Assessment of the Bone Mineral Density and Microstructure of the Human Femoral Head according to Different Tip-apex Distances Can Guide the Treatment of Intertrochanteric Hip Fractures

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Purpose: We analyzed the microstructure and bone mineral density (BMD) of the trabecular bone in the femoral head of patients with osteoporosis.

Materials and Methods: Sixteen femoral heads with osteoporotic femoral neck fractures underwent microcomputed tomography scanning. In each tip-apex distance (TAD) of 15, 20, and 25 mm, five regions of interest (ROIs) were extracted from the central, anterior, posterior, superior, and inferior sections. A total of 15 ROIs were extracted from TADs of 15, 20, and 25 mm. The measurement parameters included BMD, percent bone volume: bone volume/total volume (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), structural model index (SMI), and degree of anisotropy (DOA).

Results: The lowest BMD and BV/TV values were observed in the inferior region and differed significantly from those in other regions (P<0.05). Lower Tb.Th and Tb.N values were observed in the inferior region compared with those in the central region (P<0.05). The highest SMI value was observed in the inferior region (P<0.05). With TAD of 15 and 20 mm, the DOA values in the inferior region were lower than those in the anterior region (P<0.05). Lower BMD and BV/TV values were observed in the anterior regions of TAD of 15 mm compared with those in the corresponding regions of TAD of 25 mm (P<0.05).

Conclusion: Positioning the lag screw between TAD of 20 to 25 mm and in the inferior region is recommended, and TAD of less than 15 mm is not recommended.

Key Words: Osteoporosis, Femur head, Microarchitecture, Micro-computed tomography, Bone density

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INTRODUCTION

As the population ages, the incidence of hip fractures in the elderly is increasing, and intertrochanteric fractures account for more than half of hip fractures¹). A lag screw or dynamic hip screw is generally used for fixation in the surgical treatment of intertrochanteric fractures, and the position of the screw in the femoral head is an important factor in predicting fixation failure²). In order to reduce the occurrence of fixation failure, the concept of tip-apex distance (TAD) has been introduced³), and many studies have shown that it is an important predictor of fixation failure³⁻⁵).

TAD represents the distance from the tip of the screw to the apex of the femoral head as measured on the anteroposterior (AP) and lateral views. According to the most widely used guidelines at present, some studies report that TAD less than 25 mm is recommended⁶⁻⁸⁾. The results of many retrospective studies have not been in uniform agreement on the optimal position of screws, and there is no persuasive basis to explain the correlation between these specific screw positions and a good prognosis9-12). In addition, some studies have reported a positive correlation between bone microarchitecture around screws and the pullout resistance of screws¹³⁾. Most studies on the optimal position of the lag screw in the femoral head are finite element modeling. The optimal position of the lag screw is rarely proposed according to the heterogeneity of the bone microarchitecture region in the femoral head of osteoporotic patients, and no study on the optimal position of the lag screw through bone microarchitecture and bone mineral density (BMD) analysis has been reported.

Therefore, the purpose of this study was to analyze the microarchitecture and BMD of the femoral head in osteoporotic patients using micro-computed tomography (CT) images and to investigate the optimal position of the femoral head lag screw.

MATERIALS AND METHODS

The study was approved by the institutional review board (IRB) of our institution (AJIRB-BMR-KSP-21-516), and all patients provided informed consent to participate. The study protocol complied with the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

Sixteen femoral head specimens were collected from elderly patients with low-energy femoral neck fractures between October 2018 and December 2019 at our institution. The average age of patients was 79.1 years (range, 68 to 85 years), with a male:female ratio of 5:11. All patients underwent artificial hip replacement.

All specimens were immersed in 70% alcohol for two weeks and then scanned by micro-CT (Skyscan 1173; Bruker, Kontich, Belgium). Shadow-projection images were taken at 0.3° steps for a full 360° stage rotation. The pixel resolution was 29.83 µm. A random motion of 5 was used, and four frames were averaged at each step to reduce signal noise. An aluminum filter (1.0 mm) was used to reduce beam hardening, with voltage of 80 kV, current of $120 \,\mu$ A. Scanning time for each specimen was approximately 40 minutes. The images were reconstructed into axial slices using NRecon (ver. 1.7; Skyscan). Imaging data were subsequently transferred to a workstation for analysis. First, the femoral head fovea capitis was identified based on the anatomical landmarks on the DataViewer (ver. 1.5: Skyscan) software. The femoral head was rotated so that the fovea was adjusted to the medial. In the coronal image, the center of the femoral head and the center of the femoral neck were connected to form the Y-axis, and in the sagittal image, the center of the femoral head and the center of the femoral neck were connected to form the Z-axis (Fig. 1). The axial image was saved. Further processing and analysis were performed using the software package CTAn (ver. 1.16; Skyscan). In order to establish the reliability of each parameter, using this software, the regions of interest (ROIs) of different TADs in 3D coordinates were manually input by an experienced orthopedic surgeon (Q.H.S.); the software's automatic threshold function, as well as the software program, were used in automatic measurement of each parameter. The measurement parameters included BMD, percent bone volume: bone volume/total volume (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), structural model index (SMI), and degree of anisotropy (DOA). SMI was used to evaluate whether the trabecular bone was rod-like or plate-like, with a smaller value indicating that it was closer to a plate-like structure.

In each TAD of 15, 20, and 25 mm, five ROIs were extracted from the central, anterior, posterior, superior, and inferior sections. Each ROI was a cuboid measuring 5 mm \times 5 mm \times 10 mm. A total of 15 ROIs were extracted from TADs of 15, 20, and 25 mm (Fig. 2). The size of ROIs was chosen for two reasons: 1) The tip of the most used lag screw has a thread length of 10 mm, so that the ROIs length was 10 mm. 2) The square with a width and height of 5 mm was to meet the continuous assumption of three-dimensional morphology analysis of bone¹⁴). When

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Fig. 1. Definition of the coordinates. The femoral head was rotated so that the fovea was adjusted to the medial. In the coronal image, the center of the femoral head and the center of the femoral neck were connected to form the Y-axis (blue), and in the sagittal image, the center of the femoral head and the center of the femoral neck were connected to form the Z-axis (green). The X-axis (red) was defined as perpendicular to both the Y-axis and the Z-axis.



Fig. 2. Position of the regions of interest (ROIs) created for the femoral head microstructure measurements. In each tip-apex distances (TAD) of 15, 20, and 25 mm, five ROIs were extracted from the central (red), anterior (purple), posterior (green), superior (yellow), and inferior (blue) sections. Each ROI was a cuboid measuring 5 mm × 5 mm × 10 mm. A total of 15 ROIs were extracted from TADs of 15, 20, and 25 mm.

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TAD was 10 mm, except for the ROI in the middle region, the tip of the ROI in the other four regions crossed the femoral head, thus we excluded TAD 10 mm.

Statistical analysis was performed using IBM SPSS Statistics (ver. 19.0; IBM, Armonk, NY, USA). The data were presented as mean±standard deviation. Microstructural parameters were compared among each region using ANOVA. Statistical analysis was performed on parameters according to the change in TAD, in addition to the change in regions. The significance level was set at P < 0.05.

RESULTS

The results under the same TAD conditions are as follows. The lowest BMD and BV/TV values were observed in the inferior region and differed significantly from those in

	1		7.5	-	5					
	Region	n	Mean±SD	<i>P</i> -value						
TAD				Anterior	Centerior	Inferior	Posterior	Superior		
TAD15	Anterior	16	0.61 ± 0.13	-	0.411	0.004*	0.404	0.029*		
	Centerior	16	0.65 ± 0.13	0.411	-	0.000**	0.986	0.167		
	Inferior	16	0.48 ± 0.14	0.004*	0.000**	-	0.000**	0.000**		
	Posterior	16	0.65 ± 0.13	0.404	0.986	0.000**	-	0.173		
	Superior	16	0.72±0.13	0.029*	0.167	0.000**	0.173	-		
TAD20	Anterior	16	0.66 ± 0.13	-	0.101	0.007*	0.767	0.241		
	Centerior	16	0.74 ± 0.14	0.101	-	0.000**	0.178	0.635		
	Inferior	16	0.53 ± 0.12	0.007*	0.000**	-	0.003*	0.000**		
	Posterior	16	0.67 ± 0.12	0.767	0.178	0.003*	-	0.379		
	Superior	16	0.71 ± 0.14	0.241	0.635	0.000**	0.379	-		
TAD25	Anterior	16	0.72 ± 0.14	-	0.118	0.011*	0.802	0.892		
	Centerior	16	0.79 ± 0.15	0.118	-	0.000**	0.070	0.090		
	Inferior	16	0.59 ± 0.12	0.011*	0.000**	-	0.021*	0.016*		
	Posterior	16	0.70 ± 0.13	0.802	0.070	0.021*	-	0.908		
	Superior	16	0.71 ± 0.16	0.892	0.090	0.016*	0.908	-		

Table 1. Comparison of Bone Mineral Density (g/cm³) in Different Regions

TAD: tip-apex distances, SD: standard deviation.

* *P*<0.05, ** *P*<0.001.

Table 2. Comparison of Percent Bone Volume (%) in Different Regions

TAD	Region	n	Moon+SD	<i>P</i> -value						
			MeanT2D	Anterior	Centerior	Inferior	Posterior	Superior		
TAD15	Anterior	16	27.36±4.39	-	0.413	0.004*	0.403	0.029*		
	Centerior	16	28.70 ± 4.60	0.413	-	0.000**	0.986	0.165		
	Inferior	16	22.60 ± 4.95	0.004*	0.000**	-	0.000**	0.000**		
	Posterior	16	28.73 ± 4.55	0.403	0.986	0.000**	-	0.171		
	Superior	16	30.97 ± 4.42	0.029*	0.165	0.000**	0.171	-		
TAD20	Anterior	16	28.92 ± 4.62	-	0.102	0.007*	0.770	0.240		
	Centerior	16	31.56±4.81	0.102	-	0.000**	0.177	0.638		
	Inferior	16	24.52 ± 4.00	0.007*	0.000**	-	0.003*	0.000**		
	Posterior	16	29.39 ± 4.15	0.770	0.177	0.003*	-	0.376		
	Superior	16	30.81±4.86	0.240	0.638	0.000**	0.376	-		
TAD25	Anterior	16	30.84 ± 4.65	-	0.118	0.011*	0.799	0.893		
	Centerior	16	33.52 ± 5.11	0.118	-	0.000**	0.070	0.090		
	Inferior	16	26.41±4.11	0.011*	0.000**	-	0.021*	0.016*		
	Posterior	16	30.40 ± 4.40	0.799	0.070	0.021*	-	0.904		
	Superior	16	30.61 ± 5.59	0.893	0.090	0.016*	0.904	-		

TAD: tip-apex distances, SD: standard deviation.

* P<0.05, ** P<0.001.

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other regions (P<0.05) (Table 1, 2). With TAD of 25 mm and TAD of 20 mm, the highest BMD and BV/TV were located in the central region, and with TAD of 15 mm, they were located in the superior region. A lower Tb.Th value was observed in the inferior region of TAD of 15 mm compared with that in the central and superior region (P<0.05). A lower Tb.Th value was observed in the inferior region of TAD of 20 mm compared with that in the anterior, central, and superior regions (P < 0.05). A lower Tb.Th value was observed in the inferior region of TAD of 25 mm compared with that in the anterior and central regions (P < 0.05) (Table 3). With TAD of 15 mm, a lower Tb.N value was observed in the inferior region compared with that in the other four regions (P < 0.05). With TAD of 20 mm, a lower Tb.N value was observed in the inferior region compared with that in the other four regions (P < 0.05). With TAD of 20 mm, a lower Tb.N value was observed in the inferior region compared with that in the central, posterior, and superior regions

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Table 3. Comparison of Trabecular Thickness (mm) in Different Regions

TAD: tip-apex distances, SD: standard deviation.

* *P*<0.05.

Table 4. Comparison of Trabecular Number (1/mm) in Different Regions

TAD	Region	n	Moon+SD	<i>P</i> -value					
		11	MedilT2D	Anterior	Centerior	Inferior	Posterior	Superior	
TAD15	Anterior	16	1.02 ± 0.12	-	0.387	0.032*	0.085	0.032*	
	Centerior	16	1.06 ± 0.12	0.387	-	0.003*	0.385	0.195	
	Inferior	16	0.91 ± 0.13	0.032*	0.003*	-	0.000**	0.000**	
	Posterior	16	1.11 ± 0.14	0.085	0.385	0.000**	-	0.665	
	Superior	16	1.13 ± 0.17	0.032*	0.195	0.000**	0.665	-	
TAD20	Anterior	16	1.06 ± 0.15	-	0.091	0.101	0.201	0.130	
	Centerior	16	1.15 ± 0.12	0.091	-	0.001*	0.675	0.858	
	Inferior	16	0.97 ± 0.13	0.101	0.001*	-	0.004*	0.002*	
	Posterior	16	1.13 ± 0.14	0.201	0.675	0.004*	-	0.810	
	Superior	16	1.14 ± 0.18	0.130	0.858	0.002*	0.810	-	
TAD25	Anterior	16	1.12 ± 0.17	-	0.079	0.172	0.466	0.582	
	Centerior	16	1.22 ± 0.15	0.079	-	0.002*	0.297	0.223	
	Inferior	16	1.04 ± 0.15	0.172	0.002*	-	0.038*	0.057	
	Posterior	16	1.16 ± 0.14	0.466	0.297	0.038*	-	0.858	
	Superior	16	1.15 ± 0.20	0.582	0.223	0.057	0.858	-	

TAD: tip-apex distances, SD: standard deviation.

* P<0.05, ** P<0.001.

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(P<0.05). With TAD of 25 mm, a lower Tb.N value was observed in the inferior region compared with that in the central and posterior regions (P<0.05) (Table 4). The highest SMI value was observed in the inferior region (P<0.05) (Table 5), indicating that the trabecular bone was rod-like in this region. With TAD of 15 mm, the DOA value was lower in the inferior region than in the anterior, posterior, and superior regions (P<0.05). With TAD of 20 mm, a

lower DOA value was observed in the inferior region compared with that of the anterior region (P<0.05) (Table 6, Fig. 3).

The results under different TAD conditions were as follows. Lower BMD and BV/TV values were observed in the anterior, central, and inferior regions of TAD of 15 mm compared with those in the corresponding regions with TAD of 25 mm (P<0.05). Tb.N values in the inferior and

ТАП	Pogion	n	Moon+SD	<i>P</i> -value						
TAD	Region		Medil_SD	Anterior	Centerior	Inferior	Posterior	Superior		
TAD15	Anterior	16	0.79±0.43	-	0.963	0.009*	0.712	0.027*		
	Centerior	16	0.79 ± 0.41	0.963	-	0.008*	0.746	0.031*		
	Inferior	16	1.16 ± 0.34	0.009*	0.008*	-	0.003*	0.000**		
	Posterior	16	0.75 ± 0.33	0.712	0.746	0.003*	-	0.064		
	Superior	16	0.49 ± 0.38	0.027*	0.031	0.000**	0.064	-		
TAD20	Anterior	16	0.73 ± 0.39	-	0.353	0.016*	0.900	0.181		
	Centerior	16	0.61 ± 0.39	0.353	-	0.001*	0.292	0.678		
	Inferior	16	1.03 ± 0.31	0.016*	0.001*	-	0.022*	0.000**		
	Posterior	16	0.74 ± 0.32	0.900	0.292	0.022*	-	0.144		
	Superior	16	0.56 ± 0.33	0.181	0.678	0.000**	0.144	-		
TAD25	Anterior	16	0.67 ± 0.38	-	0.199	0.008*	0.760	0.612		
	Centerior	16	0.52 ± 0.37	0.199	-	0.000**	0.113	0.433		
	Inferior	16	0.99 ± 0.31	0.008*	0.000**	-	0.018*	0.002*		
	Posterior	16	0.71 ± 0.29	0.760	0.113	0.018*	-	0.417		
	Superior	16	0.62 ± 0.29	0.612	0.433	0.002*	0.417	-		

Table 5. Comparison of Structural Model Index in Different Regions

TAD: tip-apex distances, SD: standard deviation.

* P<0.05, ** P<0.001.

Table 6. Comparison of Degree of Anisotropy in Different Regions

TAD	Region		Maan+SD	<i>P</i> -value					
		n	Mean±SD	Anterior	Centerior	Inferior	Posterior	Superior	
TAD15	Anterior	16	1.92±0.19	-	0.320	0.007*	0.959	0.950	
	Centerior	16	1.85 ± 0.16	0.320	-	0.077	0.296	0.290	
	Inferior	16	1.73 ± 0.23	0.007*	0.077	-	0.006*	0.005*	
	Posterior	16	1.93 ± 0.17	0.959	0.296	0.006*	-	0.991	
	Superior	16	1.93 ± 0.20	0.950	0.290	0.005*	0.991	-	
TAD20	Anterior	16	1.98 ± 0.25	-	0.164	0.020*	0.504	0.190	
	Centerior	16	1.87 ± 0.19	0.164	-	0.334	0.464	0.934	
	Inferior	16	1.79 ± 0.31	0.020*	0.334	-	0.092	0.295	
	Posterior	16	1.93 ± 0.13	0.504	0.464	0.092	-	0.516	
	Superior	16	1.87 ± 0.22	0.190	0.934	0.295	0.516	-	
TAD25	Anterior	16	2.04 ± 0.31	-	0.160	0.107	0.274	0.068	
	Centerior	16	1.90 ± 0.23	0.160	-	0.834	0.752	0.668	
	Inferior	16	1.88 ± 0.42	0.107	0.834	-	0.599	0.827	
	Posterior	16	1.93 ± 0.20	0.274	0.752	0.599	-	0.457	
	Superior	16	1.85 ± 0.23	0.068	0.668	0.827	0.457	-	

TAD: tip-apex distances, SD: standard deviation.

* P<0.05.

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BMD: bone mineral density, TAD: tip-apex distance, BV/TV: bone volume/total volume, Tb.Th: trabecular thickness, Tb.N: trabecular number, SMI: structural model index, DOA: degree of anisotropy.

central regions of TAD of 15 mm were lower than those in the corresponding regions of TAD of 25 mm (P<0.05). No significant differences in the values of Tb.Th, SMI, DOA in each region were observed between different TAD regions (Table 7).

DISCUSSION

We used micro-CT images to evaluate the microstructure of the trabecular bone in the femoral head of patients with osteoporosis, and found that as TAD decreased in most regions, BMD and BV/TV decreased with screw depth (P<0.05); however, BMD and BV/TV in the superior and posterior regions were not significantly altered with changes in TAD (P<0.05) (Table 7). The lowest bone quality was observed in the inferior region of the femoral head. The highest bone quality was observed in the central area of the femoral head with TAD of 20 mm and TAD of 25 mm. The main compressive trabeculae was located in the central area, which is the weight-bearing area. Therefore, the bone quality index was very high. The SMI was most rod-like in the inferior region, and the parameters measured in this study indicated that the weakest bone was in the inferior region.

It is generally recommended that patients with intertrochanteric fractures undergo intramedullary nail or dynamic hip screw surgery to ensure recovery and to facilitate a return to the functional state before the injury as soon as possible. Screw cut-out is a serious complication, with a reported incidence of 17.5% to 20%^{2,15-20}. The most important predictor of screw cut-out is TAD, followed by screw position, fracture type, reduction, and patient age²¹. TAD is closely related to the positioning of lag screws. Therefore, the optimal placement of lag screws plays an important role in the reduction of complications. The current belief is that the best position of the femoral head lag screw is in the central or inferior region on the AP view, and in the central region on the lateral view^{9,11}.

Jenkins et al.²²⁾ reported that through the use of CT for measurement of the trabecular bone microstructure of the femoral head, the highest bone strength was in the central region of the femoral head. They recommended placing the lag screw in the center of the femoral head to achieve the best fixation effect. Reports involving radiographic surveys have found that the cut-out rate of lag screws is higher in the superior region than in other regions²⁾. Some reports have suggested that the central-inferior region is the ideal position for the lag screw⁹⁻¹²⁾. One explanation for this difference

Table 7. Comparison of Bone Mineral Density (BMD) and Bone Microstructure in Specific Areas between Different Tip-apex

 Distances (TAD) Regions

Index	TAD			<i>P</i> -value					
much			Anterior	Centerior	Inferior	Posterior	Superior		
BMD (g/cm³)	TAD15	TAD20	0.336	0.101	0.222	0.667	0.931		
	TAD15	TAD25	0.036*	0.007*	0.018*	0.282	0.843		
	TAD20	TAD25	0.240	0.258	0.227	0.515	0.911		
BV/TV (%)	TAD15	TAD20	0.337	0.101	0.222	0.668	0.929		
	TAD15	TAD25	0.036*	0.007*	0.018*	0.283	0.840		
	TAD20	TAD25	0.241	0.259	0.228	0.515	0.910		
Tb.Th (mm)	TAD15	TAD20	0.560	0.590	0.582	0.934	0.680		
	TAD15	TAD25	0.288	0.560	0.393	0.866	0.365		
	TAD20	TAD25	0.628	0.965	0.760	0.932	0.620		
Tb.N (1/mm)	TAD15	TAD20	0.476	0.079	0.232	0.699	0.869		
	TAD15	TAD25	0.078	0.002*	0.015*	0.306	0.757		
	TAD20	TAD25	0.284	0.137	0.194	0.522	0.885		
SMI	TAD15	TAD20	0.634	0.206	0.281	0.983	0.580		
	TAD15	TAD25	0.401	0.062	0.153	0.755	0.311		
	TAD20	TAD25	0.714	0.529	0.720	0.772	0.642		
DOA	TAD15	TAD20	0.525	0.878	0.657	>0.999	0.484		
	TAD15	TAD25	0.186	0.528	0.225	0.922	0.357		
	TAD20	TAD25	0.486	0.633	0.437	0.922	0.822		

BV/TV: percent bone volume, Tb.Th: trabecular thickness, Tb.N: trabecular number, SMI: structural model index, DOA: degree of anisotropy.

* *P*<0.05.

is that when the screw is placed in the inferior region, it does not damage the area where the bone is the strongest. In our study, higher bone quality was observed in the superior region of the femoral head compared with that of the inferior region. In addition, no significant change in bone quality was observed in the superior region between TAD of 15 to 25 mm (Table 7). Regarding the TAD value, no significant difference in bone quality was observed between the anterior and posterior regions (P<0.05). If the screw was placed eccentrically in the sagittal plane, then the upward migration of the screw would not be impeded by the strongest bone in the central region, and cut-out would be more likely as compared to a screw in the central region. These findings are of great significance for operations associated with proximal femoral fractures.

The central region of the femoral head was previously considered the most ideal position for screw placement. Screw insertion into the anterior or posterior region of the femoral head would increase the risk of screw cut-out. Our data support this conclusion, particularly when considering the BV/TV distribution of the entire femoral head, the central region was associated with the highest value. Due to poor X-ray imaging during operations, screws might occasionally be inserted incorrectly. Insertion of the screw into the anterior or posterior region of the femoral head will increase the risk of screw cut-out and the requirement for further corrective surgery. Regarding the inferior region, BMD and BV/TV indicated it was the area with the lowest bone quality in the femoral head, whereas relatively strong bone would not be damaged by screw insertion. Most of the cut-out region of the screw was found at the top of the femoral head²). Therefore, when the screw was in the inferior region, more strong bone was retained at the tip of the screw, which would prevent the screw from passing through.

In this study, the screw position in the superior region was found to be the most unacceptable. Location of the screws in the inferior region was more acceptable. As the TAD value became smaller, the bone quality of the four regions except for the superior region gradually decreased as the depth of the screw increased. Therefore, the trabecular bone in the femoral head of patients with osteoporosis exhibited a heterogeneous region-specific distribution. The trabecular bone in the central and superior region is composed of predominantly compressive trabeculae. Even in patients with severe osteoporosis, the main compressive trabeculae remain. Therefore, in osteoporotic hip fracture operations, careful selection of the screw position of the internal fixation device is critical. The current study has several limitations. First, the number of femoral heads was relatively small, but we found statistically significant differences in bone microarchitecture among different ROIs. Second, femoral head size was not considered, which may affect the difference in changes in bone microarchitecture between ROIs, but we did not find too large or too small femoral heads (femoral head diameter ranged from 43 to 52 mm) as measured after MicroCT filming. Third, if the lag screw is inserted into the femoral head specimen followed by a screw pullout experiment, it may be more persuasive for our conclusions.

CONCLUSION

The trabecular bone in the femoral head of elderly patients with osteoporosis exhibits heterogeneous and region-specific distribution. In general, positioning of the lag screw between TAD of 20 to 25 mm and in the inferior region is recommended, and TAD of less than 15 mm is not recommended.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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