Sex differences in cortical bone of humeral head region

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Research

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Abstract

Background Proximal humerus fractures are highly related to age, and are particularly high in women. The goal of this study was to investigate sex-related similarities and differences in humeral head structure. **Methods** Computed tomography (CT) scans of 147 healthy subjects (76 men /71 women) spanning a wide range of ages (20-88 years) were analyzed. Three groups of subjects were identified according to age: group A (aged 20-39 years), group B (aged 40-59 years), and group C (aged > 60 years). For each subject, cortical bone mapping (CBM) was applied to create color 3D thickness map for the proximal humerus. Regions of interest (ROI) were defined in three walls of humeral head which corresponded to the anterior, lateral and posterior aspects. Cortical parameters, including the cortical thickness (CTh), cortical mass surface density (CM), and the endocortical trabecular density (ECTD) were measured using CBM. **Results** In both sexes, the CTh value of proximal ROIs in lateral and anterior wall tended to decrease with age. No significant difference was detected between three age groups for each parameter in the posterior wall in men and women. In ROIs 1-9, the ECTD tended to show a notable decline with age in women. In contrast, the ECTD remained unchanged in men. When pooled across all decades, the CTh, CM and ECTD values of ROI 1-9 were approximately equivalent between men and women. **Conclusions** There was no sex difference in cortical bone parameters in the humeral head region. However, the endocortical trabecular density decreased significantly with age only in women.

Introduction

Proximal humerus fractures are the third frequent fragility fracture type in elderly patients, after wrist and hip fractures [1–3]. Although proximal humerus fractures recently increasing and associated with excessive mortality [3], the structural basis of the fracture remains unclear. Previous studies have concentrated on age-related changes of trabecular microstructure [4, 5]. However, cortical bone makes up approximately 80% of the skeletal mass of an adult, particularly at appendicular sites where the cortex accounts for the majority of axial load transfer [6, 7]. In the femoral neck, complete removal of trabecular bone leads to an only 7% reduction in load needed to fracture [7]. Recent studies on radius, femur and humerus had found the vast majority of bone loss is cortical, not trabecular, and occurs age over 65 years by intracortical remodeling [8, 9]. Marked thinning and high porosity of femoral neck cortex with advancing age had been shown to result in increased fracture incidence [10–13]. Structural property of cortical bone is a key element of bone strength, although trabecular bone may be the first site to display obvious microarchitectural weakness [8–13].

Similar to other primarily osteoporotic fractures, women have higher risk of low-energy fractures of the proximal humerus than men. It has been postulated that the sexual dimorphism was associated with smaller bone size, lower bone mass or to the greater bone loss in women [12, 13]. There is steadily increasing evidence that focal weaknesses of cortical bone are linked to hip fracture [15–20]. Cortical thinning in superior surface of the mid-femoral neck was important in determining resistance to femoral neck fracture [13–15]. Focal differences in cortical bone properties were related to several factors, including age [14, 15], drug treatment [17, 18] and exercise regimes [19, 20]. Meanwhile, superior femoral neck geometry between genders was significantly different [13, 21]. The cortical thickness of superior region in femoral neck was 27.4% lower in Chinese women, compared to men [21]. In a longitudinal study, the elderly women had found to lost thickness, total volumetric bone mineral density (vBMD) and cortical vBMD more rapidly than elderly men over a median follow-up of 5.1 years, especially in the superior region of femoral neck [13]. Those finding suggested that sex might play a significant role in the relationship between spatial bone properties and hip fracture susceptibility.

We previously found that cortical bone distribution is asymmetric in the humeral head region [22]. However, no data are available for sex differences in the spatial distribution of cortical bone in proximal humerus, one of most common site of osteoporotic fracture. The aim of this study was to examine sex-related similarities and difference of specific regions of the humeral head region using cortical bone mapping (CBM).

Materials And Methods

Subjects and study design

Our analytical sample included 147 healthy subjects, with the goal of studying sex-related variations in cortical bone of humeral head region in the dominant upper extremity. Data were acquired as part of the aging and osteoporotic proximal humerus fracture Study, a single-center prospective ongoing population study of Chinese men and women. The early part of study has been reported [22]. The subjects consisted of 71 men and 76 women, with range from 20 to 88 years (mean, 49.79 years). Arm dominance was determined as the arm with which subjects would throw a ball. Subjects with a history of or evidence of metabolic bone disease, as well as those receiving chronic treatment that may affect bone metabolism were excluded from the study. Three groups of volunteers were identified according to age: group A (aged 20-39 years), group B (aged 40-59 years), and group C (aged > 60 years). There were 24 men and 22 women in group A, with average age of 29.35 years (range, 20-39 years). Group B consisted of 27 men and 22 women, with average age of 49.67 years (range, 40-59 years). Group C consisted of 20 men and 32 women, with average age of 67.98 years (range, 60-88 years). For this study, no DXA screening was performed prior to enrollment; therefore, no bone mineral density (BMD) inclusion/exclusion criteria were used. Written informed consent was obtained from all participants and the study was approved by the Institutional Review Board of Tianjin Hospital.

Cortical bone mapping

CT scans of the proximal humerus were performed with a GE Light Speed VCT (GE, Milwaukee, WI, USA). Scan parameters for CT scanners were 120 kVp, mA Auto, 5mm slice thickness, 50 cm field of view, and 512×512 matrix in spiral and standard reconstructions. CT values of pixels were recorded in Hounsfield units (HU). Subjects were positioned in supine with their arms in neutral position and centered within the gantry of the machine. Each image was analyzed from the slice that included the top of acromion to the slice that included the inferior angle of scapula. The entire CT scanning was performed by Dr. Jian Li. HU values were automatically corrected for HU values below the water equivalent of the European Forearm Phantom (EFP) by adjusting the histogram.

The cortical parameter measurement and mapping technique has been previously described [14, 15]. Cortical thickness measurement was performed using CBM, implemented by a freely available in-house program called Stradwin (<http://mi.eng.cam.ac.uk/~rwp/stradwin/>). First, an approximate segmentation of each proximal humerus from the CT data was performed using Stradwin, and results in a triangulated surface mesh with $\sim 10^4$ vertices distributed uniformly over the proximal humerus surface. Secondly, the CT data was sampled at each vertex of the mesh using 18 mm lines perpendicular to and passing through the humeral cortex and trabeculae. Finally, a model that accounts for the imaging blur was fitted to the data samples. This validated model-based deconvolution process allows the measurement of much smaller features than would normally be visible in the CT data. This process was repeated at all vertices. As a result, color maps on the proximal humerus were created for accurately estimating the cortical thickness (CTh, mm) and cortical mass surface density (CM, the cortical mass per unit cortical surface area, HUmm), as well as endocortical trabecular density (ECTD, HU). ECTD is the average trabecular density immediately adjacent to the cortex, to a depth of about 8 mm, excluding any effects due to blurring of the endocortical edge.

Definition of the regions of interest for cortical bone distribution assessment

For the evaluation of the bone morphometric analysis, specific regions of interest (ROIs) were defined within the proximal end of the humerus. The specific methodology has been described in detail previously and will be briefly outlined here [22]. The cortical bone in humeral head region was defined as anterior, lateral and posterior wall. In anatomical perspective, the anterior wall is equivalent to the less tuberosity. The lateral and posterior part of greater tuberosity corresponds to lateral and posterior wall. After creation of a single 3D thickness map, the humeral head

height was determined by measuring the distance between the highest point of the humeral head and the most distal margin of the articular surface (Fig. 1). The height of humeral head was then quartered by parallel plane 1-3. In each slice, to obtain more details of cortical bone tissue, the longest line (Line 1) between the joint surface and greater tuberosity was drawn; this line was divided into a medial and a lateral segment by line 2 (Fig.2). The intersection of the above two lines with cortical shell in each plane was the measurement point (ROI 1-9) (Fig.3).

Statistical Analysis

The age group difference within the same gender was compared using one-way ANOVA for normally distributed values and Kruskal-Wallis Test for non-normally distributed values. Gender and age differences were evaluated using generalized linear models (GLMs). Correlation between cortical parameters and age in ROI 1-9 was studied by linear regression analysis. All statistical analysis was performed using IBM SPSS Statistics for Windows version 20.0 (IBM SPSS Inc., Chicago, IL). Significance level was set at $P < 0.05$ for all statistical tests.

Results

In the lateral wall, the CTh and CM value of ROI 1-3 tended to decrease with age in men, whereas the age-related decrement was seen only in ROI 1 in women. In the anterior wall, the CTh of ROI4 appeared to have a significantly negative association with age in both sexes, whereas no significant relationship was observed in ROI5-6. In the posterior wall, no statistically significant difference was detected between three age groups for each parameter in both sexes (Table.1).

In ROI1-9, the ECTD tended to show a notable decline with age in women, although the value in ROI 4 and 8 didn't reach the significant level. But in contrast, the ECTD remained unchanged in men (Table.1).

When pooled across all decades, the CTh, CM and ECTD values of ROI 1-9 were approximately equivalent between men and women. Moreover, cortical parameters in ROIs tended to decline with age, except the CTh and CM in ROI7-9, ECTD in ROI4 (Tab.2, Fig. 4). We also found that age-sex interaction was not significant in cortical parameters of ROIs in regression models (Tab.2).

Discussion

This study presented the sex differences in cortical thickness, cortical mass surface density and endocortical trabecular density in specific regions of the humeral head region measured in a Chinese cohort by CBM technique. Our principal findings are (1) cortical parameters in ROIs were approximately equivalent between men and women. (2) the endocortical trabecular density in ROIs was found to decrease with age in women, but not men; (3) the CTh of proximal ROIs of lateral and anterior wall was significantly associated with age in both sexes; (4) CTh and CM value of cortex in posterior wall didn't change with advancing age in both men and women.

Cortical bone is integral to the mechanical strength of bone, with good correlation between bone density and compressive strength [7, 8, 22]. Our early regional analysis revealed that cortical structure of the humeral head region varied dramatically in cross-section, with focal cortical thinning in the posterior wall [22]. Fractures occur when mechanical stress is disproportionately concentrated on a portion of the bone relative to the surrounding area. Majed found that simple head split or three-part fracture pattern emanated from the greater tuberosity in a biomechanical testing [23]. Hasan analyzed the common location and orientation of the proximal humeral fracture lines using three dimension computed tomography. They found that fractures frequently split the greater tuberosity and were closely related to the intervals of the rotator cuff attachments [24]. Combined with these data, we believed that cortical thinning in the posterior wall may be the starting point for a cascade of changes that ultimately culminate in proximal humeral

fractures. Previous studies had mainly focused on identify spatial differences in proximal femoral vBMD and cortical bone properties [13, 21]. The thumbnail-sized patches of cortical thinning in the superior femoral neck were found to be associated with femoral neck fracture in vivo. Substantially thinned cortex was more pronounced in majority of elderly women, compared to men [12, 13, 25]. However, no sex difference was detected in the posterior wall regarding cortical parameters in our study. A possible explanation for this discrepancy is that mechanical environment of the humeral head is different from that of femoral neck.

Noticeably, our results indicated the endocortical trabecular density appeared to be negatively associated with age in women while the ECTD remained unchanged in men. These findings were in agreement with earlier histomorphometric analysis [4]. The pronounced decrease of density of trabecular bone adjacent to cortical bone in posterior wall points to a structural weakness, which can partly explain the higher incidence of fractures of the proximal humerus in women.

Age, osteoporosis, inactivity or pathology of the shoulder joint may influence cortical bone quality. Proximal humerus fragility in old age is usually attributed to age-related bone loss [4, 9]. However little is known about the cortical changes in specific regions of the humeral head. In this study, we found that the CTh of proximal ROIs of lateral and anterior wall was significantly associated with age in men and women, but not cortex in posterior wall. The results showed significant location-dependence in bone loss with aging. Anatomically, the supraspinatus, infraspinatus, and teres minor muscles attach to the greater tuberosity and the subscapularis tendon attaches to the lesser tuberosity. Our results lead to the conclusion that age-related bone loss of proximal portion of lateral and anterior wall is not entirely prevented by routine rotator cuff activity.

Our study has several limitations. The most obvious limitation is the cross-sectional nature of the study which limits the ability to reflect age-related changes in bone geometry. A longitudinal study or randomized controlled trial (RCT) is needed to predict changes in proximal humerus bone health. Second, we have evaluated age- and gender-related cortical bone effects in Chinese cohort. The current data are not directly translatable to individuals of other racial or ethnic backgrounds since previous data suggesting structural differences of the proximal femur between Asian and other ethnicities [16, 21, 26]. Finally, microarchitectural changes of cortical bone in humeral head region could not been analyzed in the study. Some authors recently reported that cortical porosity and thickness has significant impact on bone loss and mechanical stability [8, 9, 11]. So our data were limited in predicting the risk of proximal humeral fractures.

Perspectives And Significance Section

In this study, no sex difference was found in cortical bone parameters in the humeral head region. However, the endocortical trabecular bone decreased significantly with age only in women. Cortical thickness in proximal ROIs of lateral and anterior wall, as measured by CBM, exhibits significant age-related decrease in both sexes. Obvious reduction of ECTD value in posterior wall with aging in women may contribute materially to greater risk of proximal humerus fracture in elderly women than men.

Ethics Approval And Consent To Participate

Institutional Review Board (IRB) approval was obtained from the ethics committee of Tianjin Hospital, and signed informed consent form was obtained from the participants prior to participation. All the participants were admitted to Tianjin hospital due to shoulder trauma. CT examination was performed in the emergency department to exclude minor fractures.

Declarations

Availability of data and materials

The datasets generated and analyzed during the current study are available in the tables as provided in this manuscript. Any additional information on the data can be requested from the corresponding author.

Author contributions

Yeming wang designed the study and prepared the first draft of the paper. He is guarantor. Jian li and Jianhua Yang contributed to the experimental work. Jingming dong was responsible for statistical analysis of the data. All authors revised the paper critically for intellectual content and approved the final version. All authors agree to be accountable for the work and to ensure that any questions relating to the accuracy and integrity of the paper are investigated and properly resolved.

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Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics and measurement parameters of the subjects

Group	Male				Female			
	Group A	Group B (n=27)	Group C (n=20)	P	Group A (n=22)	Group B (n=22)	Group C (n=32)	P
	(n=24)			value				value
Plane 1								
CTh(mm)								
ROI1	5.28±1.52	3.93±2.34	2.81±1.52	0.00	5.58±1.40	3.82±1.98	3.36±1.67	0.00
ROI4	4.94±1.91	3.68±2.13	3.34±1.75	0.02	4.76±1.48	3.58±1.71	3.67±1.52	0.02
ROI7	2.56±0.87	2.30±1.13	2.28±1.59	0.68	2.69±1.01	2.79±1.48	2.77±1.25	0.96
CM(HUmm)								
ROI1	58965.03±16602.73	45330.56±28202.34	38253.51±20736.39	0.01	62353.77±16700.97	42498.57±22765.58	37079.39±20020.55	0.00
ROI4	55793.20±22459.91	42561.87±25750.87	35146.66±19679.23	0.01	52075.73±20049.62	40484.42±20032.37	40563.67±17870.26	0.07
ROI7	28258.22±9688.71	26856.47±13368.73	26704.28±17011.34	0.91	29537.38±14167.54	31987.52±16672.55	31031.23±15251.93	0.87
ECTD(HU)								
ROI1	10113.21±45.83	10088.15±64.49	10090.40±89.75	0.37	10108.82±40.04	10106.59±71.00	9998.16±250.42	0.03
ROI4	10120.38±35.10	10093.18±60.17	10153.69±274.09	0.40	10165.91±246.88	10088.99±61.99	10020.65±248.07	0.05
ROI7	10119.22±73.82	10105.79±50.00	10094.85±95.49	0.54	10128.64±74.39	10113.13±69.72	10009.22±232.36	0.01
Plane 2								
CTh(mm)								
ROI2	3.98±1.57	2.93±1.82	2.26±1.41	0.00	3.37±1.39	2.56±1.41	2.67±1.52	0.13
ROI5	4.57±1.90	3.59±2.02	3.44±2.17	0.13	4.17±1.57	3.63±1.76	3.41±1.64	0.26
ROI8	2.53±1.10	1.87±1.12	1.82±1.13	0.08	2.34±0.82	2.14±0.87	2.17±0.89	0.70
CM(HUmm)								
ROI2	45072.51±18622.35	34116.59±21765.01	25207.57±15539.30	0.00	38629.34±16626.21	30269.01± 20060.41	30129.44±17700.39	0.19
ROI5	50785.69±22734.68	41320.42±24009.80	36474.76±22527.39	0.12	47050.19±19149.40	40106.79±19605.90	38498.38±19928.54	0.28
ROI8	28719.83±12628.67	23596.45±14638.41	20986.59±11807.83	0.15	25874.30±10139.09	24294.59±10614.09	24319.83±10200.56	0.87
ECTD(HU)								
ROI2	10105.91±46.63	10074.85±57.94	9982.63±317.29	0.06	10088.40±48.23	10065.63±53.47	9960.20±243.91	0.01
ROI5	10103.45±43.71	10156.04±370.54	10064.48±116.10	0.42	10108.75±61.17	10089.88±62.69	9981.76±240.30	0.01
ROI8	10107.25±44.71	10096.96±56.27	10078.78±86.48	0.18	10091.34±67.28	10083.61±66.69	9989.18±250.20	0.05
Plane3								

CTh(mm)								
ROI3	3.69±1.31	2.82±1.69	2.08±0.97	0.00	3.13±1.14	2.69±1.38	2.38±1.09	0.08
ROI6	4.72±1.68	3.71±1.96	3.49±1.83	0.06	4.24±1.63	3.54±1.51	3.64±1.88	0.34
ROI9	3.29±1.26	2.72±1.42	2.58±1.29	0.17	2.99±1.22	2.58±1.29	2.83±1.18	0.53
CM(HUmm)								
ROI3	41790.40±15471.57	32862.49±20578.13	24862.73±10739.48	0.00	35604.43±14371.72	31621.87±18161.02	26528.42±12281.51	0.09
ROI6	53290.22±19443.60	23397.49±4502.85	38670.51±19337.23	0.06	48604.97±19449.13	40300.30±18599.93	40824.80± 21714.83	0.29
ROI9	37731.15±14605.35	33475.45±20018.34	29646.70±14463.99	0.29	35324.39±16020.84	30706.82±17079.09	32423.41± 14189.31	0.61
ECTD(HU)								
ROI3	10086.04±39.89	10057.58±54.61	10044.79±82.99	0.07	10068.39±58.19	10047.57±58.34	9937.55±246.79	0.01
ROI6	10113.24±50.95	10082.69±47.92	9991.84±300.19	0.04	10115.75±56.63	10110.37±97.19	9977.78±240.26	0.00
ROI9	10108.43±44.78	10080.32±45.46	10021.71±248.46	0.11	10093.13±62.88	10071.81±67.24	9958.12±251.95	0.01

The values are given as the mean and the standard deviation. CTh cortical thickness, CM cortical mass surface density, ECTD the endocortical trabecular density.

Table 2 Sex-related differences in variables of ROIs of the subjects

Variables	Male	Female	Age (p value)	Sex (p value)	Sex × age interaction (p value)
CTh(mm)					
ROI1	4.07±2.09	4.14±1.92	0.00	0.40	0.64
ROI2	3.09±1.75	2.84±1.48	0.00	0.47	0.25
ROI3	2.91±1.51	2.68±1.22	0.00	0.54	0.28
ROI4	4.01±2.05	3.96±1.62	0.00	0.97	0.75
ROI5	3.88±2.06	3.69±1.67	0.03	0.67	0.83
ROI6	3.98±1.89	3.78±1.71	0.02	0.57	0.69
ROI7	2.38±1.19	2.75±1.25	0.92	0.07	0.72
ROI8	2.12±1.14	2.21±0.86	0.07	0.51	0.40
ROI9	2.87±1.34	2.81±1.22	0.13	0.78	0.55
CM(HUmm)					
ROI1	47945.85±23954.49	45964.37±22469.68	0.00	0.95	0.77
ROI2	35310.42±20440.76	32630.34±18287.64	0.00	0.57	0.30
ROI3	33626.92±17670.90	30360.11±15074.93	0.00	0.46	0.47
ROI4	44945.64±24230.78	43873.17±19613.61	0.00	0.97	0.53
ROI5	43154.97±23573.34	41439.50±19695.31	0.03	0.79	0.81
ROI6	45214.40±21581.01	42925.13±20274.38	0.02	0.62	0.71
ROI7	27287.43±13276.51	30875.63±15201.40	0.98	0.14	0.79
ROI8	24593.13±13408.00	24762.50±10190.55	0.15	0.84	0.44
ROI9	333835.47±16911.09	32771.47±15491.99	0.22	0.77	0.64
ECTD(HU)					
ROI1	10097.25±67.48	10061.58±175.35	0.03	0.23	0.09
ROI2	10059.37±178.34	10027.83±171.73	0.00	0.56	0.98
ROI3	10063.60±61.54	10007.28±175.28	0.00	0.04	0.11
ROI4	10119.42±150.80	10082.48±217.40	0.27	0.32	0.05
ROI5	10112.47±238.12	10049.82±171.71	0.04	0.16	0.54
ROI6	10067.34±169.14	10056.11±178.68	0.00	0.85	0.82
ROI7	10107.25±72.71	10073.87±168.35	0.02	0.28	0.11
ROI8	10079.98±63.74	10046.08±175.45	0.03	0.27	0.29
ROI9	10073.31±139.22	10030.12±180.27	0.00	0.26	0.64

The values are given as the mean and the standard deviation. CTh cortical thickness , CM cortical mass surface density, ECTD the endocortical trabecular density.

Figures

Figure 1

Region of investigation. The humeral head height (H) was the distance between the highest point of the humeral head and the most distal margin of the articular surface. In the humeral head region (HHR), cortical parameters were determined at 3 different planes.

Figure 2

Locations of the measuring points in the humeral head region. Line 1, Longest diameter between articular surface and greater tuberosity. Line 2, Vertical bisection of line 1.

Figure 3

Placement of the regions of interest Nine regions of interest (ROI) were defined in the humeral head region. (A) Anterior view (B) Posterior view.

Figure 4

Age-related changes in cortical thickness (CTh) at the ROI 1-3. Men are shown with open circles and dashed fit-lines, while women are shown with open boxes and solid fit-lines.