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Growth in bone strength, body size, and muscle size in a juvenile longitudinal sample

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Abstract

A longitudinal sample of 20 subjects, measured an average of 34 to 35 times each at approximately 6-month intervals from near birth through late adolescence, was used to investigate relationships between body size, muscle size, and bone structural development. The section modulus, an index of bone strength, was calculated from humeral and femoral diaphyseal breadth measurements obtained from serial radiographs. Muscle breadths of the forearm and thigh, also measured radiographically, were used to estimate muscle cross-sectional areas. Body size was assessed as the product of body weight and bone length (humeral or femoral). Stature was also investigated as a surrogate body size measure. Growth velocity in femoral strength was strongly correlated with growth velocity in body weight · femoral length ($r^2 = 0.65–0.80$), very poorly correlated with growth velocity in stature ($r^2 < 0.06$), and weakly but significantly correlated with growth velocity in thigh muscle size ($r^2 = 0.10–.25$). Growth velocity in humeral strength was moderately correlated with that for body weight · humeral length ($r^2 = 0.40–0.73$), very poorly correlated with that for stature ($r^2 < 0.05$), and showed a marked sex difference with forearm muscle area velocity, with males having a stronger correlation ($r^2 \approx 0.65$) and females a much weaker correlation ($r^2 \approx 0.15$). Ages at peak adolescent growth velocity were nonsignificantly different between bone strength, body weight · bone length, and muscle area, but significantly earlier for stature. Thus, while there was an early adolescent "lag" between stature and bone strength, there was no such "lag" between a more mechanically appropriate measure of body size and bone strength. "Infancy peaks" in bone strength velocities, earlier in the humerus than in the femur and not paralleled by similar changes in body size, may be the result of the initiation of walking, when mechanical loads relative to body size are changing in both the upper and lower limbs. These results argue strongly for the importance of mechanical factors in the development of the preadult skeleton. Body size is the most important element in the weight-bearing lower limb skeleton, while both body size and muscle strength are important in the upper limb, especially in males.

Keywords: Growth; Skeletal; Bone; Body; Muscle; Mechanical

Introduction

Bone growth and development is a product of a complex interaction between genetic and environmental factors, including diet, hormonal influences, and mechanical stimuli [1,2,3,4]. A better understanding of such relationships is important for several reasons, including identification of metabolic bone diseases [5] and fracture risk [6,7] in children and elucidation of mechanisms affecting the attainment of peak bone mass by young adulthood [4,8,9].

Several studies have indicated that body mass (or lean body mass) and muscle strength have important influences on long bone strength in children and adolescents [10,11,12,13,14–16]. These conclusions have been based on observed associations between bone structural properties and anthropometric parameters in cross-sectional samples. Longitudinal growth samples have the advantage of allowing comparisons between growth rates, and changes in growth rates, between different properties within the same individuals. Thus, cause-and-effect relationships, e.g., between a change in body size or muscle strength and a change in bone strength, can be more clearly discerned.

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Longitudinal samples also allow more accurate identification of growth spurts and growth timing [17,18]. In addition, comparisons across individuals within age groups can be made without potential cohort effects when the same individuals are followed across each age point.

Longitudinal studies of skeletal growth have been largely limited to relatively short-term observations over periods of 1 to 4 years [8,19,20,4,21,22] or to adolescence [17,23,24], although there are exceptions [25]. None of these studies included indices of bone strength per se, but rather measured age changes in bone size (bone mass, volume) and/or density. While such measures are correlated with bone strength, better estimates of bone strength can be obtained using engineering theory through calculation of second moments of area (moments of inertia) or section moduli [26,27,28,29]. Only a few growth studies have included these parameters [10,12,13,30,14,16], and they have all been cross-sectional in design and in most cases limited to adolescence or to relatively small samples (Ref. 30 is an exception to the latter). Furthermore, only one study has directly compared growth changes in bone strength in a weight-bearing (lower limb) and non-weight-bearing (upper limb) bone [31], and this study was of an archaeological sample, where body mass and most other anthropometric parameters (and sex prior to adolescence) are unknown.

This study presents the results of an analysis of longitudinal changes in femoral and humeral strength, muscle size, and body size in a sample of 20 individuals followed radiographically from near birth through late adolescence. Correlations between growth velocities for these different parameters as well as correlations across parameters within successive age groups were used to examine the relationships between bone strength and anthropometric variables across the entire pre-adult age span.

Materials and methods

Sample

The study sample was drawn from the database collected by the Denver Child Research Council between 1927 and 1967 [32], although all of the individuals in the present study were measured between 1941 and 1967. All individuals were stated to be of European ancestry, with most from northern Europe; most were of middle to upper middle class socioeconomic status and all lived in the Denver area [32]. Children were examined at 2 and 4 months, and at 6-month intervals from 6 months to mid adolescence (about 14–15 years) and thereafter at half-yearly or yearly intervals until late adolescence or early adulthood. Twenty individuals, 10 males and 10 females, with the most complete radiographic records (see below) were selected for inclusion in this study. A total of 690 examinations with usable data were included; thus, an average of 34.5 observations per individual (range, 29–38) were available. All individuals had measurements beginning before 1 year of age, with the mean age at last measurement 18.4 years (range, 16.5–21.5 years).

Radiographic measurements

A–P radiographs of upper and lower limbs at each examination were taken using a long (2.3-m) tube-film distance and with the limb held in contact with the film to minimize distortion [33]. Details of the technique utilized have been previously published [33,34]. Data included in the present study were corrected for radiographic magnification using information from Green and co-workers [35], adjusted for differences in technique, as described elsewhere [36]. Radiographs were checked for proper orientation by comparing the positions of landmarks, e.g., the medial and lateral humeral epipcondyles, on films. Any radiographs showing evidence of significant rotation from standardized planes were not included in the study.

Radiographs are housed and were measured at the Lifespan Health Research Center of Wright State University School of Medicine (Dayton, OH). Clear acetate templates of various sizes, marked with a longitudinal axis and a perpendicular axis, were placed over each femoral and humeral radiograph, aligned with the longitudinal axis of the diaphysis, and moved until the perpendicular axis was at the appropriate cross-sectional level of the bone. For the femur, the cross-sectional level is at midshaft, based on length measured from the average distal projection of the femoral condyles to the superior surface of the femoral neck at its intersection with the longitudinal diaphyseal axis [37]. For the humerus, the cross-sectional level is at 40% of bone length from the distal end, with length measured from the distal projection of the lateral lip of the trochlea (or the capitulum prior to formation of the trochlea) to the superior surface of the humeral head [38]. To obtain section locations in the youngest children (prior to 3 or 4 years of age) who had not yet formed sufficiently developed epiphyses for total length measurements, sections based on total length were first located in a series of radiographs of 3- to 6-year-olds, along with total diaphyseal length. In both the femur and humerus the resulting locations relative to diaphyseal length fell in a narrow range (±1%), with means of 45.5% of diaphyseal length in the femur and 41% of diaphyseal length in the humerus (both from the distal end of the diaphysis). These locations were then used in the youngest children. All lengths were taken parallel to the longitudinal axis of the diaphysis using a clear ruler to the nearest millimeter.

Medial and lateral cortical breadths, and total periosteal breadth (T), were measured perpendicular to the diaphysis at each location, using the template for alignment, with sharp pointed digital calipers to the nearest 0.01 mm. Medullary breadth (M) was derived as total breadth minus the summed cortical breadths. Assuming a cyclindrically shaped section, the polar moment of inertia (J) was calculated as $\pi/32 \cdot$

(T^4-M^4) [39]. The polar section modulus, a measure of torsional and (twice) average bending strength, was then derived as $J/(T/2)$. The polar section modulus, Z_p, is an appropriate parameter for assessing bone strength changes here, since bending and torsion are the predominant loadings in long bone diaphyses [40,41,42].

The midshaft and 40% locations in the femur and humerus were chosen for measurement in part because they are relatively circular in cross section. The assumption of circularity can be tested by comparison of section moduli measured in A–P and M–L planes in similarly aged individuals where three-dimensional data are available, with A–P/M–L ratios close to 1.0 indicating near circularity. Two archaeological samples of juvenile femora and humeri with such data, derived through CT scanning, have been reported [31,43] (and Sumner, pers. comm., Ruff, unpublished data). The ratios of A–P/M–L section moduli in neonates through 19 year olds [31] ($n = 63$) averaged 1.03 (SD ± 0.11) for the midshaft femur and 1.00 (±0.10) for the midshaft humerus and for 4 to 19 year olds [43] 0.95 (±0.13) for the midshaft femur ($n = 31$) and 0.98 (±0.20) for the 40% humeral location ($n = 30$). Thus, on average, the assumption of circularity here appears well justified. There is, however, individual variation in how well this assumption is met, as well as some systematic age changes in cross-sectional shape in the archaeological samples that are not reflected in these average numbers. It will be assumed here that any errors introduced by this factor are randomly distributed throughout the study sample at any particular age interval, i.e., that such errors will not affect comparisons between growth rates of different parameters or different individuals at the same age.

For use in body size analyses, maximum lengths of the femur and humerus, taken between the most proximal and distal projections of the bones (i.e., not necessarily parallel to the longitudinal axis of the diaphysis), were also measured from radiographs. To standardize comparisons between older and younger children that included this variable, maximum bone lengths were estimated from diaphyseal lengths, when necessary, using average ratios between the two calculated from children with both dimensions available. The average ratio of maximum to diaphyseal length in the femur was 1.10 (SD ± 0.01) and in the humerus 1.08 (±0.01).

Measurement error was assessed by remeasuring radiographs from two individuals at 10 ages from near birth through late adolescence, several weeks following their initial measurement. Mean absolute percent differences over these 20 duplicates are less than 0.5% for bone lengths, less than 1% for total periosteal breadth, and less than 5% for cortical breadths, except for the medial cortex of the humerus, where it is 7.5%. For the derived section modulus, this results in an average difference between measurements of 3.1% in both the femur and humerus.

Anthropometric data

All anthropometric data were obtained from the stored computer files for the Denver growth sample (Siervogel, pers. comm.). Body weight and stature (supine length to 1.5 or 2 years) had been measured at each examination to the nearest ounce (approximately 0.1 kg) and millimeter, respectively. Supine lengths in infants were converted to standing heights by calculating a regression from individuals under 5 years of age included in the present study sample who had both dimensions recorded at the same examination ($n = 76$ observations): standing height = 0.995 (supine length)−0.84 ($r = 0.997$; %SEE, 0.8%). This yields a correction (subtraction) of 1.1–1.25 cm over the range of supine lengths of infants here, consistent with other estimates [44,45].

Bending and torsional loads on long bones should be proportional to the product of body weight (mass) and a moment arm, which can be taken to be roughly proportional to bone length [6,46]. Thus, the most appropriate measure of body “size” for evaluating long bone strength should be body weight multiplied by that bone’s length, i.e., body weight · femoral length and body weight · humeral length. In addition, because stature is often used as a body “size” measure, especially during growth, the relationship between stature and bone strength was evaluated.

Fat, muscle, and total limb external breadths at the mid-femur level and at the maximum width of the forearm had been measured from radiographs by the original investigators [47,48]. For the mid-femur level, only the lateral muscle and fat shadows were measured. Bone (external) widths had also been taken at the same locations. Using these data, and again assuming cylindrical geometries, approximate muscle cross-sectional areas were derived for the thigh and forearm. No soft tissue measurements of the upper arm were available. However, correlations between muscle area measured at maximum forearm width and in the mid-upper arm are high in children ($r = 0.72–0.91$) [49]; thus, forearm muscle area is taken to be representative of muscular development in the upper limb.

Data analysis

Although the study sample was chosen on the basis of completeness of available records, some missing data, both anthropometric and radiographic, are inevitable in a long-term study of this kind. If radiographs for both the humerus and femur were missing or unmeasurable, data for that examination were not included in the analysis. If radiographs for one limb could be measured, then the examination was included, and the missing data were estimated through linear interpolation between adjacent ages. No data estimates were made through extrapolation, i.e., at either the beginning or the end of the longitudinal records. (This explains the slightly different sample sizes for femoral and humeral measurements in some of the analyses.) In addi-

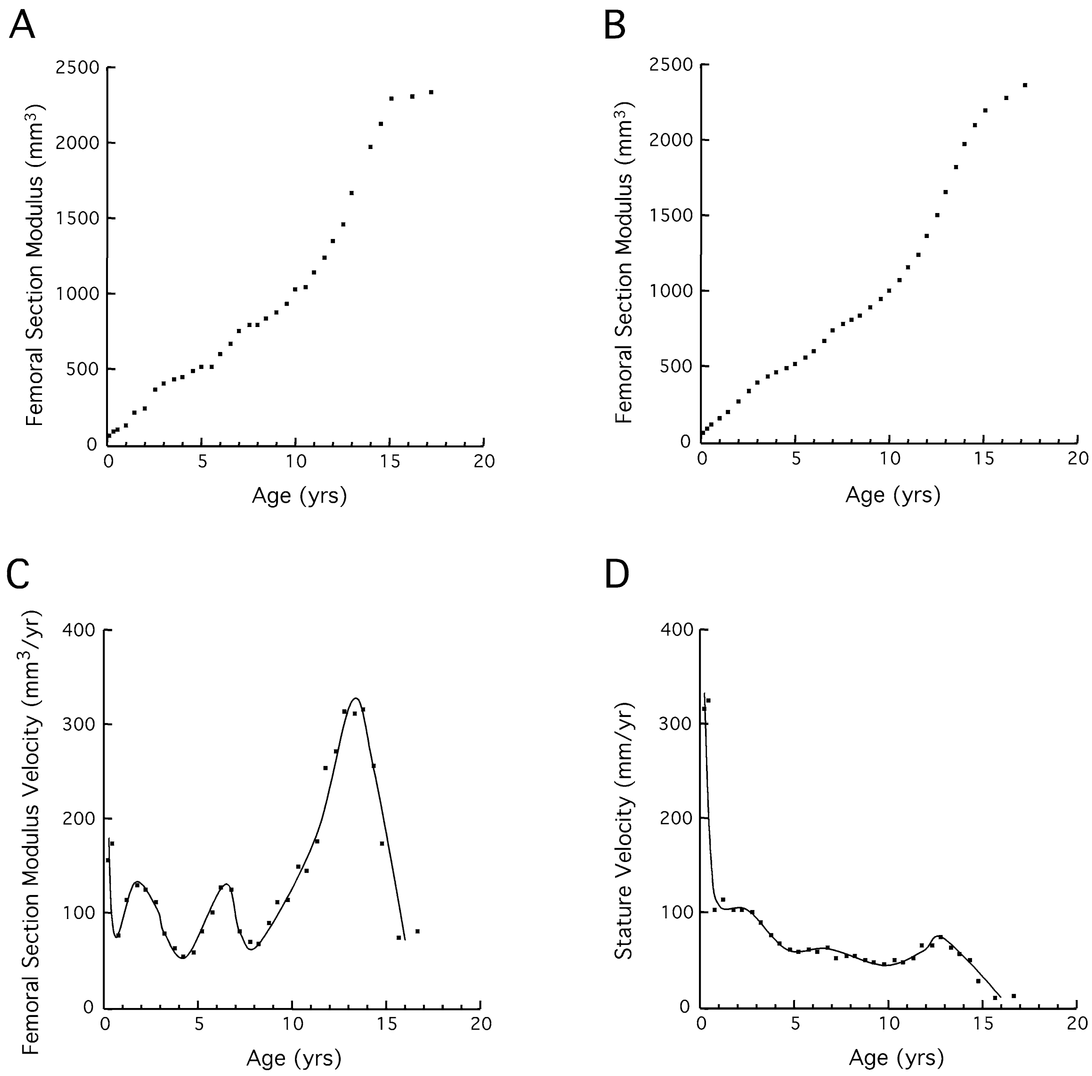

Fig. 1. (A) Raw data for femoral section modulus (Z_p) measured at 33 time points in one individual. (B) The same data as in (A), smoothed using LOWESS. (C) Growth velocities (mm^3/year) based on smoothed data in (B). Curve drawn manually for illustration purposes only—actual data points used in statistical analyses. (D) Growth velocities for stature (mm/year) in the same individual.

tion, a few missing anthropometric data were estimated in the same way. The total number of estimated data points ranged from 1% for thigh and forearm muscle areas to 10% for humeral length · body weight.

Although many studies have analyzed growth data relative to developmental markers, such as age at peak adolescent height velocity [23,25], sexual maturity stages [6,11,30,50,7,22], or bone developmental age [8], this was not done here, for several reasons. First, no data on sexual maturity and only very limited data on skeletal maturity were available for the study sample. As shown later, the age at peak adolescent height velocity is not well correlated with peak adolescent growth velocities of any of the other parameters examined and as such is not a particularly good developmental marker. Use of different, parameter-specific growth peaks to standardize ages would result in comparisons of growth rates for different dimensions over variable (absolute) time periods within individuals, which negates the possibility of assessing temporal cause-and-effect relationships. Also, the present study covers the entire growth period, including infants and preadolescent children, for whom age to adolescent growth peaks has little relevance. Therefore, absolute rather than relative developmental ages were used here.

Prior to growth velocity analyses, all data were smoothed relative to age using a robust locally weighted least squares technique, LOWESS [51], as implemented in SYSTAT [52]. The "tension value" (local moving window within which smoothing is carried out) was set at 0.20, or 20% of the total age range. This is a fairly narrow range—about 3–4 years—chosen so that minor fluctuations in growth velocities would still be preserved after smoothing. Fig. 1A

Table 1

Coefficients of determination between growth velocity in bone strengths (section moduli, Z_p) and growth velocity in predictor variables

Sample	Femoral Z_p			Humeral Z_p		
	Wt · length[a]	Stature	Muscle[b]	Wt · length[a]	Stature	Muscle[b]
r^2, Pooled data						
Combined sex ($n = 632$)	0.698	0	0.131	0.504	0.009	0.529
Males ($n = 312$)	0.733	0.010[c]	0.108	0.543	0.001[c]	0.626
Females ($n = 320$)	0.658	0.014	0.181	0.408	0.048	0.148
r^2, Mean of individuals and proportion of significant individual r^2's						
Combined sex	0.746 (20/20)	0.048 (2/20)	0.218 (12/20)	0.566 (19/20)	0.006 (4/20)	0.392 (16/20)
Males	0.791 (10/10)	0.057 (1/10)	0.245 (6/10)	0.731 (10/10)	0.001 (0/10)	0.684 (10/10)
Females	0.702 (10/10)	0.057 (1/10)	0.245 (6/10)	0.422 (9/10)	0.035 (4/10)	0.180 (6/10)

[a] Body weight · bone length (femoral or humeral).

[b] Muscle: estimated cross-sectional area of muscle at mid thigh (for femur) or maximum breadth of forearm (for humerus).

[c] Nonsignificant correlation ($P > 0.05$).

shows original, unsmoothed data for the femoral mid-shaft section modulus and Fig. 1B shows the same data smoothed using LOWESS (data are for a female subject).

Growth velocities were then calculated by dividing the difference between successive measurements by the time elapsed between examinations (to the nearest day). Fig. 1C shows the same data as in Fig. 1B converted to velocities. Age on the *x* axis is the midpoint age between examinations. The line shown in Fig. 1C and lines in all subsequent figures were fitted to the data by eye and are for illustration purposes only. The actual data point values were used in statistical analyses.

Fig. 1D shows growth velocities for stature in the same individual. A very high growth rate is evident in early infancy, followed by some minor fluctuations during childhood and an adolescent growth spurt. Growth velocities for the study parameters are often very high in early infancy, tending to swamp out variation in other periods. There is also more chance for introduction of artifacts through the smoothing process in terminal data points where data are changing rapidly. In addition, data collected during early infancy were among the most frequently missing (and often could not be estimated except through extrapolation). Therefore, growth velocity data prior to 6 months of age were not used in this study.

Several types of analyses of these data were carried out. First, correlations between growth velocities in bone strength and body weight · bone length, stature, and muscle area were calculated over the whole sample and within individuals. Multiple analysis of variance (ANOVA) was then used to partition the effects of body size and muscle area velocities on femoral and humeral strength velocities. Differences in timing of the peak adolescent growth spurt were compared between bone strength and other parameters. All of these analyses were carried out in both pooled sex and separate sex samples. Finally, ANOVA was used to partition the effects of body size, muscle, and sex on bone strengths, across individuals, in four different age groups: 0.5 years, 1.5 years, 7 years, and 17 years, corresponding to early infancy, late infancy, middle childhood, and late adolescence, respectively. Throughout, a 0.05 probability level was considered statistically significant. All analyses were carried out using SYSTAT [52].

Results

Table 1 lists coefficients of determination (r^2) between growth velocities in bone strength and other parameters. Average within-individual correlations are similar to pooled sample correlations, although usually somewhat higher. The number of individuals showing significant ($P < 0.05$) correlations for each comparison is also shown.

The strongest growth velocity correlations are between femoral strength and body weight · femoral length, with about 65–80% of the variation in bone strength accounted for by variation in body weight · bone length and with every individual showing a significant correlation. In contrast, correlations between femoral strength and stature velocities are extremely low, explaining less than 6% of the variance on average, and are nonsignificant in almost all individuals. Thigh muscle and femoral strength velocity correlations are moderately low, explaining about 10–25% of the variance; slightly over half of all individuals have significant correlations.

In the upper limb, body weight · bone length velocity shows a moderately high correlation with humeral strength velocity, with 54–73% of the variance explained in males and just over 40% explained in females. All but one individual shows a significant correlation. Correlations are significantly lower than those between femoral strength and body weight · femoral length ($P < 0.0001$, Fisher Z tests, combined and sex-specific comparisons in pooled data set). Stature velocity again shows a very weak association with bone strength velocity (r^2's less than 0.05, most individuals nonsignificant). Forearm muscle velocity shows a high correlation with humeral strength velocity in males, accounting for about 60–70% of the variance (all individuals significant), but a much lower correlation in females, accounting for only 15–18% of the variance (just over half of all

Table 2
ANOVA of growth velocities: prediction of femoral and humeral bone strength (section moduli, Z_p) velocities from body and muscle size velocities

	Femoral Z_p velocity				Humeral Z_p velocity			
	n	r^2	*F* ratio	*P*	*n*	r^2	*F* ratio	*P*
Model, combined sex	634	0.739			632	0.689		
Wt · length[a]			1229.43	$\ll 0.000001$			211.46	$\ll .000001$
Muscle[b]			12.18	< 0.001			151.47	$\ll .000001$
Individual[c]			4.76	$\ll .000001$			7.24	$\ll .000001$
Model, males	321	0.763			320	.742		
Wt · length[a]			790.85	$\ll .000001$			60.22	$\ll .000001$
Muscle[b]			11.31	$< .001$			105.63	$\ll .000001$
Individual[c]			3.13	$< .01$			10.85	$\ll .000001$
Model, females	313	0.721			312	.465		
Wt · length[a]			459.44	$\ll .000001$			157.87	$\ll .000001$
Muscle[b]			0.20	n.s.			16.15	$< .0001$
Individual[c]			8.37	$\ll .000001$			1.74	n.s.

[a] Body weight · bone length (femoral or humeral) velocity.

[b] Estimated cross-sectional area of muscle at mid thigh (for femur) or maximum breadth of forearm (for humerus) velocity.

[c] For 20 (combined sex) or 10 (separate sex) individuals, treated as a categorical variables.

individuals significant). This sex difference is highly significant ($P \ll 0.0001$, Fisher Z test, comparison between sexes). In males, muscle area velocity is a much stronger predictor of bone strength velocity in the upper limb than in the lower limb ($P \ll 0.0001$, Fisher Z test), while in females the two limbs are equivalent ($P > 0.30$, Fisher Z test).

These observations are further supported by multiple ANOVA (using procedure MGLH in SYSTAT), with bone strength velocities as dependent variables. The effects of body weight · bone length and muscle area are shown in Table 2, for combined sex and separate sex samples. In addition to body size and muscle variables, "individual" was entered as a categorical independent variable, to test for the effects of individual variation (i.e., differences between the 20 individuals in the sample). In most comparisons there is a significant effect of individual, although significance levels are lower than those for body size or muscle area in the male femur and the female humerus.

In the femur, growth velocity in body weight · bone length has a more significant effect on bone strength than does muscle area, in both pooled sex and sex-specific analyses. In the humerus, both body weight · bone length and muscle area have highly significant effects on bone strength in the pooled sex and male analyses, but muscle area has a less significant effect in females.

In Table 3 the effects of age and sex together with body and muscle size velocities are examined. Age is not a significant factor in either bone, while sex is a significant factor in both. The inclusion of age and sex has relatively little effect on relationships between body or muscle size and bone strength velocities (compare probability levels with those for combined sex in Table 2).

Patterns of growth velocities in one typical individual (a male) are illustrated graphically in Fig. 2. The close correspondence in timing and relative magnitude of femoral strength and body weight · femoral length velocities is clearly evident (Fig. 2A). In addition to the adolescent growth spurt, in this individual there is also a smaller growth spurt in both parameters in mid childhood. This second peak in femoral strength velocity between 4 and 9 years of age is characteristic of half of the individuals in the sample. The only noncorrespondence between curves is a small but distinct growth spurt in femoral strength in late

Table 3
ANOVA of growth velocities: prediction of femoral and humeral bone strength velocities (section moduli, Z_p) from body and muscle size velocities, age, and sex

	Femoral Z_p velocity				Humeral Z_p velocity			
	n	r^2	*F* ratio	*P*	*n*	r^2	*F* ratio	*P*
Model	634	0.710			632	.624		
Wt · length[a]			647.89	$\ll 0.000001$			113.57	$\ll .000001$
Muscle[b]			10.13	$< .01$			146.05	$\ll .000001$
Age			1.74	n.s.			.01	n.s.
Sex			17.31	$< .0001$			8.07	$< .01$

[a] Body weight · bone length (femoral or humeral) velocity.

[b] Estimated cross-sectional area of muscle at mid thigh (for femur) or maximum breadth of forearm (for humerus) velocity.

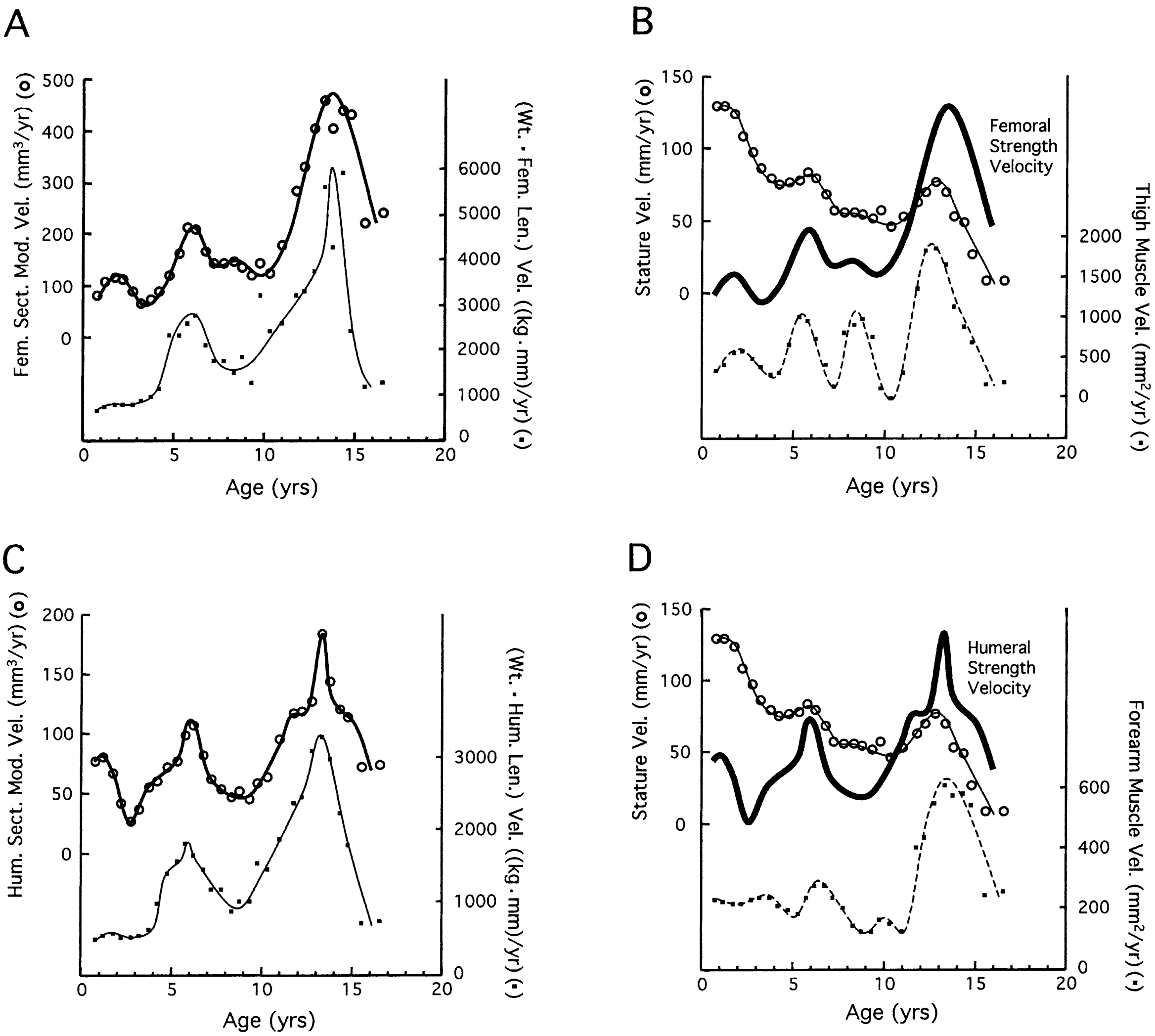

Fig. 2. Growth velocities in one individual: (A) femoral strength (section modulus, Z_p) and body weight · femoral length; (B) stature and thigh muscle area (femoral strength curve plotted for reference); (C) humeral strength (section modulus, Z_p) and body weight · humeral length; (D) stature and forearm muscle area area (humeral strength curve plotted for reference).

infancy (about 1–2 years of age) that has no definite counterpart in the body size measure. This "infancy peak" in femoral strength velocity is apparent in all but one individual in the sample (see Fig. 1C for another example), always occurring in this age range (mean age of peak, 1.4 years).

The pattern of growth velocity in thigh muscle area is also generally similar to that of femoral bone strength (Fig. 2B), although there is more variability in the muscle curve. In addition to adolescent and mid-childhood peaks, there is a small "infancy peak" in thigh muscle velocity, which was characteristic of about half the sample. Stature also shows evidence of adolescent and mid-childhood velocity peaks in this individual (Fig. 2B), but the overall correspondence between stature and femoral strength curves is weak.

Humeral strength and body weight · humeral length velocities correspond relatively closely (Fig. 2C), except for infancy–early childhood (6 months–3 years), where humeral strength shows a peak velocity around 1 year of age followed by a precipitous decline that is not mirrored in the body size parameter. A general pattern of high velocity in humeral strength prior to about 1.5 years, followed by a decline, is present in every individual in the sample. The mean age of the humeral strength "infancy peak" is 1.1 years, significantly earlier than the corresponding femoral strength peak ($P < 0.001$, paired *t* tests). A mid-childhood peak in humeral strength velocity is present in most (17/20) of the individuals in the sample, although in some cases it appears to be more of a "rebound" from very low values in early childhood.

Forearm muscle area velocity shows a good general correspondence to humeral strength velocity (Fig. 2D), although without any marked peak or decline in infancy in this individual. Most individuals in the sample (about three quarters) did have a peak and decline here in muscle area velocity. Despite some correspondence in adolescent and mid-childhood peaks, stature and humeral strength velocities again show relatively poor association.

Table 4
Ages of adolescent peak growth velocities

Sample	Z_p[a]	Stature	Stature − Z_p	Wt · length[b]	Wt · length − Z_p	Muscle[c]	Muscle − Z_p
Femur							
Total $(n = 20)$	13.64 ± .40[d]	12.80 ± .31	−0.84 ± .28**	13.78 ± .38	.14 ± .21	13.26 ± .45	−.38 ± .44
Males $(n = 10)$	15.02 ± .35	13.75 ± .31	−1.27 ± .50*	15.00 ± .25	−.02 ± .30	14.18 ± .66	−.85 ± .80
Females $(n = 10)$	12.25 ± .33	11.85 ± .33	−0.40 ± .16*	12.55 ± .47	.30 ± .28	12.35 ± .49	.10 ± .38
Humerus							
Total $(n = 20)$	14.20 ± .37		−1.40 ± .23***	13.99 ± .37	−.21 ± .28	14.21 ± .41	.01 ± .24
Males $(n = 10)$	15.32 ± .39		−1.57 ± .36**	14.98 ± .39	−.35 ± .48	12.88 ± .23	.30 ± .27
Females $(n = 10)$	13.08 ± .40		−1.23 ± .30**	13.00 ± .46	−.08 ± .32	15.62 ± .45	−.28 ± .39

[a] Bone section modulus.

[b] Body weight · bone length (femoral or humeral).

[c] Estimated cross-sectional area of muscle at mid thigh (for femur) or maximum breadth of forearm (for humerus).

[d] years, mean ± SE.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, paired t test.

The timing of peak adolescent growth spurts (defined as velocity peaks after 9 years of age) is shown in Table 4, together with the results of paired t tests between ages of peak adolescent growth velocities for bone strength and other parameters. Stature has an age of peak adolescent growth velocity consistently earlier than those for femoral and humeral strengths, with differences greater in males than in females and greater in the humerus than in the femur. In contrast, ages of peak growth velocity for both body weight · bone length and muscle area are nonsignificantly different from those of their respective bone strength velocities. Ages of peak growth velocities in humeral strength and forearm muscle area are later than those for femoral strength and thigh muscle area in the combined sex sample (by 0.56 years for bone strengths and 0.95 years for muscle areas, $P < 0.05$, paired t tests), although when broken down by sex this is only significant for females in bone strength and near-significant ($P = 0.08$) for males in muscle area.

The effects of body weight · bone length, muscle area, and sex on bone strength in four different age groups—0.5, 1.5, 7, and 17 years—are assessed in Table 5 using stepwise entry of variables into an ANOVA. There are no significant effects of any variables on bone strengths in the 0.5-year (6-month-old) age group. Body weight · bone length has a significant effect more often on femoral strength than on humeral strength, especially in adolescents. Conversely, muscle area is never a significant factor in determining femoral strength, while it has an effect on humeral strength in 1.5 and 17 year olds. However, when sex is added to the model, muscle area is no longer a significant factor in adolescents. In general, sex has little effect prior to adolescence on either femoral or humeral strength.

Discussion

The results of this study support and extend previous conclusions regarding the importance of mechanical factors, in particular body mass loadings, on the development of long bone strength during childhood and adolescence [10,14–16]. Growth velocities from early infancy through late adolescence were found to be strongly correlated between an appropriate measure of mechanical loading due to

Table 5
Results of ANOVA (probability levels) carried out at four ages in the same individuals $(n = 20)$, with femoral and humeral bone strengths (section moduli, Z_p) as dependent variables

Age (years)	Wt · length[a]	Wt · length/sex	Muscle[b]	Muscle/sex	Wt · length/muscle	Wt · length/muscle/sex
Femoral Z_p						
0.5	n.s.	n.s./n.s.	n.s.	n.s./n.s.	n.s./n.s.	n.s./n.s./n.s.
1.5	0.001	0.0004/.03	n.s.	n.s./n.s.	.003/n.s.	.001/n.s./n.s.
7	.001	.02/n.s.	n.s.	n.s./n.s.	.02/n.s.	.02/n.s./n.s.
17	.002	n.s./.02	n.s.	n.s./n.s.	.005/n.s.	.03/n.s./.01
Humeral Z_p						
0.5	n.s.	n.s./n.s.	n.s.	n.s./n.s.	n.s./n.s.	n.s./n.s./n.s.
1.5	.006	.006/n.s.	.004	.004/n.s.	n.s./.05	n.s./.05/n.s.
7	.003	.003/n.s.	n.s.	n.s./n.s.	.02/n.s.	.01/n.s./n.s.
17	n.s.	n.s./.003	.0006	n.s./n.s.	n.s./.003	n.s./n.s./n.s.

[a] Body weight · bone length (femoral or humeral).

[b] Muscle: estimated cross-sectional area of muscle at mid thigh (for femur) or maximum breadth of forearm (for humerus).

body size (body weight · bone length) and bone strength, as assessed by the section modulus. This correlation was particularly strong in the femur, as would be expected given its role in weight support. Correlation of body weight · bone length with humeral strength was significantly lower, again as would be expected from functional considerations. While mechanical loadings on the femur during normal activity (walking) in children have been estimated, similar data for the humerus are not available [31]; thus, precise predictions of the differences in loads experienced by each limb cannot be made. However, it seems intuitively obvious that loads on the femur would increase relative to those on the humerus after the initiation of walking, a hypothesis also supported by direct comparisons between femoral and humeral strengths during development [31,53].

Growth in stature has little effect on changes in bone strength. Stature is a poor body size measure in mechanical terms, since it does not capture either loads (body weight) or moment arms (limb lengths) directly; thus, this result is not surprising. A dissociation between change in stature and change in bone mass in adolescents has been previously noted [22]. Growth increments in femoral cortical area have been reported to be more highly correlated with growth in body weight than with stature in adolescents [21]. Better correlations between stature and bone mass have been claimed for preadolescents [50], although this study was cross-sectional in design and did not include younger children (under 9 years of age), before the beginning of the adolescent growth spurt (see Figs. 1 and 2). Correlations between stature and bone strength growth velocities among only the preadolescents in the present study sample are still low: r^2 values for individuals under 9 years of age are less than 0.10 (versus 0.40–0.45 for bone strength to body weight · bone length). Subdivision by sex yields similar results. The lack of association between change in bone strength and change in stature suggests that it is not simply alterations in general skeletal growth rates that determine rates of increase in bone strength during development.

Muscle strength has also been suggested to be an important determinant of bone strength in the upper limb [11,12,13], and again this is supported here. However, there is a marked sex difference in this relationship: over the entire age range growth in upper limb muscle size is highly correlated with change in humeral strength in males, but is much less closely related in females. A relative increase in muscle size and strength in males relative to females during adolescence is well documented [25,54,55,56] and is probably attributable, at least in part, to a rise in testosterone levels in males [56]. There is also evidence that this sex difference is more marked in the upper than in the lower limb [25,55,57]. In fact, controlling for body size (body weight · bone length) in the present sample, there is still a highly significant ($P < 0.0001$) sex difference in forearm muscle area, while the sex difference in thigh muscle area is nonsignificant ($P > 0.80$). If the sample is broken down into preadolescents (≤9 years) and adolescents (>9 years), the sex difference in forearm muscle area controlling for body size remains highly significant in both groups ($P = 0.001$ in preadolescents, $P < 0.0001$ in adolescents). Interestingly, the highly significant effect of forearm muscle on humeral strength in adolescents disappears when sex is included as a factor (Table 5). Thus, the sex difference in the development of upper body (muscular) strength during adolescence appears to have a direct influence on relative bone strength, with relatively stronger muscles in males contributing to the development of relatively stronger humeri. In general, though, even when controlling for the effects of sex, muscular development has more of an effect on humeral strength than on femoral strength (Table 3). This may be due in part to the overwhelming influence of body size on the weight-bearing lower limb (Tables 2 and 3).

Several authors have reported low correlations between muscle and bone dimensions of the same limbs, including the upper limb in males, which would imply weak functional interrelationships [25,54,57, and references therein]. However, none of these studies examined correlations between growth *velocities* in muscle and bone, which as noted earlier should be more sensitive indicators of causal relationships. In addition, none of them included estimations of the most mechanically relevant properties, muscle cross-sectional area and bone section modulus, but rather relied exclusively on external breadth dimensions. The use of mechanically appropriate structural parameters in testing mechanical hypotheses has been emphasized in many recent investigations of skeletal development and aging [6,10,14,16,29–31,58–60].

Beyond general correlations over the entire preadult age span, comparisons within particular age ranges give some interesting insights into mechanisms of change in these parameters. The earlier adolescent growth spurt in stature than in bone strength is consistent with previous findings based on bone mass measurements [17,22,61]. A greater time lag among males than among females has been reported [61]. This was also found here (Table 4), although the difference is more marked in the femur than in the humerus. Sex-related effects of this kind appear to be more apparent in the femur than in other regions of the body or the body as a whole [17,61]. The data shown here suggest that these results can be explained by considering differences in the timing of growth spurts in body weight · bone length versus stature. While differences in age of growth peaks in stature and bone strength are relatively large and variable (0.4–1.6 years), differences between body weight · bone length and strength are uniformly small (≤0.35 years) (Table 4). Thus, relative to a more mechanically appropriate measure of body size—body weight · bone length—there is little variation in the timing of peak adolescent growth spurts for bone strength and body size between the femur and humerus or between males and females.

This finding has implications for theories regarding the etiology of fractures in children and adolescents. It has been hypothesized that a transient increase in forearm fractures in

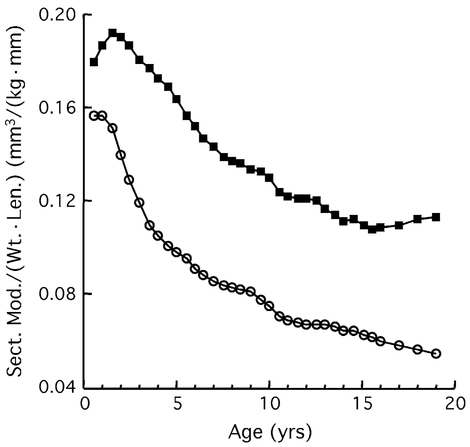

Fig. 3. Age changes in section moduli divided by body weight · bone length in one individual. Filled squares, femur; open circles, humerus.

early adolescence may be due in part to a lag between growth in height or weight and growth in skeletal mass or strength [6,7,17,61]. The present study data appear to indicate no lag, on average, between peak velocities for bone strength and body weight · bone length, at least in the femur and humerus. If the ratio of bone strength to body weight · bone length is calculated and plotted against age, the evidence for any appreciable dip or minimum in the curves in early adolescence or near peak height velocity, followed by a rise in late adolescence, is inconsistent at best. Fig. 3 shows two such curves for the femur and humerus in one individual (a female), illustrating the variation in age patterns observed. Eight of 20 femora and 6 of 20 humeri exhibited a minimum in bone strength relative to body size during early–mid adolescence, defined as a low point after age 9 years followed by a rise of at least 5% (upper curve in Fig. 3). The mean age at such a minimum, when present, was 13.9 years (±1.9 SD). However, the majority of both femora and humeri showed either a continual decline in relative strength through adolescence (bottom curve in Fig. 3) or a leveling off or small rise in mid adolescence followed by another decline in late adolescence. This is contrary to the age patterns reported by Rauch at al. [6] for a very similar type of analysis carried out for the distal radius (4% of forearm length from the distal end). The difference in results may reflect the different bones examined or, more generally, a difference in responsiveness to mechanical loading between diaphyseal and metaphyseal regions [62]. The degree of variation possible between skeletal sites, even within the same individual (Fig. 3), argues for localized mechanical rather than, or in addition to, general systemic explanations for age changes in relative bone strength.

The "infancy peaks" in femoral and humeral bone strength velocities found here have not, to my knowledge, been reported previously. The increased velocity in femoral strength in the second year of life appears to correspond to the beginning of walking, representing the response of a relatively "underbuilt" bone to its new mechanical environment. This is then followed in the third year by a decline in velocity, after the femur has reached an equilibrium with its environment. In contrast, humeral strength velocity declines earlier, during the second year of life, when humeral loads (e.g., from crawling and assistance in standing and walking) would also be expected to decline. This is the only part of the growth period when changes in bone strength in either bone consistently do not parallel those for body size (Fig. 2). This is logical if bone strength is mechanically dependent, since this is the only phase of life where there is a fundamental shift in the relationship between body size and mechanical loading of the upper and lower limbs.

The "mid-childhood" peak in bone strength velocity, observed in many individuals in the study, is sometimes (e.g., Fig. 2) but not always associated with a corresponding small peak in body size velocity (body weight · bone length). In at least some cases, particularly in the humerus, this peak appears to be more of a recovery from very low velocities in early childhood, following the late infancy decline. A similar "overshoot" followed by a recovery occurs in the femoral bicondylar angle, also dependent on mechanical loading for normal development [63,64]. The bicondylar angle begins postnatal life at a varus angle, goes into extreme valgus between 3 and 4 years, and finally reaches a normal adult valgus angle at about 6–7 years [65]. It is possible that many features of the skeleton are subject to such "fine tuning" during development, particularly after such a major event as the acquisition of bipedality.

There are several limitations to this study. The error in extrapolating bone dimensions from planar radiographs to two-dimensional cross sections was discussed earlier. It is impossible to assess the exact degree of error in the present study, although comparisons with true cross-sectional data collected for other juvenile samples indicated that the assumption of circularity for the chosen section locations was not unreasonable, at least on average. It should also be noted that the same assumption has been made in other studies using different techniques to estimate bone cross-sectional properties, e.g., those based on DXA measurements [10,14]. Similarly, the thigh and forearm are not perfectly circular in cross section, especially the forearm, which is wider mediolaterally; thus, the extrapolation of radiographically determined muscle breadths to muscle areas also carries some error. The assumption that these regions do not vary drastically in basic shape between individuals or age groups may not be too inaccurate, however. The forearm was the only upper limb region with available soft tissue data; thus the muscles measured here do not actually act directly on the humerus. However, as noted earlier, muscle areas in the arm and forearm are highly correlated in children [49]. And, of course, muscle area is not equivalent to muscle strength, although again the two are well correlated [66]. The general advantages of using radiographic data, particularly in long-term longitudinal studies of geometric parameters, have been discussed by Heaney et al. [67].

The bone geometric measurements used here to calculate bone strengths do not account for reported changes in bone material properties during growth and development, particularly in young children (<6 years), who have a lower modulus of elasticity and yield and ultimate stress [68,69,70]. When age changes in bone material properties are incorporated, the decline in apparent relative bone strength during childhood (Fig. 3) is much less pronounced [53]. It is possible that rates of mineralization and increase in bone stiffness during infancy could be correlated with the initiation of walking and so could affect the timing and magnitudes of "infancy peaks" in bone strength velocities, although there does not appear to be any abrupt change in material properties during the second year of life [70].

No information on developmental status, e.g., menarche, Tanner puberty stages, or bone development stages, diet, or activity levels, was available for these individuals. Such data would be valuable for placing results into a broader developmental and environmental context. The results reported here are also strictly valid for only the skeletal regions investigated, especially given the apparent regional heterogeneity in bone mass aquisition during development that has been documented [8,50]. However, these findings may well be broadly applicable to diaphyseal regions in the upper and lower limbs.

Finally, the number of individuals in the study sample was small—only 20 individuals—and may not be representative of children generally. Where they can be compared, however, age changes in different parameters found here appear to be very similar to those reported elsewhere, e.g., ages of peak adolescent height velocities in males and females are within 0.35 and 0.05 years, respectively, of those reported by Bailey et al. [17]. Also balanced against the small number of individuals is the very complete record of growth for each individual, which can be contrasted with the more usual cross-sectional or at best mixed cross-sectional/longitudinal sampling used in other studies. Correlations between changes in variables over this developmental period, within individuals, should be valid reflections of functional interrelationships.

In summary, growth velocities in bone strength in the upper and lower limbs appear to be strongly correlated with changes in mechanical loadings. In the femur, these loadings are predominated by body size (body weight · bone length), while in the humerus a combination of both body size and muscular loadings is apparent, especially in males. Stature is a poor body size proxy in any analysis. The timing of growth spurts in bone strength is closely related to those in body size, except in infancy and early childhood, when the initiation of walking produces changes in upper and lower limb bone strength that are uncorrelated with change in body size. While genetic and other "intrinsic" factors are undoubtably also important in determining bone form, these results argue for a major role of mechanical factors throughout development in shaping of the preadult skeleton.

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