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ORIGINAL ARTICLE

A longitudinal comparison of appendicular bone growth and markers of strength through adolescence in a South African cohort using radiogrammetry and pQCT

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Abstract

Summary To compare growth patterns and strength of weight- and non-weight-bearing bones longitudinally. Irrespective of sex and ethnicity, metacarpal growth was similar to that of the non-weight-bearing radius but differed from that of the weight-bearing tibia. Weight- and non-weight-bearing bones have different growth and strength patterns.

Introduction Functional loading modulates bone size and strength.

Methods To compare growth patterns and strength of weight- and non-weight-bearing bones longitudinally, we performed manual radiogrammetry of the second metacarpal on hand-wrist radiographs and measured peripheral quantitative computed tomography images of the radius (65%) and tibia (38% and 65%), annually on 372 black and 152 white South African participants (ages 12–20 years). We aligned participants by age from peak metacarpal length velocity. We assessed bone width (BW, mm); cortical thickness (CT, mm); medullary width (MW, mm); stress-strain index (SSI, mm^3); and muscle cross-sectional area (MCSA, mm^2).

Results From 12 to 20 years, the associations between metacarpal measures (BW, CT and SSI) and MCSA at the radius (males $R^2 = 0.33–0.45$; females $R^2 = 0.12–0.20$) were stronger than the tibia (males $R^2 = 0.01–0.11$; females $R^2 = 0.007–0.04$). In all groups, radial BW, CT and MW accrual rates were similar to those of the metacarpal, except in white females who had lower radial CT (0.04 mm/year) and greater radial MW (0.06 mm/year) accrual. In all groups, except for CT in white males, tibial BW and CT accrual rates were greater than at the metacarpal. Tibial MW (0.29–0.35 mm/year) increased significantly relative to metacarpal MW (− 0.07 to 0.06 mm/year) in males only. In all groups, except white females, SSI increased in each bone.

Conclusion Irrespective of sex and ethnicity, metacarpal growth was similar to that of the non-weight-bearing radius but differed from that of the weight-bearing tibia. The local and systemic factors influencing site-specific differences require further investigation.

Keywords Functional loading · Growth patterns · Muscle · pQCT · Radiogrammetry · Stress-strain index

Introduction

Bone geometry and strength determine fracture risk [1]. Sex differences in metacarpal, radial and tibial bone size and strength have been documented in US adults [2] and children [3–5]. In South African (SA) children, in addition to sex differences, studies using radiogrammetry and peripheral quantitative computed tomography (pQCT) have shown distinct ethnic differences in bone diameter, the ratio of cortical thickness to medullary cavity diameter [6–8], and, in muscle cross-sectional area (MCSA) relative to bone size [6, 9].

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Bone size, mass and strength are modulated by mechanical loading due to body weight and muscle force [10–12]. Furthermore, muscle elicits a differential response to mechanical forces dependent on its cross-sectional area [6, 9]. The role of muscle in determining bone size and strength has been established at the radius [13, 14] and tibia [15], but its role at the metacarpal remains unclear [16].

Bone strength and resistance to fracture are dependent on the triad of its mass, geometry and the material properties of its matrix [17]. Historically, radiogrammetry was the means by which cortical measures from radiographs were translated into indices used as proxies for bone strength [3, 18]. Whilst radiogrammetry is a simple, accessible and inexpensive method which yields information about the amount of bone and its spatial organisation [3, 18]. pQCT, however, is a more advanced mode of assessing bone size and strength, and provides a 3-dimensional perspective of the quantity and matrix properties of both cortical and trabecular bone [19]. From the pQCT image, the stress-strain index (SSI) is derived using measures of bone geometry and volumetric bone density to provide a proxy for bone strength [20].

Whilst recent longitudinal studies from South Africa and Canada have reported on sex and ethnic differences in growth of the metacarpal bone (by radiogrammetry) [7], and the radius and tibia (by pQCT) [5, 8], to the best of our knowledge, the influence of muscle size on bone growth during adolescence has not been investigated longitudinally in African children. Our aim was to compare, in two ethnic groups, bone growth and strength patterns measured using two different technologies at weight- and non-weight-bearing appendicular sites, controlling for the influence of the associated musculature. We hypothesised firstly that, due to the metacarpal being a non-weight bearing bone, metacarpal bone measures and strength would correlate more closely with MCSA at the non-weight-bearing radius than at the weight-bearing tibia; therefore, radial MCSA could be used as a proxy for metacarpal MCSA. Secondly, irrespective of sex and ethnicity, the pattern of growth of the non-weight-bearing metacarpal and radial bones would be similar to each other and that metacarpal growth would differ from that of the weight-bearing tibia.

Materials and methods

Study participants and protocol

The participants in this study were black and white children from the Bone Health Cohort (BHC) which is a subgroup of the Birth to Twenty (Bt20) longitudinal birth cohort. The details of recruitment into both cohorts have previously been described [7, 21]. Briefly, the Bt20 cohort comprised 3273 singleton children born between April and June 1990 in the greater Johannesburg-Soweto metropolitan area, South Africa. At age 9 years, 563 of these children were included in the BHC to investigate bone development and its influencing factors during adolescence. Children were classified as black (African descent) or white (European descent) based on the race classification used in South Africa for demographic and restitution purposes. Ethnic classification was self-reported by the parents and only those children whose parents both belonged to the same ethnic group were included in this study. Previous genetic studies have shown little ethnic admixture between the groups in the Bt20 cohort [22]. Due to the small numbers of white participants originally enrolled into the Bt20 cohort, which represented the SA population demographics at that time, and, attrition of participants over time, an additional 120 9-year-old white children born during the same period were recruited into the BHC. Their mean birth weight, socioeconomic status and maternal age and education were commensurate with those of the original white participants of the BHC. Children with chronic illnesses such as epilepsy and asthma were excluded due to the possible negative effects of their medication on bone mass. Informed assent from adolescent participants and consent from parents were obtained for inclusion in this study. Ethics clearance was obtained from the University of the Witwatersrand Committee for Research on Human Subjects. At approximately the same time annually, participant height and weight were measured, and hand-wrist radiographs and peripheral quantitative computed tomography scans of the radius and tibia were obtained.

Anthropometric measurements

Weight and height of participants were measured whilst wearing light clothing and no shoes. Weight was measured to the nearest 100 g using a digital scale (Dismed, Miami, FL, USA) and height to the nearest millimetre using a stadiometer (Holtain, Crymych, UK). Quality control annual training and monitoring ensured a coefficient of variation between measurers of less than 2%.

Puberty

We used age at peak metacarpal length velocity (PLV) as an indicator of pubertal development [7]. The use of age at PLV allowed us to align black and white females and males on a common biological maturity indicator. Metacarpal bone length of participants aged between 9 and 21 years was modelled using Superimposition by Translation and Rotation (SITAR) in R (version 3.2.2, R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/) [23] to obtain age at PLV for each participant [7]. SITAR is a shape invariant model with a single fitted curve that summarises individual growth patterns with three parameters—size (amplitude), tempo and velocity [23]. Individual curves are modelled and matched to the mean curve by shifting vertically

(to represent differences in individual size), or horizontally for differences in tempo (timing) of growth. Individual differences in velocity cause a stretching or shrinking of the age scale resulting in an increase or decrease of the slope [23].

Metacarpal, radial and tibial growth for each sex and ethnic group was standardised on PLV. Age from PLV for metacarpal, radial and tibial bone measures was calculated by subtracting the age at PLV from the chronological age at measurement. Age at PLV coincided with age at peak height velocity (unpublished data).

Radiography

Postero-anterior hand-wrist radiographs of the left hand were taken annually between 9 and 21 years of age by certified radiographers at the Charlotte Maxeke Academic Hospital in Johannesburg. The x-ray beam was focussed on the distal aspect of the third metacarpal of the left hand. Radiographs were taken using cassettes with single-emulsion film under standard conditions of tube to film distance of 76 cm and exposure at 42 kV and 12 mA/s, and processed in an automatic developer in line with the optimal conditions described by Tanner et al. [24].

Radiogrammetry

Radiogrammetry was performed on hand-wrist radiographs of 572 participants aged between 9 and 21 years to obtain age at PLV [7]. To compare growth patterns of the metacarpal bone to that of the radius and tibia, data was only used from 524 participants aged between 12 and 20 years to coincide with the availability of pQCT data. Second metacarpal dimensions were measured on a total of 4730 hand-wrist radiographs by a single reader (AM). Measurements were carried out using a digital calliper calibrated to 0.01 mm. The following parameters were measured in millimetres: total length of bone from proximal to distal end, and outer bone width and inner medullary width at the midshaft of the metacarpal. The cortical thickness was calculated as the difference between the bone and medullary widths. The SSI was calculated from the hand-wrist radiographs as described by Cointry and co-workers [25]. To assess intra-observer reliability and reproducibility, measurements of 30 randomly selected radiographs were repeated by the same researcher (AM) 1 month after initial measurement and again 16 months later. The coefficients of variation for the radiogrammetry measures were as follows: (i) metacarpal length, 0.14%; (ii) bone width, 0.80%; and (iii) medullary width, 6.20%.

Peripheral quantitative computed tomography imaging

Peripheral QCT imaging was carried out on the left forearm and lower leg annually on 524 participants of the BHC cohort between 12 and 20 years of age. At each visit, images were obtained from 2.3 mm thick diaphyseal slices taken at the tibia (38% and 65% sites) and the radius (65% site) (Stratec XCT-2000, Stratec Medical, Pforzheim, Germany). Forearm length was measured from the most distal end of the ulna styloid process to the tip of the olecranon process. The tibial length was measured from the distal end of the medial malleolus to the superior aspect of the medial tibial condyle. A 0.5-mm voxel size and a scan speed of 25 mm/s were used. Image processing and calculation of numerical values were performed using the manufacturer's software package (version 6; Stratec Medical, Pforzheim, Germany) at thresholds of 710 mg/cm^3 for cortical bone and 180 mg/cm^3 for total bone.

Analyses at the 38% tibial site and the 65% radial sites were done using the Cort mode 1 (threshold = 710 mg/cm^3) for total cross-sectional area (TotA, mm^2) and cortical bone area (CoA, mm^2). Bone measures were calculated as follows [6]: bone width = $2 \times \sqrt{(\text{TotA}/\pi)}$; medullary width = $2 \times \sqrt{(\text{TotA-CoA})/\pi}$; cortical thickness = bone width − medullary width. The SSI was determined from the pQCT bone measures at a threshold of 280 mg/cm^3 [8]. The individual density of each voxel was used in the calculation of the SSI to minimise the error due to the partial volume effect [26].

The 65% radial and tibial sites are associated with the largest muscle belly and were assessed for MCSA (cm^2). Muscle CSA, calculated as the area with a density between 40 and 180 mg/cm^3, was analysed using contour mode 3.

A scan of a phantom was performed daily for quality control. Throughout the study, all measurements and analyses were performed by two trained operators. The inter-operator variation was less than 1%. All pQCT scans were analysed by a single qualified individual. Images that had been distorted by movement during scanning or incorrect limb placement were excluded from this study.

Statistical analyses

Bivariate regression

All analyses were performed separately for each sex and ethnic group due to known differences in their bone geometry [7]. A bivariate regression was performed to determine the association between metacarpal bone width, thickness and SSI, and MCSA of the radius and tibia, and, between metacarpal SSI, and radial and tibial SSI. A Hausman test was performed on the data and the fixed effects model deemed to be appropriate for assessing the bone measures. The metacarpal outcome variables were log-transformed to approximately conform to normality. Fixed effects using the least squares dummy variable model (LSDV) removed the time-invariant characteristics of the data and assessed the net effect of the

predictors on the outcome variable. The level of significance was set at $p < 0.05$.

Mixed-effects modelling

Analyses were conducted using Stata 14.0 (Stata Corporation Inc., College Station, TX, USA). Regression analyses showed that sex ($p < 0.0001$) and ethnicity ($p < 0.05$) were significantly associated with rates of bone growth; therefore, all analyses were conducted separately for each sex and ethnic group.

We used mixed-effects models to compare the growth patterns of bone width, cortical thickness, medullary width, and SSI as measured by radiogrammetry and pQCT, in the four groups when aligned by years from PLV. No imputation of missing data was undertaken as the mixed-effects model manages missing data by using information from other participants to obtain an overall curve. The regression model used was:

$$Y_{ij} = \beta_0 + \beta_1 \mathrm{Age}_{ij} + \beta_2 \mathrm{Age}^2{}_{ij} + \beta_3 \mathrm{Site}_j + \beta_4 \mathrm{MCSA}_j + \beta_5 \mathrm{Age}_{ij} \times \mathrm{Site}_j + \beta_6 \mathrm{Site}_j \times \mathrm{MCSA}_j + u_0 + u_1 \mathrm{Age}_{ij} + \varepsilon_{ij}$$

Y_{ij} is the bone variable of individual i measured at time j.

In the fixed effect of the model, β_0 and β_1 represent the average value of the bone variable for each individual and the overall slope of time (age from PLV), respectively. To adjust for the effect of bone site (metacarpal, radius and tibia) on the relationship between the bone variable and age, an interaction term for age and bone site (Age × Site) was included in the model. An additional interaction term Site × MCSA was included in the model to adjust for the effect of the associated musculature of each bone. Radial MCSA was used as a proxy for metacarpal MCSA. A quadratic function for age was included in the model as it improved model fit by lowering the Bayesian Information Criterion (BIC).

In the random effect of the model, u_0 is the individuals' residual distance from the intercept of the overall trajectory, u_1 is the residual difference for individuals' slopes around the overall effect of time (age from PLV), and, ε_{ij} is the residual of the individual points around the subject-specific trajectory. Random intercepts and slopes were included in all models as they improved model fit by lowering the BIC. The random effects allowed each individual's profile to vary around the average curve and for variation in the rate of growth between individuals. We used maximum log likelihood (−2log likelihood) to determine the significance of random effect variances and covariances between nested models. The level of statistical significance was $p < 0.05$.

Results

Participant recruitment, the number of participants in each sex and ethnic group, together with the total number of observations per group are shown in Supplementary Fig. 1. A total of 524 participants aged between 12 and 20 years had valid hand-wrist radiographs and radial and tibial pQCT scans. They comprised 174 (33%) black females (BF), 79 (15%) white females (WF), 198 (38%) black males (BM) and 73 (14%) white males (WM). The mean number of visits over the study period was 5 for black participants and 3.5 for white participants.

Associations of metacarpal bone measures with MCSA of radius and tibia

Metacarpal bone measures were associated with MCSA of the radius in all four groups (Table 1). The variance in metacarpal bone width and cortical thickness explained by radial MCSA was 34–45% in males ($R^2 = 0.34$–0.45) and 12–19% in females ($R^2 = 0.12$–0.19). There was no significant association between any of the metacarpal bone measures and tibial MCSA, except in black males (Table 1).

Associations of metacarpal SSI with MCSA and SSI of radius and tibia

The SSI of the metacarpal bone was significantly associated with MCSA of the radius in all four groups, although the variance explained in males was 36–44% ($R^2 = 0.36$–0.44) and only 15–20% in females ($R^2 = 0.15$–0.20) (Table 1; Supp. Fig. 2). Metacarpal SSI was associated with tibial MCSA in the black males only ($R^2 = 0.11$) (Table 1; Supp. Fig. 3).

Metacarpal SSI was significantly associated with radial and tibial SSI in all four groups (Table 1). The variance in metacarpal SSI explained by the radial SSI was 20–35% in females and 38–51% in males (females, $R^2 = 0.20$–0.35; males, $R^2 = 0.38$–0.51). Tibial SSI explained only 11–21% variance in metacarpal SSI in females but 27–30% in males (females, $R^2 = 0.11$–0.21; males, $R^2 = 0.27$–0.30).

Bone width

Metacarpal, radial and tibial bone width growth patterns are presented in Supplementary Fig. 4, and the average annual changes in bone width are shown in Table 2. Bone width over the period of study increased significantly in each of the three bones in all four groups, except for radial bone width in white females which did not increase significantly (Table 2). Metacarpal and radial bone width growth rates were similar to each other in both sex and ethnic groups. However, comparisons between the tibia

Table 1 Fixed-effects regression estimates of metacarpal bone measures as the outcome and radial and tibial bone measures as predictors in black and white females and males

	Black female ($N = 174$)		White female ($N = 79$)	
	Coefficient [95% CI]	R^2	Coefficient [95% CI]	R^2
BW Met/MCSA radius	6.86E-05 [6.31E-05, 7.41E-0.5]*	0.19	8.36E-05 [6.89E-05, 9.83E-05]*	0.14
BW Met/MCSA tibia	1.71E-06 [− 1.05E-06, 4.47E-06]	0.007	5.25E-07 [− 4.74E-06, 5.79E-06]	0.03
CT Met/MCSA radius	2.23E-04 [2.01E-04, 2.44E-04]*	0.12	2.68E-04 [2.22E-04, 3.15E-04]*	0.13
CT Met/MCSA tibia	− 8.71E-06 [1.91E-05, 1.71E-06]	0.01	− 4.53E-06 [− 2.06E-05, 1.15E-05]	0.01
SSI Met/MCSA radius	2.92E-04 [2.66E-04, 3.18E-04]*	0.20	3.07E-04 [2.45E-04, 3.69E-04]*	0.15
SSI Met/MCSA tibia	5.52E-06 [− 7.27E-06, 1.83E-05]	0.009	1.07E-05 [− 1.06E-05, 3.20E-05]	0.04
SSI Met/SSI radius	1.97E-03 [1.77E-03, 2.16E-03]*	0.35	2.04E-03 [1.70E-03, 2.39E-03]*	0.20
SSI Met/SSI tibia	1.35E-04 [8.35E-05, 1.87E-04]*	0.21	2.32E-04 [1.12E-04, 3.52E-04]*	0.11
	Black male ($N = 198$)		White Male ($N = 73$)	
	Coefficient [95% CI]	R^2	Coefficient [95% CI]	R^2
BW Met/MCSA radius	7.68E-05 [7.39E-05, 7.96E-05]*	0.35	7.63E-05 [6.95E-05, 8.31E-05]*	0.33
BW Met/MCSA tibia	4.09E-05 [3.56E-05, 4.61E-05]*	0.09	8.92E-06 [7.81E-09, 1.78E-05]	0.06
CT Met/MCSA radius	1.83E-04 [1.73E-04, 1.93E-04]*	0.34	1.83E-04 [1.62E-04, 2.04E-04]*	0.45
CT Met/MCSA tibia	7.82E-05 [6.38E-05, 9.26E-05]*	0.06	9.04E-06 [− 1.43E-05, 3.24E-05]	0.01
SSI Met/MCSA radius	3.53E-04 [3.40E-04, 3.67E-04]*	0.44	3.31E-04 [2.98E-04, 3.64E-04]*	0.36
SSI Met/MCSA tibia	1.85E-04 [1.60E-04, 2.09E-04]*	0.11	3.95E-05 [− 2.56E-07, 7.92E-05]	0.02
SSI Met/SSI radius	3.29E-03 [3.14E-03, 3.44E-03]*	0.51	2.49E-03 [2.17E-03, 2.80E-03]*	0.38
SSI Met/SSI tibia	7.29E-04 [6.74E-04, 7.84E-04]*	0.30	7.41E-04 [6.04E-04, 8.79E-04]*	0.27

Log-transformed data are presented as β coefficients with 95% confidence intervals [CI] and coefficients of determination (R^2)

BW bone width (mm), *CT* cortical thickness (mm), *MCSA* muscle cross-sectional area (mm^2), *SSI* stress-strain index (mm^3), *Met* metacarpal

*$p < 0.0001$

and metacarpal bone revealed that tibial bone width growth rate among black females and white females (0.23 and 0.31 mm/year, respectively) was double that of the metacarpal (0.12 and 0.14 mm/year, respectively), whilst tibial bone width growth rate among black males and white males (0.68 and 0.82 mm/year, respectively) was 3–4 times greater than that of the metacarpal bone (0.22 and 0.28 mm/year, respectively).

Cortical thickness

The cortical thicknesses at the metacarpal, radial and tibial bone sites by years from peak metacarpal length velocity are shown in Supplementary Fig. 5. In all four groups, cortical thickness increased significantly over the period of study in the metacarpal, radius and tibia (Table 3). The average annual rate of growth in cortical thickness in the metacarpal and radius was similar to each other in all groups, except in white females in whom the radial cortical thickness growth rate was 0.04 mm/year less than that of the metacarpal ($p < 0.05$). In white males, the average annual cortical thickness growth rates of the three bones were similar. In the other three groups, the average annual increase in tibial cortical thickness growth rate was significantly greater than that of the metacarpal.

Medullary width

Metacarpal, radial and tibial medullary width growth patterns are presented in Supplementary Fig. 6, and the average annual changes in medullary width are shown in Table 4. Black and white females experienced a significant average decrease in metacarpal medullary width growth rate of − 0.03 and − 0.09 mm/year, respectively. The average annual change in metacarpal medullary width in white males was − 0.07 mm/year, while in black males, a significant increase in the metacarpal medullary width of 0.06 mm/year was noted. At the radius, medullary width decreased significantly in all four groups, while at the tibia, both black and white males experienced significant increases in medullary width of 0.17–0.20 mm/year. In females, the average annual change in tibial medullary width was not significant.

When comparing the metacarpal medullary width change to that of the radius, there were no significant differences in any of the groups, except in white females who experienced a greater average increase in radial

Table 2 Results from mixed-effects growth models summarising differences in metacarpal, radial and tibial bone width growth

Outcome	Fixed effects					Random effects		
Bone width	YPLV	Bone	Intercept	Slope [CI]	Age × Site [CI]	Intercept	Slope	Residual
BF		Met	7.39	0.12 [0.11, 0.13]*				
	0.31 [0.25, 0.38]*	Rad	10.34	0.08 [0.04, 0.12]*	− 0.004 [− 0.03, 0.02]	0.72	0.0000	0.40
		Tib	21.14	0.23 [0.20, 0.26]*	0.10 [0.04, 0.15]*			
WF		Met	7.21	0.14 [0.12, 0.17]*				
	0.35 [0.23, 0.48]*	Rad	9.89	0.05 [− 0.03, 0.12]	0.02 [− 0.03, 0.07]	0.63	0.0000	0.40
		Tib	20.24	0.31 [0.25, 0.37]*	0.16 [0.06, 0.26]¥			
BM		Met	7.77	0.22 [0.20, 0.24]*				
	0.63 [0.55, 0.70]*	Rad	10.89	0.19 [0.15, 0.23]*	− 0.01 [− 0.06, 0.03]	0.87	0.001	0.71
		Tib	23.16	0.68 [0.64, 0.73]*	0.23 [0.17, 0.29]*			
WM		Met	7.35	0.28 [0.22, 0.33]*				
	0.94[0.77, 1.11]*	Rad	10.27	0.15[0.03, 0.27]¥	− 0.02 [− 0.12, 0.07]	1.04	0.005	0.65
		Tib	22.28	0.82 [0.73, 0.90]*	0.21 [0.10, 0.32]*			

Fixed effects = the intercept is the mean value for the outcome variable. Slopes represent annual rates of accrual as assessed by YPLV and are presented with 95% confidence intervals [CI]

Random effects = between-participant variation in intercepts and slopes with residual variances

Age × Site represents the slopes of the radius and tibia relative to the metacarpal bone

BF black female, *WF* white female, *BM* black male, *WM* white male, *YPLV* years from peak metacarpal length velocity, *Met* metacarpal, *Rad* radius, *Tib* tibia

Significant differences are given as $*p < 0.0001$, $**p < 0.001$, ¥$p < 0.01$

medullary width of 0.06 mm/year relative to the metacarpal. Tibial medullary width increased significantly relative to the metacarpal in males, but not in females.

Stress-strain index

The SSI at the metacarpal, radial and tibial bone sites by years from peak metacarpal length velocity are shown in Supplementary Fig. 7. In all four groups, the SSI increased significantly in each bone, except for tibial SSI in white females in whom the average annual increase was not significant (Table 5). There was a greater average annual increase in radial than metacarpal SSI in black females and white males. Tibial SSI increased significantly compared to the metacarpal SSI in white females and black males (Table 5).

Discussion

In this longitudinal study, the growth patterns of weight- and non-weight-bearing appendicular bones, measured by radiogrammetry or pQCT, were assessed in black and white SA children through puberty and adolescence. We have shown that metacarpal bone width and cortical thickness are strongly associated with radial MCSA but not with tibial MCSA. Our findings are consistent with those of a pQCT study conducted in adults which showed a strong correlation between metacarpal bone mass and forearm muscle mass in both individuals with rheumatoid arthritis and healthy controls [27]. In the present study, the variance in metacarpal bone measures explained by radial and tibial MCSA was 1–45% in males, but only 0.7–20% in females. A sex difference has been previously reported in a study of young adults aged between 19 and 22 years in whom lean mass, measured by dual-energy x-ray absorptiometry, explained 34.5% of the variability in whole-body bone mineral density in males but only 18.3% of the variability in females [28]. This sex disparity which arises during puberty, is probably related to differences in muscle mass developing during this period [29]. It is of interest that peak muscle mass gain precedes peak bone mass gain by several months, as shown in a Canadian study in which peak muscle mass gain preceded peak bone mass gain by 0.36 years and 0.51 years in boys and girls, respectively [30], suggesting a role for muscle mass in determining peak bone mass.

We showed that there were no differences in the growth of bone width between the non-weight-bearing metacarpal and radial bones in all four groups when aligned on PLV; however, bone width growth of the weight-bearing tibia was significantly greater than that of the metacarpal bone, even after adjusting for the influence of the associated musculature. The greater increases in cross-sectional bone dimensions in the tibia may have been the result of mechanical loading [31–33] due to body weight and muscle contraction, the latter

Table 3 Results from mixed-effects growth models summarising differences in metacarpal, radial and tibial cortical thickness growth

Outcome	Fixed effects					Random effects		
Cortical thickness	YPLV	Bone	Intercept	Slope [CI]	Age × Site [CI]	Intercept	Slope	Residual
BF		Met	2.88	0.14 [0.11, 0.17]*				
	0.28 [0.23,0.34]*	Rad	3.60	0.19 [0.16, 0.23]*	− 0.01 [− 0.03, 0.02]	0.24	0.0000	0.29
		Tib	7.53	0.22 [0.20, 0.25]*	0.11 [0.06, 0.16]*			
WF		Met	2.94	0.22 [0.17, 0.27]*				
	0.33 [0.23, 0.43]*	Rad	3.45	0.19 [0.14, 0.24]*	− 0.04 [− 0.08, − 0.01]	0.13	0.0004	0.23
		Tib	8.00	0.32 [0.27, 0.37]*	0.10 [0.03, 0.18]¥			
BM		Met	2.72	0.16 [0.12, 0.19]*				
	0.27 [0.22,0.32]*	Rad	3.44	0.25 [0.22, 0.28]*	0.01 [− 0.02, 0.05]	0.28	0.0000	0.37
		Tib	8.08	0.39 [0.36, 0.42]*	0.07 [0.02, 0.11]¥			
WM		Met	3.08	0.32 [0.23, 0.41]*				
	0.59 [0.48,0.70]*	Rad	3.19	0.29 [0.22, 0.35]*	− 0.05 [− 0.11, 0.01]	0.27	0.0004	0.30
		Tib	8.92	0.46 [0.40, 0.52]*	0.04 [− 0.03, 0.11]			

Fixed effects = the intercept is the mean value for the outcome variable. Slopes represent annual rates of accrual as assessed by YPLV and are presented with 95% confidence intervals [CI]

Random effects = between-participant variation in intercepts and slopes with residual variances

Age × Site represents the slopes of the radius and tibia relative to the metacarpal bone

BF black female, *WF* white female, *BM* black male, *WM* white male, *YPLV* years from peak metacarpal length velocity, *Met* metacarpal, *Rad* radius, *Tib* tibia

Significant differences are given as $*p < 0.0001$, $**p < 0.001$, ¥$p < 0.01$, $p < 0.05$

creating the largest physiologic load on bone thus influencing bone strength [34].

In this study, cortical thickness of the three bones increased significantly during adolescence with a similar average annual rate in the metacarpal and radius in all groups, except in white females who had a lower rate of cortical thickness growth at the radius than the metacarpal. Tibial cortical thickness growth rate exceeded that of the metacarpal in all groups, except in white males. In an anthropological study of individuals aged between 1 and 30 years, Sumner et al. [31] found that cortical area as a function of bone length increased more rapidly in the weight-bearing femur than in the non-weight bearing humerus. The bone width and cortical thickness growth patterns that we observed in the weight-bearing tibia compared to the non-weight-bearing metacarpal are analogous to those reported in the femur and humerus by Sumner et al. [31].

Sexual dimorphism, irrespective of ethnicity, was apparent in the velocities of bone width and cortical thickness growth of the participants in our study, particularly in the tibia. Male participants experienced greater velocities which may be associated with higher rates of bone turnover [4, 35] and greater cortical porosity [36]. Whilst we did not analyse bone turnover or cortical porosity, it bears consideration, since the inverse relationship between cortical porosity and bone strength is exponential, with even a small increase in porosity resulting in a relatively large decrease in strength [37]. Changes in microstructure that accompany the greater growth rates in males may contribute to their higher fracture incidence [38] despite having superior strength, determined by SSI, than females [5].

In this study, the medullary width growth patterns differed between the three bones. In the non-weight-bearing bones there was an overall narrowing of the medullary cavity in all groups except for the metacarpal in black males in whom it expanded. At the tibia, the increase in medullary width was only significant in males. We have previously shown that there are ethnic differences in medullary width growth between black and white males in our cohort [7]. The contraction in metacarpal medullary width in our white males differs from cross-sectional studies of white children in the USA [39] but concurs with a more recent longitudinal study in European children [40], which suggests population differences in medullary cavity growth. The overall contraction of radial medullary width in both male and female participants in our study differs from that of a cross-sectional pQCT study at the 65% radius of white individuals between 6 and 40 years of age by Neu and co-workers [33]. In their study, from Tanner stage 3 onwards, there was no change in medullary width in females, whilst in males, it increased significantly which they attributed to modelling drift, that is, endocortical bone resorption in response to bone expansion as a result of periosteal bone deposition [33]. In contrast, in both sexes in our study, radial medullary width contraction was accompanied by bone width expansion indicating that bone deposition occurred at both the

Table 4 Results from mixed-effects growth models summarising differences in metacarpal, radial and tibial medullary width change

Outcome	Fixed effects					Random effects		
Medullary width	YPLV	Bone	Intercept	Slope [CI]	Age × Site [CI]	Intercept	Slope	Residual
BF		Met	4.38	− 0.03 [− 0.06, − 0.001]				
	0.03 [− 0.05, 0.11]	Rad	6.56	− 0.12 [− 0.18, − 0.06]*	0.004 [− 0.03, 0.04]	0.80	0.0000	0.67
		Tib	13.61	0.01 [− 0.02, 0.04]	0.005 [− 0.07, 0.08]			
WF		Met	4.15	− 0.09 [− 0.14, − 0.04]**				
	0.03 [− 0.12, 0.18]	Rad	6.32	− 0.15 [− 0.26, − 0.04]¥	0.06 [0.002, 0.12]	0.38	0.0000	0.56
		Tib	12.16	− 0.02 [− 0.08, 0.05]	0.12 [− 0.001, 0.24]			
BM		Met	4.97	0.06 [0.02, 0.09]¥				
	0.33 [0.24, 0.43]*	Rad	7.41	− 0.07 [− 0.12, − 0.01]	− 0.03 [− 0.09, 0.03]	1.30	0.0000	1.20
		Tib	15.10	0.29 [0.24, 0.34]*	0.17 [0.09, 0.25]*			
WM		Met	4.09	− 0.07 [− 0.16, 0.03]				
	0.26 [0.11, 0.42]*	Rad	6.94	− 0.16 [− 0.31, − 0.02]	0.03 [− 0.06, 0.12]	0.69	0.0000	0.63
		Tib	13.33	0.35 [0.27, 0.44]*	0.20 [0.09, 0.30]*			

Fixed effects = the intercept is the mean value for the outcome variable. Slopes represent annual rates of accrual as assessed by YPLV and are presented with 95% confidence intervals [CI]

Random effects = between-participant variation in intercepts and slopes with residual variances

Age × Site represents the slopes of the radius and tibia relative to the metacarpal bone

BF black female, *WF* white female, *BM* black male, *WM* white male, *YPLV* years from peak metacarpal length velocity, *Met* metacarpal, *Rad* radius, *Tib* tibia

Significant differences are given as *$p < 0.0001$, **$p < 0.001$, ¥$p < 0.01$, $p < 0.05$

Table 5 Results from mixed-effects growth models summarising differences in metacarpal, radial and tibial stress-strain index change

Outcome	Fixed Effects					Random Effects		
Stress-strain index	YPLV	Bone	Intercept	Slope [CI]	Age × Site [CI]	Intercept	Slope	Residual
BF		Met	392.00	38.59 [33.49, 43.69]*				
	48.39 [35.65, 61.14]*	Rad	115.00	14.08 [11.80, 16.36]*	7.87 [2.30, 13.45]¥	1.53E + 04	0.0000	1.61E + 04
		Tib	915.00	41.69 [29.00, 54.38]*	2.90 [− 8.22, 14.03]			
WF		Met	357.00	34.08 [25.44, 42.71]*				
	54.62 [29.68, 79.65]*	Rad	61.97	13.61 [8.95, 18.27]*	5.29 [− 4.28, 14.85]	1.17E + 04	0.0000	1.55E + 04
		Tib	852.00	19.17 [− 4.44, 42.78]	23.49 [3.75, 43.22]			
BM		Met	324.00	66.86 [57.23, 76.49]*				
	99.79 [84.14, 115.00]*	Rad	144.00	23.35 [20.20, 26.49]*	5.07 [− 5.34, 15.49]	2.64E + 04	40.94	3.42E + 04
		Tib	1230.00	104.00 [91.68, 116.00]*	23.78 [10.28, 37.27]¥			
WM		Met	263.00	95.95 [68.29, 124.00]*				
	121.00 [84.83, 158.00]*	Rad	73.47	22.65 [12.62, 32.68]*	22.65 [1.31, 44.00]	3.37E + 04	0.0000	3.50E + 04
		Tib	1000.00	114.00 [90.19, 138.00]*	16.12 [− 8.66, 40.89]			

Fixed effects = the intercept is the mean value for the outcome variable. Slopes represent annual rates of accrual as assessed by YPLV and are presented with 95% confidence intervals [CI]

Random effects = between-participant variation in intercepts and slopes with residual variances

Age × Site represents the slopes of the radius and tibia relative to the metacarpal bone

BF black female, *WF* white female, *BM* black male, *WM* white male, *YPLV* years from peak metacarpal length velocity, *Met* metacarpal, *Rad* radius, *Tib* tibia

Significant differences are given as *$p < 0.0001$, **$p < 0.001$, ¥$p < 0.01$, $p < 0.05$

periosteal and endocortical surfaces. While we adjusted for the influence of the associated musculature on bone growth in our study, we did not assess hormonal influences, which have been shown to differentially affect bone growth in the sexes [4]. Kirmani and co-workers [4] found that radial periosteal and endocortical bone accrual were driven by insulin-like growth factor-1 (IGF-1) in girls and by testosterone in boys. The greater expansion of tibial medullary width that we observed in male participants concurs with other longitudinal studies [5] and reflects the bone's compensatory mechanism to resist bending and torsional forces as the cortices move further from the bone's neutral axis. The site-specific differences at the endocortical surface that we observed suggest that in weight-bearing bones, there is modelling drift and that this functional adaptation to increase bone strength may possibly override hormonal influences.

The SSI, which is the product of the section modulus of the bone and the ratio of measured cortical density to physiologic bone density (1200 mg/cm^3), has been shown to be a strong proxy for bone strength and failure of loading [20]. We observed greater average annual changes in SSI of the metacarpal, radius and tibia in males than in females, which is in keeping with the greater increase in male bone width and cortical thickness over the period of measurement and consistent with mixed longitudinal pQCT and high-resolution pQCT studies of the radius and tibia in Canadian adolescents [5, 41]. Of interest, was the negligible change in tibial SSI in females despite an increase in bone width and cortical thickness through adolescence. Whilst a lower SSI might suggest that females may be more susceptible to fracture, childhood tibial fractures occur relatively infrequently. Up to the age of 12 years, tibial fracture incidence has been shown to be higher in British females compared to males [42]. Sex differences in proxies for tibial strength (section modulus and bone strength index), have previously been reported in a study of stress fracture in military recruits who averaged 19 years of age [43]. In male military recruits who had fractured, lower tibial strength indices were attributed to narrower bone widths, in contrast to female recruits who had fractured in whom lower tibial strength indices were a function of thinner cortices [43]. In our study, we did not differentiate between participants with and without a history of fracture and we are therefore unable to comment on the association between SSI and tibial fracture in our cohort.

The study has a number of limitations. Although we adjusted for differences in somatic maturity by using PLV, we assumed that 1 year of biological age is equivalent to 1 year of chronological age. This only accounted for differences in the timing (tempo) of growth and not for potential differences in the rate (velocity) of growth [8, 44]. Furthermore, the timing of peak growth velocity varies according to anatomical site [8, 44]. The effects of physical activity on bone are probably mediated via muscle [45] and although we did not consider physical activity in our analyses, we included MCSA to try to account for this. Our longitudinal data of bone growth of the metacarpal, radius and tibia in black and white children are unique; however, the number of white participants was relatively small which may have led to a type II error. This study only included radiographic and pQCT measurements from chronological age 12 years, by which time peak growth may have commenced or been completed in some individuals, particularly in females. Our data were obtained using two different technologies and at different diaphyseal regions; radiogrammetry was done at the midshaft of the metacarpal bones, and pQCT at the 65% radial and 38% and 65% tibial sites. The ratio of cortical to trabecular bone and the associated musculature of the three bones at these sites may differ. Although bone growth is region-specific, we do not believe that standardising measurements of all three bones at the diaphyseal midshaft would have changed the outcomes.

In conclusion, longitudinal analyses through adolescence showed that in both sex and ethnic groups, when aligned on a physiological maturity indicator, the growth patterns of the non-weight-bearing metacarpal bone and radius were overall similar to each other but differed from that of the weight-bearing tibia. The extent of sexual dimorphism in bone width growth patterns was similar in both ethnic groups, suggestive of common biological mechanisms which regulate functional adaptation, despite different genetic backgrounds.

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Compliance with ethical standards

Conflicts of interest None.

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