this age group will likely have relevance to the interpretation of adult radiographs.

The reshaped vertebra often demonstrate a "bone-within-bone" appearance echoing the maximum deformity,[52,57,61,63] which is perhaps the vertebral equivalent of Harris' lines of arrested growth in long bones.[64] Siminoski and colleagues[65] have also reported a slight difference in the segmental distribution of vertebral fractures between children and adults, with pediatric GSQ-defined fractures clustering somewhat more rostrally and caudally than adult OVF.

Radiologists and OVF

The relationship of radiologists with OVF has often been uneasy for several reasons. The radiology of OVF is complicated by observations of OVF that radiologists too often fail to recognize and/or report on radiographic examinations done for other reasons.[66,67] The reporting of radiographs is often criticized for the use of ambiguous descriptive language such as "deformity" or "wedging," as in: "There is mild wedging of mid-thoracic vertebrae." Perhaps the confusion surrounding the diagnostic criteria for OVF has contributed to this situation and there has been existential uncertainty about what is a vertebral fracture. At the same time there is the challenge of so-called opportunistic diagnosis whereby protocols might be modified to proactively use sectional and other imaging, perhaps allied to automated tools,[49] to look for OVFs incidental to examinations done for other reasons.[68]

Given that the subject of OVF diagnosis has been fraught, the recent evidence reviewed here is, perhaps, an opportunity to reset the role of radiologists in osteoporosis care.

Conclusions

The information assembled in this review contains evidence that observer agreement is best when applied to morphologically-defined OVFs.[43,44] Furthermore, morphological vertebral fractures seem to be more strongly associated with lower BMD (both spinal and femoral),[39,44,45] incident OVF,[44] and nonvertebral osteoporotic fractures[41,44] than morphometric vertebral deformities. Furthermore, the morphologic (qualitative) criteria best identify vertebral fractures as indicating the state of bone frailty predisposing to further fracturing.[39,43–45] The anatomical spinal distribution of morphometric deformities and morphologic fractures is different.[39,43,44] We believe there is now an evidentiary basis for suggesting that morphological assessment is the preferred strategy for use in diagnosing OVF from radiographs. Furthermore, based on the information summarized in this review, we have compiled a list of recommendations (Box 1) and unresolved issues (Box 2). The diagnosis of vertebral fracture has not been subject to a consensus definition that can be applied unequivocally in a clinical setting and harmonized in

Box 1. Recommendations

It is important for patient care that vertebral fractures are clearly identified, enumerated, and graded

The language used to describe fractures should be precise, unambiguous, and avoid equivocations such as in phrases such as "mild anterior wedging in the mid-thoracic spine," which do not contribute to patient management. Fractures should be specifically identified as such.

Quantitative and qualitative tools have been proposed for fracture diagnosis but produce different estimates of fracture incidence. The evidence now available indicates that a vertebral fracture is best diagnosed on the basis of morphologic (qualitative) damage to vertebral end-plates and/or cortices.

In assessing radiographs for osteoporotic vertebral fracture (OVF), whenever possible previous spine images should be reviewed.

Deviations in vertebral dimensions from "normal" in morphometric analyses are neither a necessary nor sufficient basis for fracture diagnosis.

Morphometric tools were intended to be limited to epidemiological or interventional studies and have been shown to have considerable potential for overdiagnosis if used for the clinical assessment of individuals. This constraint must be observed.

Radiologists working in clinical care need to realize that, if using morphometric tools, particularly with respect to low-grade deformities, they should caution referring clinicians that such lesions may not be fractures at all and have, at best, a weaker predictive power for incident fracturing than morphologic fractures.

Box 2. Unresolved Issues

Do the lesser degrees of bone mineral density depletion seen with mild/moderate morphometric vertebral deformities have implications in mortality and do they deserve some response in clinical care?

Of the three recent pivotal articles discussed here, two used nearly identical criteria (the ABQ paradigm) for diagnosing morphologic fracture; the third potentially used slightly different criteria, albeit with very similar results. Jiang and colleagues[39] used both strict and looser morphologic criteria which changed the ratio of true positives to false negatives. Ideally some way needs to be found to offer evidence-based advice to radiologists and others on the practical issue of implementing the recommendations here.

There is a need for a lifelong study of the vertebral column by sex in health and disease.

If morphometry is to have any application in epidemiological research related to osteoporosis, receiver operating characteristic curves should be derived to optimize a quantitative diagnostic threshold to be used (as has been suggested by Szulc and colleagues[55]).

epidemiological studies. Before computer-guided methods can be developed for reliable use in unsupervised diagnosis, the field requires a definition to be reached that is reflected in better clinical outcomes for patients at risk of osteoporosis and fractures. With this review, we trust the field has come closer in that goal.

Disclosures

The authors state that they have no conflicts of interest.

Acknowledgments

We are grateful to our collaborators in the CaMos and Rotterdam Study for their invaluable input. Angela M. Cheung is supported by a Tier 1 Canada Research Chair in Musculoskeletal and Postmenopausal Health. In particular we thank Drs. Jonathan Adachi, David Hanley, Jeff Hu, Robert Josse, Victor Konji, Christopher Kovacs, and Suzanne Morin for constructive input. Further, we thank Richard Eastell and Eugene McCloskey from Sheffield University for their valuable feedback and critical review of the manuscript.

Authors' roles: First draft written by BCL. Revised the manuscript content, approved the final version of the manuscript and take responsibility for the content of the article: BCL, FK, JCP, LO, LW, DG, FR, WDL, LP, JP, IH, AMC, EHO.

References

1. Wasnich R. Epidemiology of osteoporosis. In: Flavus M, editor. Primer on the metabolic bone diseases and disorders of mineral metabolism. Philadelphia, PA: Lipicott-Raven; 1996:249–51.
2. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ 3rd. Population-based study of survival after osteoporotic fractures. Am J Epidemiol. 1993;137(9):1001–5.
3. Ross PD, Davis JW, Epstein RS, Wasnich RD. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. Ann Intern Med. 1991;114(11):919–23.
4. Broy SB. The vertebral fracture cascade: etiology and clinical implications. J Clin Densitom. 2016;19(1):29–34.
5. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ. 2010;182(17):1864–73.
6. Compston J, Bowring C, Cooper A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas. 2013;75(4):392–6.
7. Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis: executive summary of recommendations. Endocr Pract. 2010;16(6): 1016–9.
8. Kleerekoper M. The evaluation of patients with osteoporosis. In: Marcus R, Feldman D, Kelsey J, editors. Osteoporosis. San Diego, CA: Academic Press; 1966:1011–8.
9. McCloskey EV, Vasireddy S, Threlkeld J, et al. Vertebral fracture assessment (VFA) with a densitometer predicts future fractures in elderly women unselected for osteoporosis. J Bone Miner Res. 2008;23(10):1561–8.
10. Grados F, Fechtenbaum J, Flipon E, Kolta S, Roux C, Fardellone P. Radiographic methods for evaluating osteoporotic vertebral fractures. Joint Bone Spine. 2009;76(3):241–7.
11. Oei L, Rivadeneira F, Ly F, et al. Review of radiological scoring methods of osteoporotic vertebral fractures for clinical and research settings. Eur Radiol. 2013;23(2):476–86.
12. Jensen GF, McNair P, Boesen J, Hegedus V. Validity in diagnosing osteoporosis. Observer variation in interpreting spinal radiographs. Eur J Radiol. 1984;4(1):1–3.
13. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab. 2000;85(11): 4118–24.
14. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999;282(14): 1344–52.
15. Hurxthal LM. Measurement of anterior vertebral compressions and biconcave vertebrae. Am J Roentgenol Radium Ther Nucl Med. 1968;103(3):635–44.
16. Barnett E, Nordin BE. The radiological diagnosis of osteoporosis: a new approach. Clin Radiol. 1960;11:166–74.
17. Kleerekoper M, Parfitt A, Ellis B. Measurement of vertebral fracture rates in osteoporosis. In: Christiansen C, Arnaud C, Nordin B, Parfitt A, Peck WR, Riggs BL, editors. Copenhagen International Symposium on Osteoporosis; 1984 June 3–8; Copenhagen, Denmark.
18. Guglielmi G, Muscarella S, Bazzocchi A. Integrated imaging approach to osteoporosis: state-of-the-art review and update. Radiographics. 2011;31(5):1343–64.
19. McCloskey EV, Spector TD, Eyres KS, et al. The assessment of vertebral deformity: a method for use in population studies and clinical trials. Osteoporos Int. 1993;3(3):138–47.
20. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8(9):1137–48.
21. Nelson D, Peterson E, Tilley B, et al. Measurement of vertebral area on spine X-rays in osteoporosis: reliability of digitizing techniques. J Bone Miner Res. 1990;5(7):707–16.
22. Jackson SA, Tenenhouse A, Robertson L. Vertebral fracture definition from population-based data: preliminary results from the Canadian Multicenter Osteoporosis Study (CaMos). Osteoporos Int. 2000;11(8): 680–7.
23. Diacinti D, Pisani D, Barone-Adesi F, et al. A new predictive index for vertebral fractures: the sum of the anterior vertebral body heights. Bone. 2010;46(3):768–73.
24. Minne HW, Leidig G, Wuster C, et al. A newly developed spine deformity index (SDI) to quantitate vertebral crush fractures in patients with osteoporosis. Bone Miner. 1988;3(4):335–49.
25. Smith-Bindman R, Cummings SR, Steiger P, Genant HK. A comparison of morphometric definitions of vertebral fracture. J Bone Miner Res. 1991;6(1):25–34.
26. Rosol MS, Cohen GL, Halpern EF, et al. Vertebral morphometry derived from digital images. AJR Am J Roentgenol. 1996;167(6): 1545–9.
27. Gardner JC, von Ingersleben G, Heyano SL, Chesnut CH 3rd. An interactive tutorial-based training technique for vertebral morphometry. Osteoporos Int. 2001;12(1):63–70.
28. Jergas M. Radiology of osteoporosis. In: Grampp S, editor. Radiology of osteoporosis. Berlin, Germany: Springer; 2008. p. 77–103.
29. Diacinti D, Guglielmi G. Vertebral morphometry. Radiol Clin North Am. 2010;48(3):561–75.
30. Griffith J, Adams J, Genant H. Diagnosis and classification of vertebral fractures. In: Rosen C, Bouillon R, Compston J, Rosen V, editors. Primer on the metabolic bone diseases and disorders of mineral metabolism. Philadelphia, PA: Wiley-Blackwell; 2013. p. 317–35.
31. Ross PD, Wasnich RD, Davis JW, Vogel JM. Vertebral dimension differences between Caucasian populations, and between Caucasians and Japanese. Bone. 1991;12(2):107–12.
32. Ning L, Song LJ, Fan SW, et al. Vertebral heights and ratios are not only race-specific, but also gender- and region-specific: establishment of reference values for mainland Chinese. Arch Osteoporos. 2017;12(1):88.

33. Fechtenbaum J, Briot K, Paternotte S, et al. Difficulties in the diagnosis of vertebral fracture in men: agreement between doctors. Joint Bone Spine. 2014;81(2):169–74.
34. Wu CY, Li J, Jergas M, Genant HK. Comparison of semiquantitative and quantitative techniques for the assessment of prevalent and incident vertebral fractures. Osteoporos Int. 1995;5(5):354–70.
35. Optasia Medical, Ltd. SpineAnalyzer Literature. Cheadle, UK: Optasia Medical Ltd; 2018 [cited 2019 Jan 20]. Available from: http://www.optasiamedical.com/spineanalyzer-literature/
36. Smith RW Jr, Eyler WR, Mellinger RC. On the incidence of senile osteoporosis. Ann Intern Med. 1960;52:773–81.
37. Meunier P, Bressor C, Vignon E. Radiological and histological evolution of post-menopausal osteoporosis treated with sodium fluoride-vitamin D-calcium. In: Courvoisierm B, Donath A, Baud C, editors. Fluoride and bone. Bern, Switzerland: Hans Huber Publishers; 1978.
38. Fabreguet I, Fechtenbaum J, Briot K, Paternotte S, Roux C. Lumbar disc degeneration in osteoporotic men: prevalence and assessment of the relation with presence of vertebral fracture. J Rheumatol. 2013;40(7):1183–90.
39. Jiang G, Eastell R, Barrington NA, Ferrar L. Comparison of methods for the visual identification of prevalent vertebral fracture in osteoporosis. Osteoporos Int. 2004;15(11):887–96.
40. Lentle B, Cheung AM, Hanley DA, et al. Osteoporosis Canada 2010 guidelines for the assessment of fracture risk. Can Assoc Radiol J. 2011;62(4):243–50.
41. Johansson H, Oden A, McCloskey EV, Kanis JA. Mild morphometric vertebral fractures predict vertebral fractures but not non-vertebral fractures. Osteoporos Int. 2014;25(1):235–41.
42. Schousboe JT, Rosen HR, Vokes TJ, et al. Prediction models of prevalent radiographic vertebral fractures among older men. J Clin Densitom. 2014;17(4):449–57.
43. Oei L, Koromani F, Breda SJ, et al. Osteoporotic vertebral fracture prevalence varies widely between qualitative and quantitative radiological assessment methods: the Rotterdam Study. J Bone Miner Res. 2018;33(4):560–8.
44. Lentle BC, Berger C, Probyn L, et al. Comparative analysis of the radiology of osteoporotic vertebral fractures in women and men: cross-sectional and longitudinal observations from the Canadian Multicentre Osteoporosis Study (CaMos). J Bone Miner Res. 2018;33(4):569–79.
45. Deng M, Zeng XJ, He LC, et al. Osteoporotic vertebral fracture prevalence in elderly Chinese men and women: a comparison of endplate/cortex fracture-based and morphometrical deformity-based methods. J Clin Densitom. Forthcoming. Epub 2017 Dec 2. DOI:10.1016/j.jocd.2017.11.004.
46. Szulc P. Vertebral fracture: diagnostic difficulties of a major medical problem. J Bone Miner Res. 2018;33(4):553–9.
47. International Labour Organization. Guidelines for the use of ILO International Classification of Radiographs of Pneumoconioses. Geneva, Switzerland: International Labour Organization; 1980.
48. Choy G, Khalilzadeh O, Michalski M, et al. Current applications and future impact of machine learning in radiology. Radiology. 2018;288(2):318–28.
49. Ferrar L, Jiang G, Armbrecht G, et al. Is short vertebral height always an osteoporotic fracture? The Osteoporosis and Ultrasound Study (OPUS). Bone. 2007;41(1):5–12.
50. Ferrar L, Jiang G, Cawthon PM, et al. Identification of vertebral fracture and non-osteoporotic short vertebral height in men: the MrOS study. J Bone Miner Res. 2007;22(9):1434–41.
51. Ferrar L, Roux C, Reid DM, Felsenberg D, Gluer CC, Eastell R. Prevalence of non-fracture short vertebral height is similar in premenopausal and postmenopausal women: the Osteoporosis and Ultrasound Study. Osteoporos Int. 2012;23(3):1035–40.
52. Ward LM, Ma J, Lang B, et al. Bone morbidity and recovery in children with acute lymphoblastic leukemia: results of a six-year prospective cohort study. J Bone Miner Res. 2018;33(8):1435–43.
53. Phan V, Blydt-Hansen T, Feber J, et al. Skeletal findings in the first 12 months following initiation of glucocorticoid therapy for pediatric nephrotic syndrome. Osteoporos Int. 2014;25(2):627–37.
54. LeBlanc CM, Ma J, Taljaard M, et al. Incident vertebral fractures and risk factors in the first three years following glucocorticoid initiation among pediatric patients with rheumatic disorders. J Bone Miner Res. 2015;30(9):1667–75.
55. Szulc P, Munoz F, Marchand F, Delmas PD. Semiquantitative evaluation of prevalent vertebral deformities in men and their relationship with osteoporosis: the MINOS study. Osteoporos Int. 2001;12(4):302–10.
56. Ma J, McMillan HJ, Karaguzel G, et al. The time to and determinants of first fractures in boys with Duchenne muscular dystrophy. Osteoporos Int. 2017;28(2):597–608.
57. Ward LM, Konji VN, Ma J. The management of osteoporosis in children. Osteoporos Int. 2016;27(7):2147–79.
58. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018;17(4):347–61.
59. Birnkrant DJ, Ararat E, Mhanna MJ. Cardiac phenotype determines survival in Duchenne muscular dystrophy. Pediatr Pulmonol. 2016;51(1):70–6.
60. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med. 2006;354(2):166–78.
61. Dal Osto LC, Konji VN, Halton J, et al. The spectrum of recovery from fracture-induced vertebral deformity in pediatric leukemia. Pediatr Blood Cancer. 2016;63(6):1107–10.
62. Pandya NA, Meller ST, MacVicar D, Atra AA, Pinkerton CR. Vertebral compression fractures in acute lymphoblastic leukaemia and remodelling after treatment. Arch Dis Child. 2001;85(6):492–3.
63. Lentle B, Ma J, Jaremko JL, et al. The radiology of vertebral fractures in childhood osteoporosis related to glucocorticoid administration. J Clin Densitom. 2016;19(1):81–8.
64. Harris HA. The growth of the long bones in childhood: with special reference to certain bony striations of the metaphysis and to the rôle of the vitamins. Arch Intern Med. 1926;38(6):785–806.
65. Siminoski K, Lee KC, Jen H, et al. Anatomical distribution of vertebral fractures: comparison of pediatric and adult spines. Osteoporos Int. 2012;23(7):1999–2008.
66. Gehlbach SH, Bigelow C, Heimisdottir M, May S, Walker M, Kirkwood JR. Recognition of vertebral fracture in a clinical setting. Osteoporos Int. 2000;11(7):577–82.
67. Delmas PD, van de Langerijt L, Watts NB, et al. Underdiagnosis of vertebral fractures is a worldwide problem: the IMPACT study. J Bone Miner Res. 2005;20(4):557–63.
68. Adams JE. Opportunistic identification of vertebral fractures. J Clin Densitom. 2016;19(1):54–62.