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Original Article

Throwing enhances humeral shaft cortical bone properties in pre-pubertal baseball players: a 12-month longitudinal pilot study

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Abstract

Objectives: To explore throwing athletes as a prospective, within-subject controlled model for studying the response of the skeleton to exercise. **Methods:** Male pre-pubertal throwing athletes (n=12; age=10.3±0.6 yrs) had distal humerus cortical volumetric bone mineral density (Ct.vBMD), cortical bone mineral content (Ct.BMC), total area (Tt.Ar), cortical area (Ct.Ar), medullary area (Me.Ar), cortical thickness (Ct.Th) and polar moment of inertia (IP) assessed within their throwing (exercised) and nonthrowing (control) arms by peripheral quantitative computed tomography at baseline and 12 months. Throwing-to-nonthrowing arm percent differences (i.e. bilateral asymmetry) were compared over time. **Results:** Over 12 months, the throwing arm gained 4.3% (95% CI=1.1% to 7.5%), 2.9% (95% CI=0.3% to 5.4%), 3.9% (95% CI=0.7% to 7.0%), and 8.2% (95% CI=2.0% to 6.8%) more Ct.BMC, Ct.Ar, Tt.Ar, and I_p than the nonthrowing arm, respectively (all $p<0.05$). There was no significant effect of throwing on Ct.vBMD, Ct.Th and Me.Ar (all p=0.18-0.82). **Conclusion:** Throwing induced surface-specific cortical bone adaptation at the distal humeral diaphysis that contributed to a gain in estimated strength. These longitudinal pilot data support the utility of throwing athletes as a within-subject controlled model to explore factors influencing exercise-induced bone adaptation during the critical growing years.

Keywords: Bone, Exercise, Pre-puberty, Throwing, pQCT

Introduction

The skeleton is most responsive to exercise during growth[1], with exercise during this period increasing bone mass to reportedly prime the skeleton for the progressive bone loss and subsequent increased risk for osteoporotic fracture later in life[2,3]. However, we recently observed that the bone mass benefits of exercise performed when young do not persist lifelong[4]. In contrast, one-half and one-third of the bone size and strength benefits of exercise completed when young persisted throughout the lifespan, respectively. These data suggest exercise when young should be encouraged to optimize bone size for lifelong bone health, as opposed to the current paradigm of focussing on bone mass.

Numerous studies over recent decades have explored the skeletal benefits of exercise when young in an effort to identify appropriate types, dosages and timing of introduction of activities. Most studies focussed on bone mass accrual given the historical focus on exercise to enhance peak bone mass, with popular means of study including the performance of randomized controlled trials of forced exercise[5,6] and the longitudinal assessment of bone changes in individuals performing varying amounts of voluntary physical activity[7,8]. These approaches have provided useful data in terms of demonstrating the responsiveness of the skeleton to exercise-generated mechanical loads, particularly prior to and during the pubertal growth period. However, trials incorporating forced exercise have issues with adherence and the between-individual analysis approach used in most longitudinal observational studies does not fully control for the effects of skeletally relevant systemic factors (e.g. genetics, hormones,

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and nutrition). The latter factors are often used as covariates, but they ultimately increase data variability necessitating the study of large sample sizes.

A powerful and popular method of minimizing the influence of systemic factors when studying skeletal adaptation in response to exercise is to use a within-subject approach in individuals who perform unilateral dominant exercise. Comparing side-to-side differences (i.e. bilateral asymmetry) within individuals who unilaterally exercise enables the contralateral 'nonexercise' side to serve as an internal control for systemic factors, including growth-related factors. Systemic influences may modulate bone responses to exercise; however, these effects are considered small relative to the overall exercise effect.

Racquet sport players have developed as the most commonly used unilateral exercise model as they expose their dominant or racquet arm to repeated mechanical overload, which can be defined as loading beyond that experienced during habitual activities[9-18]. Studies utilizing racquet sport players as a model system have yielded important observations; however, studies have historically been cross-sectional providing a 'snap shot' at a single point in time of adaptation to past unilateral dominant exercise. Whether findings withstand more powerful longitudinal investigation remains relatively unknown as study designs assessing unilateral bone adaptation in racquet sport players over time have rarely been employed[19-21].

Throwing athletes may be a useful alternative population for studying the skeletal effects of mechanical loading during growth, with participation in baseball and fast-pitch softball in the United States and other countries being more ubiquitous with youth than racquet sport playing. Overhand throwing exposes the dominant upper extremity to repeated mechanical overload enabling the contralateral side to be used as an internal control site. The net result is more extreme bilateral asymmetry (i.e. greater effect size) within the humeral diaphysis compared to that observed in racquet sport players. For instance, we recently observed the humeral shaft within the throwing arm of Major/Minor League Baseball players had nearly double the estimated strength compared to within their nonthrowing arm[4].

The aim of the current pilot study was to further recent cross-sectional data by prospectively following male pre-pubertal throwing athletes over 12 months to explore the magnitude of gain in throwing-to-nonthrowing arm difference in bone mass, size and estimated strength. These data will be informative towards establishing throwing athletes as a useful model for longitudinally studying the gain in bone size and strength when young for lifelong bone health.

Materials and methods

Participants

This was a 12-month longitudinal study that recruited 12 male throwing athletes (i.e. baseball) aged 8-11 years with a sexual maturation rating of 1 or 2 for genital development at baseline (see 'questionnaires' section below). Subjects were assessed at 0 (baseline) and 12 months following enrollment into the study, and were included if they anticipated playing a minimum of 5 months in the upcoming year to ensure adequate exposure and adaptation to the mechanical forces associated with throwing. Participants were excluded if they had: 1) any condition that compromised their ability to comply with study procedures; 2) any known metabolic bone disease (i.e. osteomalacia or osteogenesis imperfecta) or developmental disease (i.e. cerebral palsy) which may influence bone health; 3) a history of taking pharmacological agents known to influence skeletal metabolism; 4) participated more than twice per month for no longer than 6 months in an athletic activity that primarily involves unilateral upper limb use (except baseball); 5) shoulder pain in the previous 12 months that required professional advice; 6) a history of a humerus fracture or stress fracture; 7) a fracture or stress fracture of any other upper extremity bone within the past 2 years, or; 8) a previous history of glenohumeral joint dislocation. The study was approved by the Institutional Review Board of Indiana University, and written informed assent was provided by all participants and written informed consent was provided by parent/guardians.

Anthropometry

Standing height (to nearest 0.1 cm) and weight (to nearest 0.1 kg) were measured using a wall mounted digital stadiometer and electronic balance scale, respectively. Body mass index (BMI, kg/m^2) was calculated as mass divided by height squared. Humeral length (to nearest 1 mm) was measured using a sliding anthropometer as the distance between the lateral border of the acromion and the radiohumeral joint line.

Questionnaires

Stage of sexual maturation was self-reported, with parental/guardian guidance, by using the 5 stage Tanner scale[22]. Subjects looked at 5 photographs and/or drawings of genital areas and circled the image most closely resembling themselves. Estimation of the calcium intake per day (mg/day) and hours per week participating in throwing activities were obtained from calcium and throwing questionnaires, respectively. Calcium intake data were analyzed using the University of Minnesota Nutrition Data System for Research software program (2014 version).

Dual-energy x-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) using an Discovery-W machine (Hologic, Inc., Waltham, MA) equipped with Apex v4.0 software was used to obtain whole-body lean mass (kg), fat mass (%), and bone mineral content (BMC, kg), and hip and spine areal bone mineral density (aBMD; g/cm^2). Scans were performed per the manufacturer's instructions with the subject lying supine on the padded table of the scanner.

Peripheral quantitative computed tomography

Bone health within the upper extremities was assessed using a Stratec XCT 3000 pQCT machine (Stratec Medizintechnik GmbH, Germany). Scans were performed on both the throwing and nonthrowing upper extremity at the distal humeral diaphysis. Subjects were positioned supine on a padded plinth/table with one upper extremity positioned in 90° shoulder abduction. The upper extremity was centered within the gantry of the pQCT machine and strapped down using stretchable Velcro straps in order to limit movement during the scans. A scout scan was performed to enable tomographic scan localization, and a tomographic slice (thickness=2.3 mm; voxel size=400 μm) was taken at 75% (distal humeral diaphysis) of humeral length from its distal end. This location was the site of maximal throwing-to-nonthrowing arm difference in our previous work[4]. The procedure was repeated on the contralateral side so that tomographic slices of the distal humeral diaphysis in both the throwing and nonthrowing arms were obtained.

Analyses were restricted to cortical bone due to the absence of trabecular bone at the distal humeral diaphysis. Cortical mode 1 (threshold, 710 mg/cm^3) was used to obtain total area (Tt.Ar, cm^2), and cortical volumetric bone mineral density (Ct.vBMD, mg/cm^3), bone mineral content (Ct.BMC, mg/mm), and area (Ct.Ar, cm^2). Medullary area (Me.Ar, cm^2) was derived as Tt.Ar minus Ct.Ar. Average cortical thickness (Ct.Th, mm) was obtained using a circular ring model by analyzing the slices using contour mode 1 (threshold, 710 mg/cm^3) to define the outer bone edge and peel mode 2 (threshold, 400 mg/cm^3) to separate the cortical and subcortical/medullary compartments.

Bone strength of the distal humeral diaphysis was estimated by the density-weighted minimum (I_{MIN}, cm^4) and maximum (I_{MAX}, cm^4) second moments of area, and polar moment of inertia (I_P, cm^4) obtained using cortical mode 2 (threshold= 400 mg/cm^3). I_{MIN} and I_{MAX} were estimated according to Gere and Timoshenko[23], and represent the distribution of bone material about the planes of least and most bending resistance, respectively. I_P was calculated as $I_{MAX} + I_{MIN}$, and estimates the ability of the humeral diaphysis to resist torsion[24].

Short term precision of pQCT measures was assessed in five adults with interim repositioning. Root mean square coefficients of variation (RMS-CVs) were <1.5% for bone density, mass, structure, and estimated strength measures, consistent with precision values reported for pQCT measures at the midshaft humerus[24].

To determine the region specificity of bone geometry adaptive responses associated with throwing, polar pericortical and endocortical radii at the distal humeral diaphysis were obtained for the throwing and nonthrowing arms. Stratec pQCT image files and data were opened in ImageJ (v1.45s; National Institutes of Health) and analyzed using the BoneJ plugin[25], as previously described[26]. Images were rotated to align the bones according to the I_{MAX} and I_{MIN} axes, and right-sided images were flipped to superimpose left-side images. Using a threshold value of 350 mg/cm^3 to locate bone tissue, the distance of the endocortical and pericortical surfaces from the centroid of the medullary cavity were measured in 36 10° polar sectors. Ct.Th within each sector was calculated as the pericortical minus endocortical radius.

Statistical analysis

Two-tailed analyses with a level of significance set at 0.05 were performed with IBM SPSS Statistics (v24; SPSS Inc., Chicago, IL). Demographic and anthropometric characteristics were compared between baseline and follow-up using paired sample t-tests. Throwing versus nonthrowing effects on humeral properties were assessed by calculating mean percent differences ([throwing arm - nonthrowing arm] / nonthrowing arm × 100%) and their 95% confidence intervals (CIs). 95% CIs not crossing 0% were considered statistically significant, as determined by single sample t-tests on the mean percent differences with a population mean of 0%. Throwing effects between baseline and follow-up were determined by comparing the percent difference values between the time periods using paired sample t-tests. This provided a single value for each subject indicating the amount of bone gain in the throwing upper extremity solely due to exercise and not due to growth.

To explore the regional-specificity of bone geometry adaptation associated with throwing, polar pericortical and endocortical radii and polar Ct.Th data in the throwing arm were assessed using two-way repeated measures ANOVA, with time (baseline vs. follow-up) and sector (1 through 36) as the repeated variables. Data in each sector were corrected *a priori* for baseline vs. follow-up differences observed in the nonthrowing arm to remove any regional differences attributable to growth. In the presence of a significant time x sector interaction, post-hoc paired t-tests were used to compare baseline vs. follow-up differences within each individual sector, with a false discovery rate threshold set at q=0.05 used to correct for multiple comparisons[27].

Results

Self-assessed stage of sexual maturity did not change between baseline and follow-up (χ^2=3.08; p=0.21; Table 1). Over the course of 12 months, participants gained 5.4% (95%CI=2.7% to 8.1%) in height, 17.8% (95%CI=10.9% to 24.7%) in mass and 14.8% (95%CI=10.2% to 19.4%) in whole body lean mass (all p<0.001; Table 1). Whole body BMC and spine aBMD were significantly greater following 12 months of throwing (all p<0.05; Table 1); however, hip aBMD showed no differences (p=0.21).

There was no throwing-to-nonthrowing arm differences at baseline or follow-up in Ct.vBMD (all p=0.19-0.57; Table 2). At baseline and follow-up the throwing arm had greater Ct.BMC than the nonthrowing arm (all p<0.001; Table 2). The extra mass was distributed on the pericortical and endocortical surfaces, with the throwing arm having greater Tt.Ar and smaller Me.Ar compared to

Table 1. Demographic and anthropometric charcteristics of throwers[a].

	Baseline	Follow-up
Demographics		
Age (yr)	10.3 ± 0.6	11.3 ± 0.6**
Tanner Stage (1/2/3)	6/6/0	3/7/2
Playing position (P/C/F)[c]	2/2/8	1/2/9
Preferred throwing arm (L:R)	1:11	-
Age starting competitive baseball (yr)	4.8 ± 1.1	-
Years competing (yr)	5.4 ± 1.8	6.8 ± 1.7**
Playing time (hr/wk)	8.9 ± 4.7	12.3 ± 3.6
Calcium intake (mg/day)	1581 ± 739	1299 ± 593
Whole-body anthropometry		
Height (m)	1.43 ± 0.05	1.51 ± 0.06***
Mass (kg)	38.3 ± 5.3	44.9 ± 6.1***
BMI (kg/m^2)	18.6 ± 2.4	19.8 ± 2.9
BMC (kg)[b]	0.93 ± 0.13	1.08 ± 0.15***
Lean mass (kg)[b]	23.9 ± 2.3	27.4 ± 2.9***
Fat mass (%)[b]	26.8 ± 6.4	27.9 ± 8.7
Regional anthropometry		
Spine aBMD (g/cm^2)[b]	0.66 ± 0.07	0.72 ± 0.08*
Hip aBMD (g/cm^2)[b]	0.80 ± 0.08	0.82 ± 0.10

*[a] Data indicate mean ± SD (except for frequencies). [b] Obtained via dual-energy x-ray absorptiometry. [c] Individuals were designated as a P, pitcher; C, catcher; F, fielder if they reported playing these positions as the most percentage of their playing time. *p<0.05, **p<0.01, ***p<0.001 (paired sample t-test: baseline vs. follow-up).*

Table 2. Baseline and follow-up pQCT derived cortical bone properties.

	Baseline			Follow-up		
	Nonthrowing[a]	Throwing[a]	% diff. (95% CI)[b]	Nonthrowing[a]	Throwing[a]	% diff. (95% CI)[b]
Ct.vBMD (mg/cm^3)	1138 ± 31.2	1132 ± 36.0	-0.5% (-1.3, 0.3%)	1148 ± 35.6	1147 ± 38.3	-0.1% (-0.6, 0.4%)
Ct.BMC (mg/mm)	137.1 ± 21.1	162.8 ± 20.4	19.6% (12.6, 26.5%)***	150.8 ± 20.7	185.9 ± 23.5	23.9% (16.9, 30.9%)***
Tt.Ar (cm^2)	195.0 ± 22.6	208.8 ± 23.5	7.2% (4.2, 10.1%)***	210.8 ± 26.5	231.6 ± 27.9	10.0% (6.7, 13.4%)***
Ct.Ar (cm^2)	120.5 ± 18.2	144.0 ± 19.6	20.2% (13.0, 27.5%)***	131.4 ± 18.3	162.3 ± 21.6	24.1% (17.0, 31.2%)***
Me.Ar (cm^2)	74.5 ± 14.0	64.8 ± 15.5	-13.3% (-20.7, -5.9%)***	79.4 ± 16.5	69.3 ± 15.0	-12.7% (-17.2, -8.2%)***
Ct.Th (mm)	3.0 ± 0.4	3.6 ± 0.5	21.0% (13.1, 29.0%)***	3.2 ± 0.4	3.9 ± 0.4	23.4% (16.7, 30.2%)***
I_{MIN} (cm^4)	0.23 ± 0.1	0.28 ± 0.1	21.7% (13.5, 29.9%)***	0.27 ± 0.1	0.34 ± 0.1	25.3% (17.4, 33.2%)***
I_{MAX} (cm^4)	0.33 ± 0.1	0.38 ± 0.1	15.7% (9.1, 22.4%)***	0.39 ± 0.1	0.49 ± 0.1	27.2% (17.0, 37.4%)***
I_P (cm^4)	0.56 ± 0.1	0.65 ± 0.1	18.1% (11.6, 24.3%)***	0.66 ± 0.2	0.82 ± 0.2	26.3% (17.3, 35.2%)***

*[a] Data are mean ± SD. [b] Mean percent differences between throwing and nonthrowing were assessed using single sample t-tests with a population mean of 0. Significance is indicated by: *p<0.05, **p<0.01, ***p<0.001.*

the nonthrowing arm (all $p<0.001$; Table 2). The larger Tt.Ar area and smaller Me.Ar at baseline and follow-up resulted in the throwing arm having greater Ct.Th than the nonthrowing arm (all $p<0.001$; Table 2). Overall, the mass and geometric property changes at baseline and follow-up resulted into the throwing arm having greater I_{MIN}, I_{MAX} and I_P than in the nonthrowing arm (all $p<0.001$; Table 2).

Over the course of 12 months, the non-throwing arm had gains in most properties (*data not shown*). However, the throwing arm had greater gains in mass, size and estimated strength than the nonthrowing arm, indicating a measureable benefit of throwing over above any growth-related changes

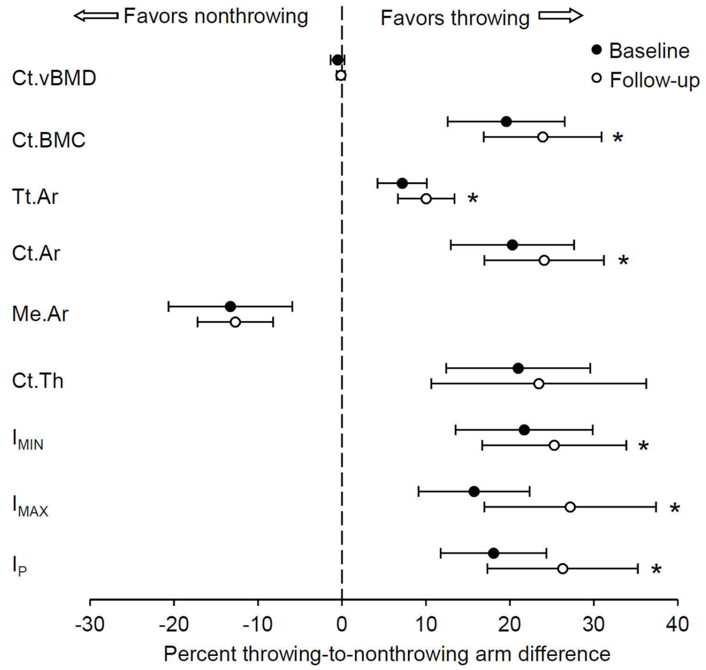

Figure 1. Effect of throwing for 12 months on pQCT measures of the distal humeral diaphysis. Data indicate the mean percent difference and 95%CI between throwing and nonthrowing arms at baseline and 12 months (follow-up). 95%Cis not crossing zero represent significant throwing-to-nonthrowing arm differences at either baseline or follow-up. *Indicates significant ($p<0.05$) follow-up vs. baseline throwing-to-nonthrowing arm differences.

(Figure 1). There was no significant effect of throwing on Ct.vBMD, Ct.Th and Me.Ar (all $p=0.18-0.82$). The throwing arm gained 4.3% (95% CI=1.1% to 7.5%) greater Ct.BMC than the nonthrowing arm over the course of 12 months ($p<0.05$). The new mass was distributed on the outer pericortical surface, as indicated by throwing-induced gains of 2.9% (95% CI=0.3% to 5.4%) and 3.9% (95% CI=0.7% to 7.0%) in Ct.Ar and Tt.Ar, respectively (all $p<0.05$). The gains in mass and size within the throwing arm over 12 months contributed to the throwing arm gaining 3.6% (95% CI=0.1% to 7.1%), 11.4% (95% CI=0.8% to 22.1%) and 8.2% (95% CI=2.0% to 6.8%) more I_{MIN}, I_{MAX} and I_P, respectively (all $p<0.05$).

There were region-specific bone structural changes in the nonthrowing arm due to growth, with increases in anterior, lateral and posterior pericortical radii and a reduction in posterior endocortical radii (Figure 2A). These surface-specific changes cumulated in growth-related increases in Ct.Th in similar anterior, lateral and posterior sectors (Figure 2B). In the throwing arm, there were gains in the anterior, medial, posterior and lateral pericortical radii and reductions in the posterior, medial and anterior endocortical radii (Figure 2C). The throwing arm exhibited gains in Ct.Th in lateral and posteromedial sectors (Figure 2D). After correcting throwing arm gains for those observed in the nonthrowing arm due to growth, increases were observed in the lateral and posterior pericortical radii and reductions in the anterior pericortical radii (Figure 2E). There were throwing-related gains in Ct.Th in lateral sectors in the throwing arm when corrected for gains observed in the non-throwing (Figure 2F).

Discussion

The findings from this prospective pilot study confirm that pre-pubertal throwing athletes have substantial throwing-to-nonthrowing arm differences (i.e. bilateral asymmetry) in humeral diaphyseal properties and show that throwing for a period of 12 months results in further and measurable bilateral asymmetry. The latter data suggest that throwing athletes can be used as a prospective within-subject controlled model to explore factors impacting the skeletal response to the mechanical loading associated with exercise. Factors of interest may include the influence of exercise dosage, pubertal status, nutrition, race, and omic-based factors, to name a few.

Participants had bilateral asymmetry at baseline consistent with a history of competing in overhand throwing activities[4,28-30]. The throwing arm had a 7% larger distal humerus diaphysis (Tt.Ar) with 20% more mass (Ct.BMC), a 13% smaller medullary cavity (Me.Ar) and 21% thicker cortex (Ct.Th) than the contralateral nonthrowing arm. There was no bilateral asymmetry in measures of vBMD as mechanical loading mostly results in the addition of new tissue to existing surfaces, as opposed to increasing the mineralization of existing volumes of tissue. The mass and structural

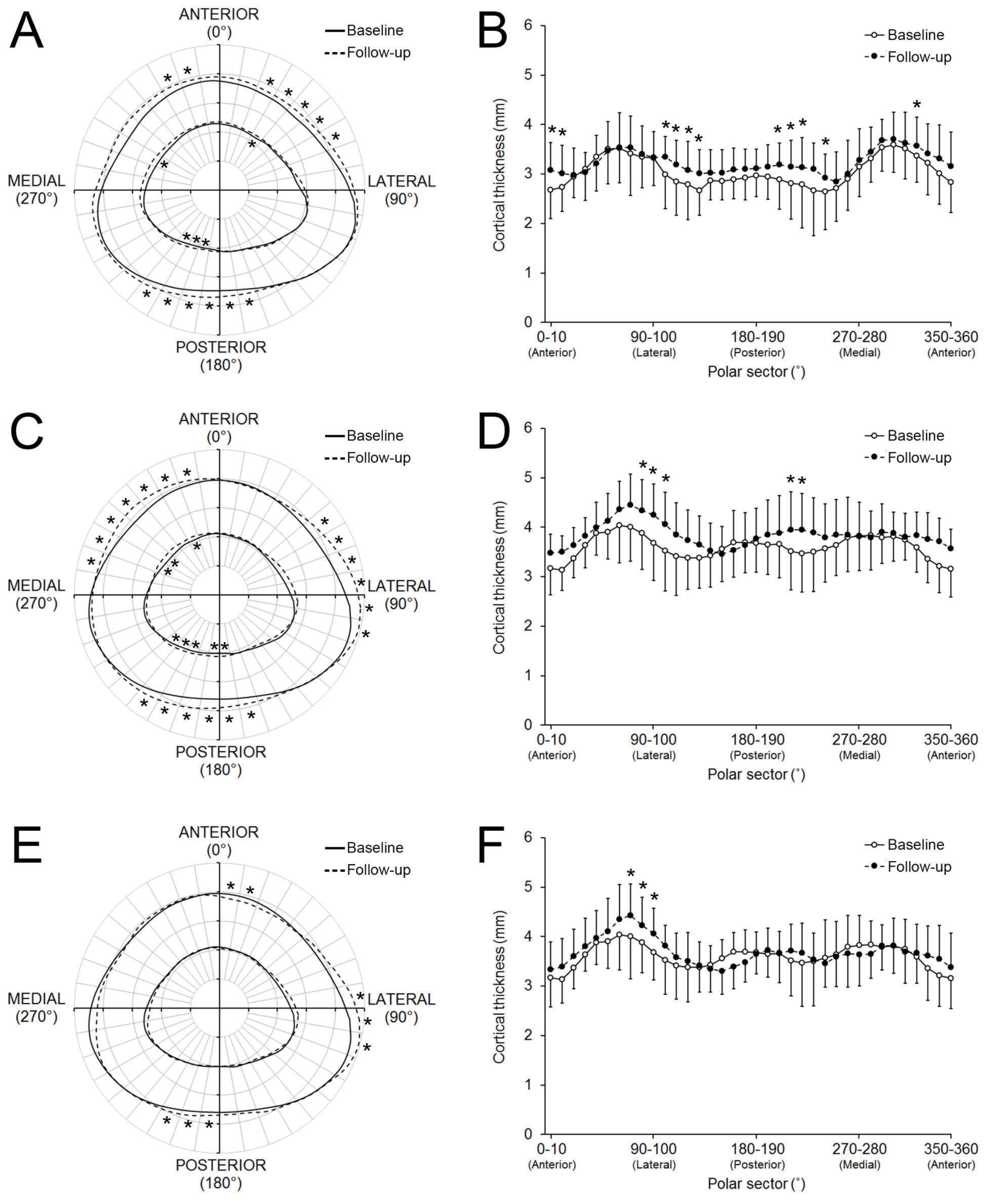

Figure 2. Changes between baseline and 12 month follow-up at the distal humeral diaphysis in regional bone geometry (pericortical and endocortical radii) and cortical thickness in 10° polar sectors in the nonthrowing (**A** and **B**) throwing arms (**C** and **D**). When corrected for changes in the nonthrowing arm, the throwing arm exhibited significant gains in pericortical radii in lateral and posterior polar sectors, and less gains in anterior polar sectors (**E**) over 12-months, and significant gains in cortical thickness in lateral sectors (**F**). *Indicates significant ($p<0.05$) within sector differences.

adaptations contributed to 18% greater bone strength (I_p) in the throwing arm, with I_p predicting 90% of the variance in humeral diaphyseal mechanical properties[24]. The bilateral asymmetry at baseline in throwers is not attributable to elevated habitual unilateral loading associated with simple arm dominance as we have previously shown pre-pubertal individuals who do not participate in a unilateral dominant upper extremity activity have <4% bilateral asymmetry within the humeral diaphysis between their dominant and nondominant upper extremities[30].

The magnitude of bilateral asymmetry at baseline in the current participants was larger than we previously observed at the midshaft humerus in a different cohort of prepubertal throwing athletes[30]. This can be attributed to the fact that the current study explored adaptation within the distal humeral diaphysis (75% of humeral length from its distal end) as opposed to at the midshaft humerus. The distal humeral diaphysis was chosen as the assessment site as we have previously shown it demonstrates greater bilateral asymmetry in overhand throwing athletes than any other humeral diaphyseal site[4]. Thus, it was anticipated that this site would provide the greatest potential for measurable adaptation over the 12-month observation period.

Participants had significant gains in bilateral symmetry over the study period, indicating that we could detect exercise induced changes over-and-above growth related changes over the 12-month study period. In particular, participants gained over 4% bilateral asymmetry in bone mass (Ct.BMC), which is more than the bilateral asymmetry due to a lifetime of habitual unilateral loading associated with simple arm dominance in pre-pubertal control individuals[30]. The extra bone mass was added to the outer periosteal surface and, in particular, the lateral and posterior pericortical surfaces. The pattern of adaptation matches the distribution of greatest estimated strains within the posterior and lateral surfaces of the distal humerus when throwing-related forces are applied to a non-adapted bone[4]. Periosteal adaptation on the lateral and posterior surfaces are in orthogonal planes and contributed to increases in the ability of the bone to resist bending in the planes of both maximal (I_{MAX}; mediolateral plane) and minimal (I_{MIN}; anteroposterior plane) bending resistance, as well as to resist torsional forces (I_P, which is determined by the summation of I_{MAX} and I_{MIN}).

The surface-specific apposition of new bone on the pericortical surface is functionally important for a couple of reasons. First, surface-specific accrual of new bone to the pericortical surface results in a disproportionate increase in bone strength for the gain in mass[31,32]. This occurs because bone mechanical properties are proportional to the fourth power of the distance of its material from mechanical axes. By adding bone distant from mechanical axes, the skeleton is able to meet the dual needs of being strong to resist injury, but lightweight to permit energy efficient locomotion. Second, addition of new bone to the pericortical surface has the potential to have lifelong benefits on bone health. Specific mechanisms exist for exercise-induced pericortical benefits to remain intact until senescence where they may have antifracture benefits even in the absence of any lasting benefits on bone mass. For instance, we recently observed that the bone mass benefits of exercise performed when young do not persist lifelong[4]. In contrast, one-half and one-third of the bone size and strength benefits of exercise completed when young persisted throughout the lifespan, respectively[4].

To our knowledge, only one previous study has used a longitudinal, within-subject controlled study design to investigate the surface-specific responses of cortical bone to enhanced loading[19]. Our data support those of Ducher et al.[19] who demonstrated that pre/peripubertal female tennis players had gains of 2.7% and 3.9% in Tt.Ar and Ct.Ar within the humeral diaphysis of their racquet arm compared to their contralateral non-racquet arm over a 12 month period, respectively. The cumulative data of both studies indicate that either racquet sport players or throwing athletes may be used as a within-subject controlled model to longitudinally explore influences on bone adaptation when young, with the advantage of throwing athletes being their prevalence in the United States and other countries.

There were a number of strengths of the current study, including its within-subject study design which allowed for correction of growth-related changes and longitudinal study design which allowed us to track the rate of bone adaptive changes due to exercise. However, our study also possessed a number of limitations. A relatively small sample size was studied; however, it was sufficient to achieve statistical significance which reduces concerns regarding the committing of a type II statistical error. A non-throwing control group was not included to further isolate the influence of side-to-side differences in due to habitual loading associated with simple arm dominance; however, the throwing-induced gain in bone mass and structure over the 12-month observation period exceeded that observed with a lifetime of simple arm dominance in prepubertal non-throwing individuals[30]. Finally, the data are limited to pre-pubertal males, with adaptive responses and their magnitude potentially differing in females and other maturation stages[33].

In summary, pre-pubertal baseball players followed for 12 months showed greater gains in bone mass, structure and estimated strength in their throwing arm relative to their nonthrowing arm. Specifically, throwing induced surface-specific cortical bone adaptations at the distal humeral diaphysis that contributed to a gain of 8.2% in estimated strength. These longitudinal pilot data support the utility of throwing athletes as a model to explore factors influencing exercise-induced bone adaptation during the critical growing years.

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References

1. MacKelvie K, Khan K, McKay H. Is there a critical period for bone response to weight-bearing exercise in children and adolescents? A systematic review. British journal of sports medicine 2002;36:250-7.
2. Rizzoli R, Bianchi ML, Garabédian M, McKay HA, Moreno LA. Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone 2010;46:294-305.

3. Weaver C, Gordon C, Janz K, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporosis International 2016;27:1281-386.
4. Warden SJ, Roosa SMM, Kersh ME, et al. Physical activity when young provides lifelong benefits to cortical bone size and strength in men. Proceedings of the National Academy of Sciences 2014;111:5337-42.
5. Fuchs RK, Bauer JJ, Snow CM. Jumping improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial. Journal of Bone and Mineral Research 2001;16:148-56.
6. MacKelvie KJ, McKay HA, Khan KM, Crocker PR. A school-based exercise intervention augments bone mineral accrual in early pubertal girls. The Journal of pediatrics 2001;139:501-8.
7. Bailey D, McKay H, Mirwald R, Crocker P, Faulkner R. A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the university of Saskatchewan bone mineral accrual study. Journal of Bone and Mineral Research 1999;14:1672-9.
8. Gabel L, Macdonald HM, Nettlefold L, McKay HA. Physical Activity, Sedentary Time, and Bone Strength From Childhood to Early Adulthood: A Mixed Longitudinal HR-pQCT study. Journal of Bone and Mineral Research 2017.
9. Bass SL, Saxon L, Daly R, et al. The effect of mechanical loading on the size and shape of bone in pre-, peri-, and postpubertal girls: a study in tennis players. Journal of Bone and Mineral Research 2002;17:2274-80.
10. Ducher G, Courteix D, Meme S, Magni C, Viala J, Benhamou C. Bone geometry in response to long-term tennis playing and its relationship with muscle volume: a quantitative magnetic resonance imaging study in tennis players. Bone 2005;37:457-66.
11. Ducher G, Daly RM, Bass SL. Effects of repetitive loading on bone mass and geometry in young male tennis players: a quantitative study using MRI. Journal of bone and mineral research 2009;24:1686-92.
12. Haapasalo H, Kannus P, Sievänen H, et al. Effect of long-term unilateral activity on bone mineral density of female junior tennis players. Journal of Bone and Mineral Research 1998;13:310-9.
13. Haapasalo H, Kontulainen S, Sievänen H, Kannus P, Järvinen M, Vuori I. Exercise-induced bone gain is due to enlargement in bone size without a change in volumetric bone density: a peripheral quantitative computed tomography study of the upper arms of male tennis players. Bone 2000;27:351-7.
14. Ireland A, Maden-Wilkinson T, Ganse B, Degens H, Rittweger J. Effects of age and starting age upon side asymmetry in the arms of veteran tennis players: a cross-sectional study. Osteoporosis International 2014; 25:1389-400.
15. Ireland A, Maden-Wilkinson T, McPhee J, et al. Upper limb muscle-bone asymmetries and bone adaptation in elite youth tennis players. Med Sci Sports Exerc 2013; 45:1749-58.
16. Jones HH, Priest JD, Hayes WC, Tichenor CC, Nagel DA. Humeral hypertrophy in response to exercise. J Bone Joint Surg Am 1977;59:204-8.
17. Kannus P, Haapasalo H, Sankelo M, et al. Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. Annals of Internal Medicine 1995;123:27-31.
18. Kannus P, Haapasalo H, Sievänen H, Oja P, Vuori I. The site-specific effects of long-term unilateral activity on bone mineral density and content. Bone 1994; 15:279-84.
19. Ducher G, Bass SL, Saxon L, Daly RM. Effects of repetitive loading on the growth-induced changes in bone mass and cortical bone geometry: A 12-month study in pre/peri- and postmenarcheal tennis players. Journal of bone and mineral research 2011;26:1321-9.
20. Gustavsson A, Thorsen K, Nordström P. A 3-year longitudinal study of the effect of physical activity on the accrual of bone mineral density in healthy adolescent males. Calcified tissue international 2003;73:108-14.
21. Kontulainen S, Kannus P, Haapasalo H, et al. Good maintenance of exercise-induced bone gain with decreased training of female tennis and squash players: a prospective 5-year follow-up study of young and old starters and controls. Journal of Bone and Mineral Research 2001;16:195-201.
22. Tanner JM. Growth at adolescence. 1962.
23. Gere J, Timoshenko S. Mechanics of Materials. 2nd. Boston (MA): PWS-Kent 1984:492.
24. Weatherholt AM, Avin KG, Hurd AL, et al. Peripheral quantitative computed tomography predicts humeral diaphysis torsional mechanical properties with good short-term precision. Journal of Clinical Densitometry 2015;18:551-9.
25. Doube M, Kłosowski MM, Arganda-Carreras I, et al. BoneJ: Free and extensible bone image analysis in ImageJ. Bone 2010;47:1076-9.
26. Rantalainen T, Nikander R, Heinonen A, Daly R, Sievänen H. An open source approach for regional cortical bone mineral density analysis. Journal of Musculoskeletal & Neuronal Interactions 2011;11:243-8.
27. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: a practical and powerful approach to multiple testing. J Roy Statist Soc Ser B 1995;57:289-300.
28. Bogenschutz ED, Smith HD, Warden SJ. Mid-humerus adaptation in fast pitch softballers and the impact of throwing mechanics. Medicine and science in sports and exercise 2011;43:1698.
29. Warden SJ, Bogenschutz ED, Smith HD, Gutierrez AR. Throwing induces substantial torsional adaptation within the midshaft humerus of male baseball players. Bone 2009;45:931-41.
30. Warden S, Weatherholt A, Gudeman A, Mitchell D, Thompson W, Fuchs R. Progressive skeletal benefits of physical activity when young as assessed at the midshaft

humerus in male baseball players. Osteoporosis International 2017:1-11.

31. Robling AG, Hinant FM, Burr DB, Turner CH. Improved bone structure and strength after long-term mechanical loading is greatest if loading is separated into short bouts. Journal of Bone and Mineral Research 2002;17:1545-54.
32. Warden SJ, Hurst JA, Sanders MS, Turner CH, Burr DB, Li J. Bone adaptation to a mechanical loading program significantly increases skeletal fatigue resistance. Journal of Bone and Mineral Pesearch 2005;20:809-16.
33. Burghardt AJ, Kazakia GJ, Ramachandran S, Link TM, Majumdar S. Age- and gender-related differences in the geometric properties and biomechanical significance of intracortical porosity in the distal radius and tibia. Journal of Bone and Mineral Research 2010;25:983-93.