Bone Mineral Density in Young Adult Survivors of Acute Lymphoblastic Leukemia

Thomas et al[1] demonstrated a direct relation between height and bone mineral density (BMD), expressed as *z*-scores, in 74 young adult survivors of childhood acute lymphoblastic leukemia (ALL). Height *z*-score was the only significant predictor of low BMD in their cohort in which the authors conclude they have an increased prevalence of low bone mass.

Unfortunately, the authors have failed to appreciate the technical limitations of dual-energy X-Ray absorptiometry (DXA). Pediatric bone specialists have long been aware of the direct relation between height *z*-scores and BMD *z*-scores in healthy children and adults.[2] This relationship is purely technical, caused by DXA not measuring true density (bone mass/volume), but areal BMD (bone mass/projection area). The International Society of Clinical Densitometry, therefore, states that the DXA results in children need size correcting.[3] This DXA size relationship will, of course, also apply to adults as well as children. The main observation by Thomas et al[1] that lower BMD was associated with shorter stature, therefore, is a technical necessity. In addition, the observed gender difference in BMD can be easily explained because the men (height z = −1.06) were relatively shorter than the women (height z = −0.35). Given that 36% of subjects were short-normal (height *z*-score <−1), the fact that their non-size corrected BMD *z*-scores were above average is actually remarkable. Only 24% of subjects had BMD *z*-scores <−1, compared with the 15.9% expected for healthy individuals (as per normal Gaussian distribution). We predict that with appropriate size correction, BMD of the subjects will be normal, and relations with height and gender will disappear.

Undoubtedly, ALL causes bone disease, typically within 2 years from diagnosis, comprising bone pain, vertebral fractures, and avascular necrosis.[4] However, there is poor evidence of fractures as a "late" effect of ALL, except in the case of pituitary or gonadal damage. It would be helpful if Thomas et al could provide details on fracture prevalence of their subjects, compared with controls.

In summary, what the study by Thomas et al[1] has shown is that survivors of childhood ALL are shorter than average, which may be a late effect of previous treatment. What the study has not shown is a long-term deficit in bone mass or strength.

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Reply to Bone Mineral Density in Young Adult Survivors of Acute Lymphoblastic Leukemia

We appreciate Drs. Hogler and Shaw reiterating an issue that we clearly discussed in our article[1] as a study limitation, ie, that dual-energy X-Ray absorptiometry

(DXA) measurements do not take into account volumetric density and may not be reliable in individuals who are very short. In the International Society for Clinical Densitometry 2007 Adult and Pediatric Official Positions published in *Bone* in December 2008,[2] it was recommended that areal bone mineral density (BMD) should be used for correction in pediatric subjects who have not completed puberty or linear growth. However, all the subject in our study were adults, with an average age of 30 years, and only 4 of the 18 subjects with low BMD were below the 2.25 standard deviation (SD) of age-specific, race-specific and sex-specific normative means for height. We, therefore, chose not to statistically adjust their *z*-scores, given that there is no clearly validated adult standard for doing so.

Unfortunately, we do not have data to compare fracture occurrence in our study subjects, and fracture risk is difficult to determine solely from DXA bone mineral density estimates because there are no measures of bone quality beyond bone mass.[3] We agree that focused research is needed on risk of fracture in long-term survivors of pediatric cancer. We believe that our study results suggest, but by no means prove, that adult survivors of childhood acute lymphoblastic leukemia, particularly males, are at elevated risk for early onset osteopenia and that prudent medical surveillance is justified.

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