ORIGINAL ARTICLE

Gender differences in the ratio between humerus width and length are established prior to puberty

E. M. Clark · A. R. Ness · J. H. Tobias

Abstract

Summary On a sample of 1,317 children aged 9.9 years we developed a novel method of measuring humeral dimensions from total body dual-energy X-ray absorptiometry (DXA) scans and showed that gender differences in the ratio between humeral width and length are established prior to puberty.

Introduction It is recognised that long bone cross-sectional area is greater in males compared to females, which is thought to reflect more rapid periosteal bone growth in boys. However, it is currently unclear whether these findings reflect gender differences in bone size or shape. In the present study, we investigated whether gender differences exist in the balance between longitudinal and periosteal long bone growth in children, leading to gender differences in bone shape, based on a novel method for evaluating shape of the humerus. We also examined whether these differences are established prior to puberty.

Methods Length, area and width of the humerus were estimated from total body DXA scans in 1,317 children aged 9.9 ± 0.33 years, who had participated in a nested case-control study of fractures within the Avon Longitudinal Study of Parents and Children (ALSPAC) (a geographically based birth cohort based in South West England). No differences were observed with respect to parameters of humeral geometry according to fracture history, and so both groups were pooled for further analysis. Aspect ratio (AR) of the humerus was calculated as humeral width divided by length. Total body height and weight were measured at the same time as the DXA scan. Puberty was assessed using self-completion questionnaires.

Results Humeral width and length were positively associated with age and height in boys and girls combined ($P<0.001$), and with Tanner stage in girls ($P<0.002$). In contrast, age, height and Tanner stage were not related to humeral AR. We then examined gender differences in humeral shape according to pubertal stage. In prepubertal children (i.e. Tanner stage 1), humeral length was similar in boys and girls, but width (1.92 vs 1.88 cm, $P<0.001$) and area (47.7 vs 46.9 cm^2, $P<0.001$) were greater in boys, resulting in a greater AR (7.78 vs 7.53, $P<0.001$). Similar gender differences were observed in early pubertal children (i.e. Tanner stage 2).

Conclusion We conclude that the greater periosteal diameter of boys compared to girls reflects differences in the balance between longitudinal and periosteal bone growth. Interestingly, resulting gender differences in humeral AR are established in prepubertal children.

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Introduction

Traditionally, the increased risk of osteoporotic fracture in women compared to men has been attributed to their low bone mass as a consequence of reduced peak bone mass acquisition and increased rates of bone loss following the menopause. However, more recent studies indicate that several other factors influence fracture risk independently of bone mass, such as skeletal geometry and the material properties of bone [1]. Furthermore there are gender differences in skeletal geometry that may contribute to the greater fracture risk in women compared to men. For example, long bone cross-sectional area is greater in men, which is thought to reflect higher rates of periosteal apposition from the time of puberty onwards [2]. One study of 68 girls and 59 boys aged 11.9 years, who underwent prospective peripheral quantitative computed tomography (pQCT) measurements, reported that periosteal growth was more rapid in pubertal boys compared to girls [3].

Skeletal growth is coordinated to ensure that the ratio between different skeletal dimensions is maintained despite rapid changes in size [4]. Therefore, it is possible that the greater cross-sectional area in boys compared to girls is a reflection of their larger size. On the other hand, the ratio between periosteal growth and longitudinal bone growth may be different in boys compared to girls, leading to gender differences in bone shape. However, little is known of the inter-relationships between longitudinal and periosteal bone growth, since investigation of possible gender differences in skeletal geometry have generally been confined to analysis of cross-sectional area; in the absence of techniques capable of simultaneous measurement of long bone length, it has been difficult to accurately assess how the ratio between longitudinal and periosteal growth is affected by gender and other factors such as puberty.

Recently, we developed a novel method for evaluating long bone geometry based on analysis of the humerus on total body dual-energy X-ray absorptiometry (DXA) scans. The humerus offers important advantages over other long bones in that its entire outline can readily be traced on total body DXA images, and its shape can be modelled as a cylinder with reasonable accuracy. To explore the utility of regional DXA analysis at the humerus, 'volumetric' bone density of the humerus was derived by dividing humeral bone mineral content (BMC) by estimated humeral cylindrical volume, and then analysed in relation to fracture risk. Interestingly, humeral volumetric bone density obtained in this way was indeed related to fracture risk, as analysed in a subgroup of 1,317 children from the Avon Longitudinal Study of Parents and Children (ALSPAC), in whom total body DXA scans were available at 9.9 years of age [5].

In the present study, we aimed to characterise the influence of gender and puberty on the ratio between longitudinal and periosteal growth, by exploiting this novel technique of humeral geometric analysis. In particular, we wished to determine whether, in analyses combining fracture and non-fracture controls from the study described above, gender differences exist in the ratio between width and length of the humerus, and if so whether these differences are established prior to puberty.

Methods

Study population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a geographically based cohort that recruited pregnant women residing in Avon with an expected date of delivery between 1 April 1991 and 31 December 1992. A total of 14,541 pregnancies were initially enrolled, with 14,062 children born. This represented 80–90% of the eligible population–see http://www.alspac.bris.ac.uk for further details [6]. Of these births, 13,988 were alive at 12 months. The population from ALSPAC used for this study consisted of 1,290 children: those who had DXA scans performed at aged 9.9 years, had measures of humeral dimensions performed and had data on pubertal stage available. Ethical approval was obtained from the ALSPAC Law & Ethics Committee, and Local Research Ethics Committees.

Measure of size at birth

In the immediate post-partum stage, whilst mother and child were still in hospital, trained ALSPAC staff measured crown-heel length with the Harpenden Neonatometer (Holtain Ltd., Crosswell, UK). Alternatively, this measure was collected from clinical records for babies who were not captured by the ALSPAC staff.

Measures of size at age 9.8 years

Children were seen in a research clinic at age 9.8 years (±0.33 years). Parental consent and child's assent were obtained for all measurements made. Height was measured to the last complete millimeter (mm) using the Harpenden Stadiometer. Weight was measured to the nearest 50 grams (g) using the Tanita Body Fat Analyzer (model TBF 305, HealthCheck Systems, New York, USA). Total body less head (TBLH) bone area (cm^2), TBLH bone mineral content (g), TBLH bone mineral density (g/cm^2), total body (TB) fat mass (kg) and TB lean mass (kg) were measured using a Lunar Prodigy dual-energy X-ray absorptiometer (Lunar Corp., Madison, WI, USA) on 7,444 children, using the default mode for all scans. The child was positioned

carefully on the scanner and asked to lay their hands flat on the bed, palms down.

Measures of humeral dimensions

The present investigation was based on a subgroup of 393 children reporting fractures, for whom DXA scans were available at age 9.8 years, and an additional randomly selected group of 897 children, giving a total of 1,290 children. These children had originally been chosen for a study investigating the relationships between bone mass and fractures [5]. The measurer (EC) was blinded to the fracture status of the children. Customised settings were available on the Lunar Prodigy software and these were applied to the total body DXA image on screen. (No measures were performed during the DXA scan.) A region of interest (ROI) was drawn around the right humerus where possible (in case of movement artifact, the left humerus was used) after enlargement of the image to maximum magnification. The bone edge was detected visually with ease for the shaft and head of the humerus. At the distal end a straight line was drawn across the joint space from medial to lateral epicondyle, with the head of the ulna included within the humeral ROI. Where arm positioning was not ideal (such as palms not flat on the bed) the ROI was fitted as accurately as possible. The area (cm^2) of the humeral ROI was recorded (Fig. 1). Length of the humerus was obtained by use of an electronic ruler positioned between its upper and lower extremities. Average humeral width (cm) was calculated as area divided by length. The humeral aspect ratio (AR) was calculated as humerus width divided by length and then multiplied by 100, so the AR is the humerus width expressed as a percentage of humerus length.

The precision of measurements of humeral geometry was calculated as the coefficient of variation (CV), based on ten scans with the measures repeated five times. The CV was 2.9% [95% confidence interval (CI): 2.1–3.7] for width, 1.5% (95% CI: 1.2–1.7) for length, and 3.2% (95% CI: 2.4–4.0) for humeral AR.

Other measures

The mother's, partner's and grandparent's race and ethnic group and mothers' highest educational qualification were recorded at 32 weeks gestation as described elsewhere [7]. Gender was obtained from birth notifications. At the time of the DXA scan and measurement of the anthropometric variables, the child's age was calculated from the date of birth and date of attendance at the research clinic. Puberty was assessed by self-completion questionnaires using diagrams based on Tanner staging of pubic hair distribution for boys and girls, which we have previously found to show
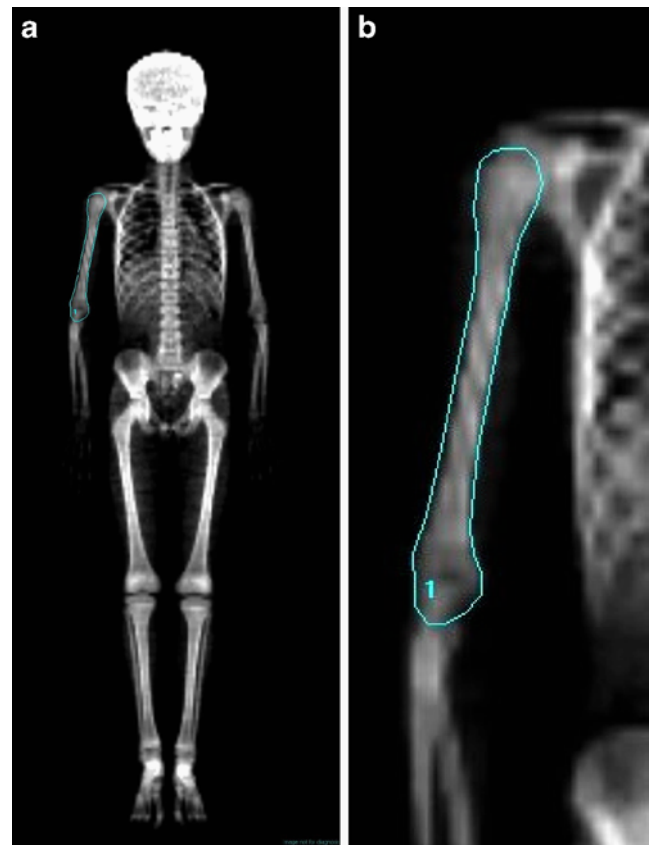

Fig. 1 Total body DXA scan showing position of the region of interest (ROI) around the right humerus. **a** Total body scan image. **b** Image following maximal (i.e. fourfold) magnification, which was selected prior to placement of the ROI and measurement of length by electronic ruler

expected relationships with DXA measures in this cohort [8]. Prepuberty was defined as Tanner stage 1, and early puberty as Tanner stage 2.

Statistical analyses

Results from children reporting previous fractures and the randomly selected subgroup were pooled. Statistical analyses were performed with STATA 8.0. A two-tailed unpaired t-test was used to test the null hypothesis of no difference in the means for boys and girls. Linear regression was used to assess the associations between gender and humerus dimensions, which were adjusted for age on the day of the DXA scan and pubertal status. Additional analyses were performed following adjustment for TB fat mass and for fracture status.

Results

No differences in gender, ethnicity, socio-economic status, body composition or humerus dimensions were found between the children with and without fractures (results

not shown) so these results were pooled for all further analyses. Length at birth, age at DXA measurement, height, weight, TB fat and lean mass and TBLH bone area of the 1,290 children in whom humeral dimensions were measured are shown in Table 1 according to gender and pubertal stage. There was no difference in age, height or weight between prepubertal boys and girls. However, boys had been longer at birth (by 0.3 cm on average), even after adjustment for gestational age and birth weight ($P<0.001$). Prepubertal girls had a greater TB fat mass ($P<0.001$), whereas prepubertal boys had a greater TB lean mass ($P<0.001$). Puberty-related differences in size measures were also seen. For example, girls in early puberty (Tanner stage 2) were on average 4.4 cm taller and 5 kg heavier than prepubertal girls (Tanner stage 1). Boys' pubertal stage showed similar trends to those observed in girls, but differences in size measures were considerably smaller.

We then examined relationships between dimensions of the humerus, age, height and puberty. As expected, height was positively related to humerus, width and length based on analyses in boys and girls combined ($P<0.001$). In spite of the relatively narrow age range of our study population, a positive association was also observed between age and width and length of the humerus ($P<0.001$). In contrast, age and height were not related to humeral AR. Similar results were seen when boys and girls were analysed separately. Girls in early puberty had greater humeral width, length and area compared to prepubertal girls, but humeral AR in these two groups was similar (Table 2). In contrast,

no differences were observed in any measure of humeral geometry between pre- and early pubertal boys.

We then investigated the effects of gender on measures of humeral geometry according to pubertal stage, following adjustment for age of DXA scan. The humerus of prepubertal boys was slightly shorter (on average 0.2 cm), but of greater width (average of 0.04 cm) and area (on average 0.8 cm^2), compared to prepubertal girls, as a result of which humeral AR was greater in prepubertal boys (an average of 3.2% greater, $P<0.001$) (Table 2 and Fig. 2). Boys in early puberty still had a shorter humeral length, but a similar humeral width and a smaller area than girls in early puberty, as a result of which humeral AR remained greater in early pubertal boys (an average of 3.7% greater, see Fig. 2). Similar gender differences were seen after adjustment for TB fat mass and fracture status (results not shown).

Discussion

Humeral width and length were positively related to age and height in boys and girls combined, and to pubertal status in girls, in this contemporary cohort of pre- and early pubertal children. These observations are similar to those previously reported for other DXA-derived measures of bone size in this cohort, such as TBLH and spinal bone area [7]. In contrast, age, height and pubertal status did not influence the ratio between humeral width and length, as reflected by humeral AR, presumably reflecting the action

Table 1 Mean age, height, weight, and DXA-derived total body fat mass and lean mass, and total body less head bone area for 648 boys and 642 girls with measurements of humeral size and dimensions[a]

	Boys					Girls						
	Prepubertal, N=551		Early pubertal, N=97		P value for difference between boys in pre- and early puberty	Prepubertal, N=548		Early puberty, N=94		P value for difference between girls in pre- and early puberty	P value for difference between prepubertal boys and girls	P value for difference between boys and girls in early puberty
	Mean	SD	Mean	SD		Mean	SD	Mean	SD			
Birth length (cm)[b]	50.9	1.5	50.9	1.5	0.995	50.6	1.5	50.7	1.5	0.658	<0.001	0.316
Age at DXA (years)	9.8	0.3	9.9	0.3	0.615	9.8	0.3	9.8	0.3	0.946	0.631	0.602
Height (cm)	139.4	6.1	140.7	6.1	0.041	138.7	6.0	143.1	6.0	<0.001	0.081	0.011
Weight (kg)	34.1	7.1	34.9	7.1	0.303	34.2	7.3	39.2	7.3	<0.001	0.795	<0.001
TB fat mass (kg)	7.3	4.9	7.7	4.9	0.471	9.3	4.9	12.1	5.0	<0.001	<0.001	<0.001
TB lean mass (kg)	25.3	3.0	25.6	3.0	0.314	23.3	2.8	25.2	2.8	<0.001	<0.001	0.332
TBLH bone area (cm^2)	1,141	154	1,161	155	0.261	1,113	157	1,217	158	<0.001	0.002	0.002

[a] Results are shown separately for boys and girls, who are further subdivided according to results of Tanner stage self-completion questionnaire. P values shown are for the difference between prepubertal boys (Tanner stage 1) and boys in early puberty (Tanner stage 2); for the difference between prepubertal girls (Tanner stage 1) and girls in early puberty (Tanner stage 2); for the difference between prepubertal boys and girls; and for the difference between boys and girls in early puberty, all calculated by an unpaired Student's t-test. For TB fat mass, TB lean mass and TBLH bone area results are adjusted for age at DXA measurement, by linear regression.
[b] Birth length adjusted for gestational age and birth weight by linear regression.

Table 2 Humeral dimensions in prepubertal boys, boys in early puberty, prepubertal girls and girls in early puberty[a]

	Boys					Girls						
	Prepubertal, $N=551$		Early pubertal, $N=97$		P value for difference between boys in pre- and early puberty	Prepubertal, $N=548$		Early puberty, $N=94$		P value for difference between girls in pre- and early puberty	P value for difference between prepubertal boys and girls	P value for difference between boys and girls in early puberty
	Mean	SD	Mean	SD		Mean	SD	Mean	SD			
Length (cm)	24.7	1.4	25.0	1.4	0.159	24.9	1.4	25.9	1.5	<0.001	0.026	<0.001
Width (cm)	1.92	0.2	1.93	0.2	0.609	1.88	0.2	1.93	0.2	0.002	<0.001	0.985
AR (%)	7.78	0.7	7.76	0.7	0.699	7.53	0.6	7.47	0.6	0.390	<0.001	0.006
Area (cm²)	47.7	6.0	48.4	6.1	0.297	46.9	65.9	50.2	65.9	<0.001	0.023	0.052

[a] Results show mean and standard deviation for humeral length, width, aspect ratio (AR) and area. P values shown are for the difference between prepubertal boys (Tanner stage 1) and boys in early puberty (Tanner stage 2); for the difference between prepubertal girls (Tanner stage 1) and girls in early puberty (Tanner stage 2); for the difference between prepubertal boys and girls; and for the difference between boys and girls in early puberty, all calculated by an unpaired Student's t-test. All analyses are adjusted for age at DXA measurement by linear regression.

Fig. 2 Associations between humeral geometry, gender and puberty, as determined in 1,290 boys and girls. Figure shows mean±SD **a** humerus width (cm), **b** humerus length (cm) and **c** humerus aspect ratio (AR) according to gender and Tanner stage of puberty. P values are for the difference between boys and girls. All analyses are adjusted for age
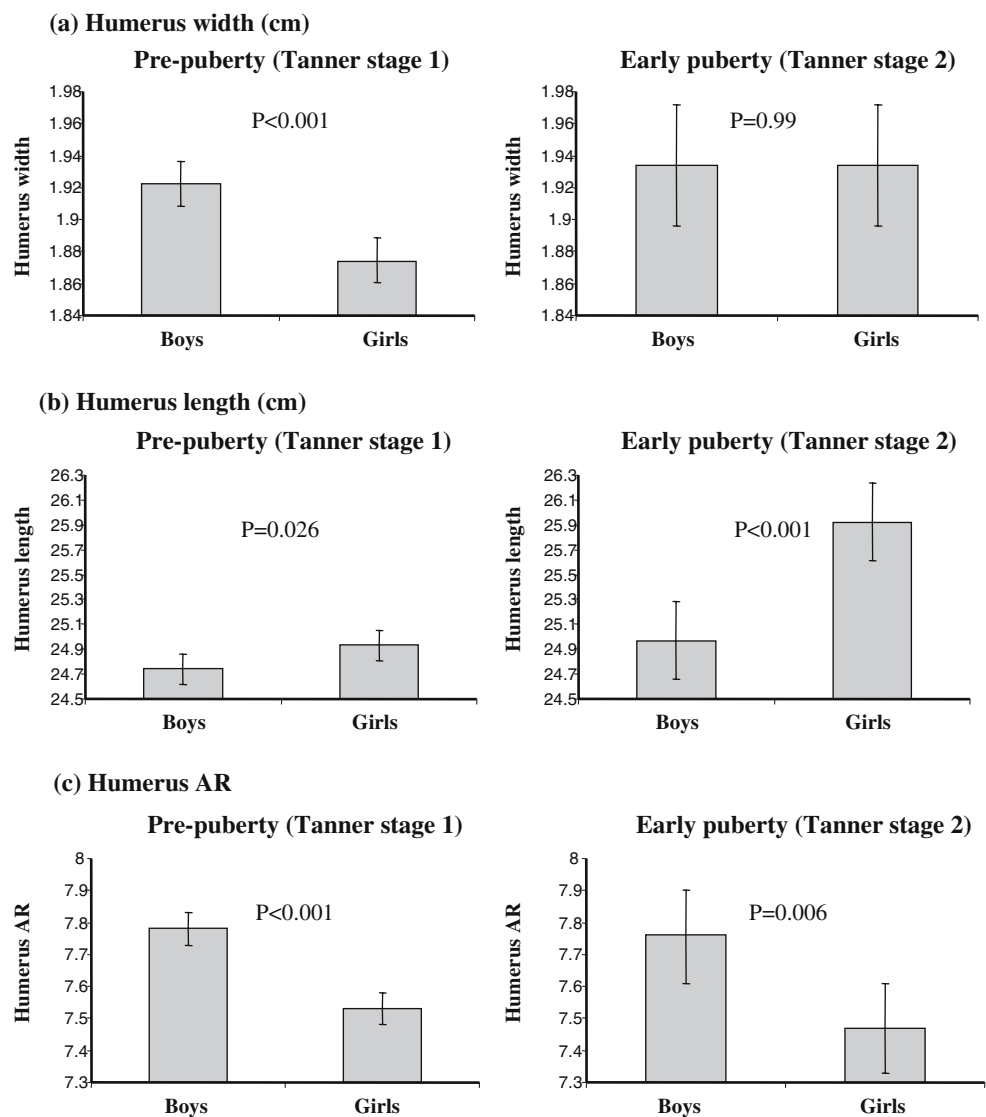
of mechanisms to ensure that skeletal shape remains constant as bones grow. In both pre- and early pubertal boys, humeral length was found to be shorter compared with girls, whereas humeral width was similar or greater, resulting in a greater humeral AR in boys. Taken together, these findings suggest that gender, but not puberty, affects the balance between periosteal and longitudinal growth. Hence, differences in overall skeletal shape between boys and girls appear to be established prior to puberty. However, from the present study we are unable to determine whether the AR changes during later pubertal stages, or during subsequent ageing.

Our observation that Tanner stage was found to affect humeral geometry in girls but not boys presumably reflects the fact that boys and girls in Tanner stage 2 are not equivalent in terms of skeletal development. The finding that height and weight differences between Tanner stages 1 and 2 were considerably greater in girls compared to boys is consistent with this view. Therefore, analyses of differences in humeral geometry between Tanner stage 2 boys and girls may have limited validity, since these may not have fully accounted for gender differences in skeletal maturity that are likely to have been present. Nevertheless, since humeral AR was unaffected by Tanner stage in the age of children studied, these reservations are unlikely to affect the main conclusion from this study, namely that humeral AR is greater in boys compared to girls as assessed at age 9.9 years.

The gender differences in skeletal shape shown in Table 2 (approximately 2–3%) were smaller than those observed in fat mass, lean mass and bone area as in Table 1 (ranging from 7 to 27%). The larger gender differences in TBLH bone area (6.5%) compared with humeral area (2.7%) suggest that greater gender differences in bone area are present at other skeletal sites. Consistent with this conclusion, vertebral body size has been reported to be 11% [8] and 15% [9] larger in boys compared to girls. Our observation of an 8% gender difference in lean mass and 27% difference in fat mass, compared to the 1% gender difference in humeral length and 2% difference in width, perhaps reflects the strength of association between fat or lean mass and bone area [10].

Our conclusion that gender differences in humeral shape are established prior to puberty is supported by a previous study in which greater humeral width was seen in prepubertal boys compared to girls, based on radiogrammetry [11]. In the present study, the humerus was selected as the most suitable site for providing an accurate measure of aspect ratio by analysis of total body DXA scans. Although other skeletal sites were not evaluated, we assume that equivalent gender differences in periosteal relative to longitudinal growth are established prior to puberty throughout the appendicular skeleton. Consistent with this

suggestion, the metacarpals and proximal radius have been found to be wider in boys compared to girls at all stages of development, as assessed by analysis of radiographs [12, 13]. Furthermore, in a recent study of 128 boys and girls, boys had higher rates of periosteal expansion relative to girls, as measured prospectively over 20 months at the radial midshaft by pQCT, and this gender difference was similar in early, peri- and postpubertal children [3]. In a recent analysis of 18-year-old males and age-, height- and weight-matched females, long bone width was found to be greater at the hip and distal tibia as measured by DXA and pQCT, respectively, in boys compared to girls [14].

Although our results suggest that gender differences in long bone width are due to more rapid periosteal apposition relative to longitudinal growth in boys prior to puberty, the precise timing of this gender effect is currently unclear. Review of the literature shows no evidence of gender differences in forearm bone width at birth [15], but studies of preschool and older children show conflicting results: Specker et al. [16] report no gender differences in radius width in children aged 1–6 years (based on 89 children), whereas Tanner et al. [17] found that the humerus is wider in boys compared to girls from age 3 years until the time of pubertal growth acceleration in girls (based on 505 children aged 3–18 years). It is also possible that the method used to measure bone size influences whether gender differences are found. For example, studies described above that used radiographs or pQCT identified gender differences [3, 11–13, 17], whereas those that used single photon absorptiometry did not [15, 16].

Prepubertal gender differences in the relative rates of longitudinal and periosteal growth that we observed may be mediated by alterations in endocrine factors. For example, prepubertal girls have higher levels of insulin-like growth factor I, estradiol and testosterone concentrations compared to prepubertal boys [18], all of which are known to have effects on both longitudinal and periosteal bone growth. In terms of the potential influence of these differences on fracture risk, according to beam theory, columns with larger aspect ratios (i.e. ratio of width to length) have a reduced fracture risk than columns with smaller aspect ratios [19]. In addition, the ratio between periosteal diameter to long bone length provides an approximate estimate of critical buckling load, such that a lower aspect ratio results in a long bone which is more prone to failure by buckling [20]. Furthermore, in children, the majority of fractures occur at the distal forearm and can be divided into two main types: simple torus fractures and the 'greenstick' variety, both of which are associated with buckling or bulging on the side of the bone in compression [21].

Therefore, theoretically, measurement of the ratio between long bone width and length from total body DXA scans as described here may provide an in vivo method for evaluating biomechanical strength of the skeleton. However, against this

suggestion, boys have a higher fracture risk than girls in childhood [22], whereas girls have a smaller humeral AR. Furthermore, we found no relationship between humeral AR as measured in the present study and fracture risk [5]. One possible explanation for this lack of association is that our assumption that the humerus is cylindrical ignores gender differences in shape at the epiphysis or metaphysis which might contribute to fracture risk. On the other hand, humeral AR may predict fracture risk in certain adult populations, in view of evidence that bone width has previously been reported to be related to stress fractures in soldiers [23]. In light of our results, which suggest that humeral AR can be evaluated with relatively good precision, further studies are justified to determine whether this parameter represents a novel bone mineral density (BMD)-independent risk factor for upper limb fracture.

The measure of humeral length from which we derived humeral AR is likely to be relatively accurate, since the upper and lower ends of the humerus are generally clearly visible on total body DXA scans (see Fig. 1). Alternative measurement techniques, such as pQCT, offer advantages over the approach described here, by measuring bone diameter directly, but do not provide a measure of bone length. Another limitation of the present study is that unlike girls, age 9.9 years appeared to be too young to evaluate possible effects of early puberty on skeletal development in boys. In future studies, we plan to repeat these analyses in older boys to confirm that as in girls, puberty increases humeral width and length whilst having no effect on humeral AR.

In conclusion, we have found that long bone shape, as reflected by humeral AR which we derived using a novel technique from total body DXA scans, is unaffected by age, height and puberty, as evaluated in a child cohort of relatively narrow age range and range of Tanner stages. This finding suggests that the ratio between longitudinal and periosteal growth is controlled to ensure it remains constant during rapid growth. However, humeral AR was related to gender, suggesting that the greater periosteal diameter of boys compared to girls, which is well recognised, is a consequence of gender differences in the balance between longitudinal and periosteal bone growth. Interestingly, these gender differences in humeral AR were present in prepubertal children, possibly resulting from prepubertal differences in sex hormone levels. Further studies are justified to determine whether humeral AR is an important determinant of biomechanical strength and fracture risk, particularly in adult populations.

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