

Position Statement

Fracture Prediction and the Definition of Osteoporosis in Children and Adolescents: The ISCD 2007 Pediatric Official Positions

Frank Rauch,^{*,1,a,c} Horacio Plotkin,^{2,a} Linda DiMeglio,^{3,b} Raoul H. Engelbert,^{4,b} Richard C. Henderson,^{5,b} Craig Munns,^{6,b} Deborah Wenkert,^{7,b} and Philip Zeitler^{8,b}

¹Shriners Hospital for Children, Montreal, Canada; ²Children's Hospital and University of Nebraska Medical Center, Omaha, NE, USA; ³Riley Hospital, Indiana University, Indianapolis, IN, USA; ⁴Utrecht University, Utrecht, Netherlands; ⁵University of North Carolina, Chapel Hill, NC, USA; ⁶Westmead Hospital, The University of Sydney, Sydney, Australia; ⁷Shriners Hospital for Children, St. Louis University, St. Louis, MO, USA; and ⁸University of Colorado, Denver, CO, USA

Abstract

Osteoporosis in adults has been defined on the basis of densitometric criteria, but at present the term osteoporosis does not have a widely recognized definition in pediatrics. Consequently, the International Society for Clinical Densitometry (ISCD) 2007 Position Development Conference reviewed the literature describing the relationship between bone densitometric studies and fractures in apparently healthy children and adolescents, and prepared Official Positions regarding the definition of osteoporosis in children and adolescents. The ISCD Official Positions with respect to the above issues, as well as the rationale and evidence used to derive these positions, are presented here.

Key Words: Dual-energy X-ray absorptiometry; fracture; pediatric.

Introduction

Dual-energy X-ray absorptiometry (DXA) was originally devised for use in adults. However, DXA studies are now performed with increasing frequency in children and adolescents as well. The clinical use of bone densitometry in adults is mainly based on epidemiological studies that have found an association between densitometric measurements, such as areal bone mineral density (BMD) bone mineral content (BMC), and fracture incidence in a number of populations (1–4). However, results in adults cannot be simply extrapolated to the pediatric age range for a variety of reasons, including the influence of growth on DXA results and the different fracture epidemiology in children and adolescents.

Received 12/05/07; Accepted 12/05/07.

*Address correspondence to: Frank Rauch, MD, Genetics Unit, Shriners Hospital for Children, 1529 Cedar Avenue, Montreal, QC H3G 1A6, Canada. E-mail: frauch@shriners.mcgill.ca

^aTask Force Chair.

^bTask Force Member.

^cTask Force Liaison.

The incidence of fracture in healthy children or adolescents is similar to the lifetime risk of osteoporotic fracture as an adult (5–7). Between a third and one half of all children will have at least one fracture by the end of their teenage years (5,8). Nevertheless, the characteristics of fractures differ markedly between healthy children and osteoporotic adults. Adults with osteoporosis frequently sustain hip and spine fractures, whereas such fractures are very rare in healthy children. In osteoporotic adults, fractures often are caused by a simple fall from standing height, but healthy children sustain fractures commonly during more forceful trauma, such as falls from playground equipment or sports activities (5,9). In adults, osteoporosis is more common in females, whereas in children more fractures occur in the male sex (7).

This task force was asked to examine the following questions:

- Are DXA measures predictive of fractures in apparently healthy children and adolescents?
- What are the densitometric criteria for the diagnosis of osteoporosis in a child or adolescent?

Methodology

A literature search was performed using the PubMed and OVID MEDLINE databases for the time period from 1966 to February 2007. Combinations of the terms “bone mineral density”, “BMD”, “BMAD”, “children”, “adolescents”, “pediatric,” and “fractures” were used. Studies were included if they utilized measurements by DXA in apparently healthy children and/or adolescents, and analyzed the relationship of the measurements with fracture occurrence. Studies in premature babies and young infants were not included, as fractures in this age group are of very different etiology from those in older children, and infant DXA software has numerous limitations related to the bone edge detection algorithms in small subjects.

The methods used to develop, and grading system applied to the ISCD Official Positions are presented in the Executive Summary that accompanies this paper. In brief, all positions were rated by the Expert Panel on quality of evidence (good; fair; poor: where Good is evidence that includes results from well-designed, well-conducted studies in representative populations; Fair is evidence sufficient to determine effects on outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; and Poor is evidence that is insufficient to assess the effects on outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or information), strength of the recommendation (A; B; C; or D: where A is a strong recommendation supported by the evidence; B is a recommendation supported by the evidence; and C is a recommendation supported primarily by expert opinion), and applicability (worldwide = W or variable, according to local requirements = L). Necessity was also considered with a response of “necessary” indicating that the indication or procedure is “necessary” due to the health benefits outweighing the risk to such an extent that it must be offered to all patients, and the magnitude of the expected benefit is not small.

Are DXA Measures Predictive of Fractures in Apparently Healthy Children and Adolescents?

ISCD Official Position

- Fracture prediction should primarily identify children at risk of clinically significant fractures, such as fracture of long bones in the lower extremities, vertebral compression fractures, or two or more long-bone fractures of the upper extremities.

Grade: Fair-C-W-Necessary

Rationale

General Assessment of the Literature. The published evidence on the relationship between DXA analyses and fractures in children and adolescents was found to be quite limited. Eleven studies were identified. In three of these

studies fractures were assessed prospectively after a baseline DXA scan (10–12). In the other studies DXA scans were obtained only after the fracture had occurred (13–19). Even though ‘fracture prediction’ implies forecasting future events, such retrospective reports were nevertheless reviewed, given the overall scarcity of information on the topic in question.

One might assume that DXA results best predict fractures at skeletal sites that are directly assessed by the analysis. However, a DXA scan at a different skeletal site might also be informative if the correlation between sites is sufficiently high. We therefore evaluated site-specific and systemic fracture prediction separately. Among the skeletal sites where regional DXA analyses are frequently performed (lumbar spine, hip, forearm), only the forearm is a common fracture location in healthy children and adolescents. Therefore, the relationship between site-specific DXA results and fracture was assessed in the forearm only.

Forearm Fractures and Forearm DXA Results

Retrospective studies by Goulding et al. found that children and adolescents with recent distal forearm fractures had lower areal BMD at the ultradistal radius and at the one-third (33%) radius, compared with controls (13,14). Comparing subjects with ultradistal areal BMD Z-scores below -1 to those with results above this value, the age- and weight-adjusted odds ratios (OR) for distal forearm fractures were 2.39 (95% confidence interval [CI]: 1.13 to 5.05) in girls, and 2.63 (95% CI: 1.27 to 5.45%) in boys. Similar results were found for the one-third (33%) radius in boys, but in girls the odds ratios were not significant for that site.

In a prospective study the same group evaluated the relationship between DXA results at the radius and subsequent fractures at the distal forearm (10). Of the 170 girls who were included in this study, 82 had sustained a forearm fracture shortly before the DXA scan was performed, whereas the other 88 age-matched girls were fracture free. Neither areal BMD at the ultradistal radius and at the one-third (33%) site of the radius, nor Bone Mineral Apparent Density (BMAD, an estimate of three-dimensional mineral density based on DXA bone area and BMC) at the one-third (33%) site of the radius were significantly associated with the occurrence of subsequent distal forearm fractures ($n = 27$) over the following 4 yr. BMC results were not indicated in that report. However, in a different study Ferrari et al. found that compared to controls, BMC was lower at the ultradistal radius and at the radius diaphysis (the size of the difference is not provided in the report) in 32 prepubertal girls who sustained upper limb fractures in the 8.5 yr following the DXA scan (12).

The Expert Panel concluded from these data that low ultradistal and one-third (33%) radius areal BMD adjusted for age and gender (Z-score) is associated with distal forearm fracture.

Forearm Fractures and DXA Results at Other Measurement Sites

In cross-sectional studies conducted after the fracture event occurred, significant relationships between DXA results

and distal forearm fractures were found for lumbar spine (13,14,20), femoral neck (14,20), trochanter (14), and total body (20). The largest cross-sectional study (321 fracture cases and 321 controls), found that areal BMD and BMAD at these sites were associated with forearm fractures to a similar extent as the metacarpal index, a measure that can be determined from standard hand radiographs (as the ratio between cortical width and bone diameter at the mid-shaft of the second metacarpal) (20). Analyses of the area under the receiver operating characteristic (ROC) curve for a variety of DXA results (BMC, areal BMD and BMAD at the lumbar spine, hip and total body), and forearm fracture risk found that spine and hip BMAD were the only DXA measures that had a statistically significant relationship with fractures in both males and females (18). However, the maximal area under the ROC curve, found for spine BMAD, was only 0.61 (95% CI: 0.55 to 0.66), indicating that this test had a rather weak predictive accuracy for forearm fractures (a value of 1 indicates a perfectly accurate prediction, a value of 0.5 means that there is no relationship between prediction and outcome).

The association between forearm fractures and DXA results at sites other than the radius was prospectively assessed in a study cohort that included a group of girls who previously had experienced distal forearm fractures, and girls who had not had a fracture before (10). Total body areal BMD, but not lumbar spine areal BMD and BMAD, was independently associated with distal forearm fractures in the 4 yr following the DXA scan. After adjustment for previous fracture, age and weight, the hazard ratio for distal forearm fracture was 2.01 (95% CI: 1.12 to 3.60) for each standard deviation (SD) decrease in total body areal BMD.

Based on these data, the Expert Panel judged that low lumbar spine areal BMD and BMAD adjusted for age and gender (Z-score) are associated with distal forearm fracture.

Fractures at all Skeletal Sites Combined and Regional DXA Scans

A retrospective study found that children who had sustained a fracture a few days before the DXA analysis had lower height- and weight-adjusted lumbar spine areal BMD and BMC (by 0.76 and 0.74 SD, respectively) than fracture-free controls (19).

In a prospective study of 125 girls (baseline age: 6–9 yr) Ferrari et al. compared BMC at the ultradistal radius; radius diaphysis; femoral neck; trochanter; femoral midshaft; and lumbar spine between girls who sustained fractures at any site ($n = 42$; 76% of fractures affected the upper limb), and those who remained fracture free ($n = 83$), in the 8.5 yr follow-up interval (12). The only significant difference between groups was found for BMC at the radial diaphysis, which was 4.3% lower in the fracture group. This difference in bone mass was due to a smaller bone diameter, whereas areal BMD and volumetric BMAD were similar between groups.

Clark et al. compared baseline DXA results at the right humerus (as derived from total body DXA scans), in 549 children who had fractures (83% in the upper extremities) in the

2 yr following the scan to those of 836 children who did not sustain fractures (11). Both areal BMD and BMAD were significantly associated with the occurrence of fractures. The highest OR for fractures, 1.40 (95% CI: 1.21 to 1.62) was found for areal BMD after adjustment for height and log-transformed weight.

Fractures at all Skeletal Sites Combined and Whole Body DXA Scans

In a retrospective study, Manias et al. found that height- and weight-adjusted total body (including head) BMC and areal BMD were lower in children who recently had sustained fractures as compared to fracture-free controls (19). As the subjects in the fracture group had casts at the time of the study, arms or legs were excluded from the total body DXA analyses, depending on which limb carried the cast. Average results of the remaining skeletal areas were between 0.81 and 1.65 SDs lower in the fracture group than in the control group.

In by far the largest study reviewed here, Clark et al. prospectively followed 6213 children and examined the relationship between baseline total body DXA results and fractures in the 2 yr following the scan (11). The head was excluded from the DXA analyses and results were given as total body less head (TBLH). The stated rationale was that “previous studies had suggested that the head is not responsive to environmental stimuli such as physical activity” (21). A total of 549 children (8.9% of the study population), sustained fractures during the follow-up period; 83% of fractures affected the upper limbs. The report does not mention cases of fractures in the femur or skeletal sites other than the limbs. Average TBLH areal BMD was 0.6% lower in fracture cases than in study participants that remained fracture-free during the follow-up period. The OR for fracture per SD decrease in TBLH areal BMD was 1.12 (95% CI: 1.02 to 1.25). No relationship between baseline age-adjusted TBLH BMC and subsequent fractures was found ($p = 0.19$). However, when height, weight, and TBLH bone area were added to the logistic regression model, the ORs for the risk of fracture increased to 1.89 (95% CI: 1.18 to 3.04). The authors concluded from this “results showed an 89% increased risk of fracture per SD decrease in size-adjusted BMC”.

Although the report published by Clark et al. is currently the most informative analysis on DXA results and fracture risk in children, there are limitations to the study that potentially may have biased the results (11). First, the final analysis was apparently based on less than half of the population that had been invited to participate, which may have selected for children where skeletal problems were a concern to the parents. Second, the fracture count was based on radiographic evidence in only 35% of cases, and solely relied on questionnaire information in the other subjects with fractures.

The Expert Panelists concluded from this evidence that low BMC of the TBLH adjusted for age and gender (Z-score), and low bone area of the TBLH adjusted for age and gender (Z-score), are not associated with fractures at all sites combined. However, the following measures are associated with

fractures at all sites combined: low BMC of TBLH adjusted for height and gender (Z-score); low BMC of TBLH adjusted for age, height, weight, and bone area; and low bone area of TBLH adjusted for age, height, and weight (Z-score).

BMAD and Fractures

DXA provides two-dimensional, 'areal' BMD results, but several techniques have been proposed to estimate three-dimensional or 'volumetric' BMD using the bone area and BMC results from the DXA scans (22–25). The idea of using estimates of volumetric BMD (termed BMAD in this article) is thus to assess whether bone mass is adequate for bone volume. This may help to decide whether a low bone mass reading is due to small bone size or low three-dimensional bone density.

Using data from a cross-sectional study on more than 300 children with upper limb fractures, Jones et al. analyzed the area under the ROC curve (18). The area under the curve was similarly low for areal BMD (range 0.55 to 0.56), or BMAD (range 0.53 to 0.59) at total body, hip and spine. In a prospective study on prepubertal girls, Ferrari et al. showed that areal BMD and BMAD at the radial diaphysis did not predict fractures in the 8.5 yr following the DXA analysis (12). In the prospective study by Clark et al., a significant association was found between fracture risk at all sites combined and both areal BMD and BMAD at the humerus. After adjustment for height and log-transformed weight, a higher OR was found for areal BMD (1.40, 95% CI: 1.21 to 1.62) than for BMAD (1.28, 95% CI: 1.14 to 1.45), although the overlapping confidence intervals suggest that the difference between ORs was not statistically significant. Thus, there is little evidence that BMAD measures are more closely associated with fractures than areal BMD.

Effect of Adjustment for Body Size

Surrogate parameters of bone strength such as bone mass should not be seen in isolation but have to be related to the loads that act on the skeleton. These loads vary from situation to situation and from bone to bone. However, in general it can be assumed that in the case of an accident such as a fall, a large body puts more loads on the bones per square centimeter (cm) cross-sectional area than a small body.

It therefore makes sense to relate surrogate measures of bone strength to measures of body size. Indeed, most studies that have examined the topic find that 'adjustment' for body size strengthens the relationship between DXA results and fractures. In the studies by Goulding and coworkers, the ORs for fractures were consistently (albeit non-significantly), higher when DXA measures were adjusted for age and weight, as compared to adjustment for age alone (10,13,14). In their prospective study, Clark et al. examined the effect of adjusting for body size in detail (11). Total body less head BMC in itself was not associated with fractures (odds ratio 1.07 [95% CI: 0.97 to 1.19]). Adjusting TBLH BMC for height increased the OR to 1.25 (95% CI: 1.06 to 1.48), and further adding weight to the model yielded an OR of 1.57 (95% CI: 1.26 to 1.96). The highest OR for fracture

risk was found when TBLH BMC was adjusted for height, weight, and bone area (1.89 [95% CI: 1.18 to 3.04]).

The Expert Panel concluded from these data that low BMC of the TBLH adjusted for height and gender (Z-score), is associated with fractures at all sites combined. Similarly, low BMC of the TBLH adjusted for age, height, weight, and bone area is associated with fractures at all sites combined.

Discussion

A fracture occurs whenever the force acting on a bone exceeds the load that the bone can withstand ('bone strength'). Bone densitometry provides surrogate measures of bone strength, but the forces acting on a bone in a given situation are unknown. Also, the load that a bone can withstand is dependent on the type of bone, direction, and type of the load (e.g., compression, tension, torsion) (26). Translated into the clinical context this means that the ability of a bone to resist fracture very much depends on the nature of the accident. Whether a given situation leads to a fracture thus depends on many factors, most of which are beyond the reach of bone densitometric analysis (26). Despite these inherent methodological limitations, the reviewed literature is suggestive of an association between a variety of DXA-based parameters and fractures in childhood and adolescence. However, the available evidence has a number of critical gaps.

In order to evaluate whether a method 'predicts' fractures, it is not sufficient to demonstrate a statistically significant difference between groups of subjects with and without fractures. Rather, it is necessary to indicate the time interval for which the forecast is made and to present data about the sensitivity and specificity of the prediction. None of the prospective pediatric studies available to date provides such information.

Associations between DXA results and fractures that have been found in children of one age group or gender may not apply to another age or gender group. For example, the most informative longitudinal study reviewed here was limited to children aged 9.9 yr (11). Whether findings from this study also apply to younger or older subjects is speculative at present. Similarly, the relations between DXA results and fractures described here may not apply to children with low bone mass due to chronic disease.

Most importantly, the clinical severity of the observed fractures was not considered in the reviewed studies. As indicated in the next section of this report, the Expert Panel endorsed a definition of osteoporosis in children and adolescents that is based on the concept of a 'clinically significant fracture history' (which is also defined in the next section). However, the large majority of fractures reported in the examined studies were isolated upper extremity fractures (mostly finger and distal forearm), or toe fractures. Distressing as such events may be to the affected individual, the goal of clinicians using DXA analyses is probably to identify patients who are at risk of more serious events. This is in accordance with the field of adult densitometry where DXA analyses are used to assess the risk of events such as hip fractures, which may have life threatening consequences. In the absence of any

evidence on the topic, the Expert Panel was unable to judge whether DXA measurements in children and adolescents identify individuals who are at risk for developing a clinically significant fracture history.

What are the Densitometric Criteria for the Diagnosis of Osteoporosis in a Child or Adolescent?

ISCD Official Positions

The diagnosis of osteoporosis in children and adolescents should NOT be made on the basis of densitometric criteria alone.

- The diagnosis of osteoporosis requires the presence of both a clinically significant fracture history and low bone mineral content or bone mineral density.
 - A clinically significant fracture history is one or more of the following:
 - Long bone fracture of the lower extremities
 - Vertebral compression fracture
 - Two or more long-bone fractures of the upper extremities
 - Low BMC or BMD is defined as a BMC or areal BMD Z-score that is less than or equal to -2.0, adjusted for age, gender, and body size, as appropriate.
- Grade: Fair-C-W-Necessary

Rationale

In the opinion of the Expert Panel, pediatricians should follow the lead of the adult bone field and reserve the term ‘osteoporosis’ for a condition that has significant morbidity. However, the fracture epidemiology of children and adolescents differs markedly from those in adults. Concepts that were developed for use in adults may therefore not be directly applicable to the pediatric age range. It is presently unknown whether densitometric parameters can identify apparently healthy children and adolescents who are at risk of developing significant morbidity as a consequence of low bone mass or density. For these reasons, the Expert Panel judged that the diagnosis of osteoporosis in children and adolescents requires the presence of both a clinically significant fracture history and low bone mass, or density.

Discussion

In 1993 an international consensus development conference defined osteoporosis as a ‘skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture’ (27). However, 1 yr later, a panel of 17 experts (WHO Study Group) recommended that osteoporosis in adults should be diagnosed on the basis of low bone densitometry readings alone, regardless of fracture history or microarchitectural deterioration (28). In their report, the study group defined osteoporosis as a value for areal BMD that is 2.5 SD or more below the young adult mean value (28).

This definition has come to be known as the ‘WHO criteria for osteoporosis’ and has been applied worldwide ever since.

The stated reason for selecting the somewhat arbitrary cut-off of 2.5 SD below the young adult mean was that “such a cutoff value identifies approximately 30% of postmenopausal women as having osteoporosis using measurements at the spine, hip or forearm. This is approximately equivalent to the lifetime risk of fracture at these sites” (28). Thus, osteoporosis was defined so that the number of postmenopausal women classified as having osteoporosis would correspond to the number of women who were expected to have osteoporotic fractures. In addition, the WHO Study Group aimed at establishing a densitometric definition of osteoporosis that would reflect the increasing incidence of osteoporotic fractures with age. Therefore, it was explicitly stated that “approaches that utilize age-matched reference ranges (e.g., the Z-score) are flawed, because the incidence of osteoporosis would not rise with age even though bone mass was decreasing with age, and the risk of fracture was increasing” (28).

The WHO criteria for osteoporosis were thus modeled to mirror the epidemiology of osteoporotic fractures in postmenopausal women. Can this approach be transferred to the pediatric age range? One might argue that the data by Clark et al. suggest that DXA-based fracture predictions are possible to the same extent in children as in adults, as long as suitable outcome measures are used (11). For example, it might be feasible to determine a level of body size-adjusted TBLH BMC below which fracture incidence is judged ‘abnormally high’. This level could then be declared to define the densitometric criteria for pediatric osteoporosis.

However, it should be noted that the WHO criteria for osteoporosis were not modeled to reflect the occurrence of any fracture, but more specifically fragility fractures at the hip, spine and forearm. It is unclear what type of fractures should be classified as ‘fragility fractures’ in children and adolescents. Also, it will be difficult to find a densitometric parameter that reflects the fracture epidemiology in children. For example, fracture incidence in British girls approximately doubles between the age of 4 and 11 yr, but subsequently decreases to levels below those observed in 4-yr olds (6). The fracture incidence in 4-yr-old boys is 20% higher than in girls of the same age, but 15-yr-old boys have three times more fractures than 15-yr-old girls (6). None of the known DXA-derived measures seems to mirror these age- and sex-dependent changes in fracture incidence.

Finally, the clinical significance of the fractures should probably be taken into account. The diagnostic criteria for osteoporosis in adults were established to capture individuals who have a high risk of developing problems that carry significant morbidity and even mortality. For example, a population-based study found that hip and vertebral fractures are associated with a 20% excess mortality over 5 yr (29). In fortunate contrast, the vast majority of fractures in children are treated without hospitalization or surgery, heal rapidly, and result in no residual deformity or deficit. It is noteworthy that in the 6213 children who were followed by Clark et al. for 2 yr, 45% of fractures affected forearms, 13% fingers,

13% toes, 6% elbow, 5% clavicle, 4% tibia/fibula and 3% humerus (11). Thus, a densitometric definition of osteoporosis based on the results by Clark et al. would mostly identify subjects with a high risk of forearm, finger and toe fractures.

In the opinion of the Expert Panel, the term ‘osteoporosis’ in children and adolescents should be reserved for a condition that has significant morbidity, as it does in the adult bone field. What constitutes ‘significant morbidity’ is certainly open to debate. Any fracture in children and adolescents is evidently painful and distressing, and can be the cause of much anxiety for patients and parents alike. However, the Expert Panel members felt that ‘significant morbidity’ includes the need for hospitalization and surgery, leads to chronic pain or residual functional deficits. Although precise data are lacking, it is clear that such complications are more likely after long-bone fractures of the lower extremities and vertebral compression fractures than after short-bone fractures. Repetitive fractures of upper extremity long bones might also carry a higher risk of significant morbidity than isolated fractures.

These considerations lead to the working definition of osteoporosis in childhood and adolescence provided above.

Additional Questions/Suggestions for Future Research

- What is the morbidity following fractures in children and adolescents?
- How often do fractures lead to hospitalization, surgery, chronic pain or residual functional deficits?
- Are DXA results predictive of further fractures in otherwise healthy children who have a clinically significant fracture history?

Summary

The ISCD Official Positions provided here define osteoporosis in the pediatric age range. The diagnosis of osteoporosis is based on both clinical information (fracture history), and densitometric criteria. As more information becomes available, the criteria for the diagnosis of osteoporosis in children and adolescents may undergo modifications in the future.

References

1. Kanis JA, Johnell O, Oden A, et al. 2001 Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int* 12:989–995.
2. Johnell O, Kanis JA, Oden A, et al. 2005 Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 20: 1185–1194.
3. Szulc P, Munoz F, Duboeuf F, et al. 2005 Bone mineral density predicts osteoporotic fractures in elderly men: the MINOS study. *Osteoporos Int* 16:1184–1192.
4. Barrett-Connor E, Siris ES, Wehren LE, et al. 2005 Osteoporosis and fracture risk in women of different ethnic groups. *J Bone Miner Res* 20:185–194.
5. Landin LA. 1983 Fracture patterns in children. Analysis of 8,682 fractures with special reference to incidence, etiology and secular changes in a Swedish urban population 1950–1979. *Acta Orthop Scand Suppl* 202:1–109.
6. Cooper C, Dennison EM, Leufkens HG, et al. 2004 Epidemiology of childhood fractures in Britain: a study using the general practice research database. *J Bone Miner Res* 19: 1976–1981.
7. Dennison E, Mohamed MA, Cooper C. 2006 Epidemiology of osteoporosis. *Rheum Dis Clin North Am* 32:617–629.
8. Jones IE, Williams SM, Dow N, et al. 2002 How many children remain fracture-free during growth? A longitudinal study of children and adolescents participating in the dunedin multidisciplinary health and development study. *Osteoporos Int* 13: 990–995.
9. Lyons RA, Delahunty AM, Kraus D, et al. 1999 Children’s fractures: a population based study. *Inj Prev* 5:129–132.
10. Goulding A, Jones IE, Taylor RW, et al. 2000 More broken bones: a 4-year double cohort study of young girls with and without distal forearm fractures. *J Bone Miner Res* 15: 2011–2018.
11. Clark EM, Ness AR, Bishop NJ, et al. 2006 Association between bone mass and fractures in children: a prospective cohort study. *J Bone Miner Res* 21:1489–1495.
12. Ferrari SL, Chevalley T, Bonjour JP, et al. 2006 Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility? *J Bone Miner Res* 21:501–507.
13. Goulding A, Cannan R, Williams SM, et al. 1998 Bone mineral density in girls with forearm fractures. *J Bone Miner Res* 13: 143–148.
14. Goulding A, Jones IE, Taylor RW, et al. 2001 Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy X-ray absorptiometry study. *J Pediatr* 139: 509–515.
15. Jones IE, Taylor RW, Williams SM, et al. 2002 Four-year gain in bone mineral in girls with and without past forearm fractures: a DXA study. Dual-energy X-ray absorptiometry. *J Bone Miner Res* 17:1065–1072.
16. Ma DQ, Jones G. 2002 Clinical risk factors but not bone density are associated with prevalent fractures in prepubertal children. *J Paediatr Child Health* 38:497–500.
17. Goulding A, Grant AM, Williams SM. 2005 Bone and body composition of children and adolescents with repeated forearm fractures. *J Bone Miner Res* 20:2090–2096.
18. Jones G, Ma D, Cameron F. 2006 Bone density interpretation and relevance in Caucasian children aged 9–17 years of age: insights from a population-based fracture study. *J Clin Densitom* 9:202–209.
19. Manias K, McCabe D, Bishop N. 2006 Fractures and recurrent fractures in children: varying effects of environmental factors as well as bone size and mass. *Bone* 39:652–657.
20. Ma D, Jones G. 2003 The association between bone mineral density, metacarpal morphometry, and upper limb fractures in children: a population-based case-control study. *J Clin Endocrinol Metab* 88:1486–1491.
21. Taylor A, Konrad PT, Norman ME, et al. 1997 Total body bone mineral density in young children: influence of head bone mineral density. *J Bone Miner Res* 12:652–655.
22. Carter DR, Bouxsein ML, Marcus R. 1992 New approaches for interpreting projected bone densitometry data. *J Bone Miner Res* 7:137–145.
23. Kroger H, Kotaniemi A, Vainio P, et al. 1992 Bone densitometry of the spine and femur in children by dual-energy X-ray absorptiometry. *Bone Miner* 17:75–85.

24. Kroger H, Vainio P, Nieminen J, et al. 1995 Comparison of different models for interpreting bone mineral density measurements using DXA and MRI technology. *Bone* 17:157–159.
25. Leonard MB, Shults J, Zemel BS. 2006 DXA estimates of vertebral volumetric bone mineral density in children: potential advantages of paired posteroanterior and lateral scans. *J Clin Densitom* 9:265–273.
26. Currey JD. 2001 Bone strength: what are we trying to measure? *Calcif Tissue Int* 68:205–210.
27. Anonymous. 1993 Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 94:646–650.
28. Kanis JA, Melton LJ 3rd, Christiansen C, et al. 1994 The diagnosis of osteoporosis. *J Bone Miner Res* 9:1137–1141.
29. Cooper C, Atkinson EJ, Jacobsen SJ, et al. 1993 Population-based study of survival after osteoporotic fractures. *Am J Epidemiol* 137:1001–1005.