Assessment of Porosity Index of the Femoral Neck and Tibia by 3D Ultra-Short Echo-Time MRI

Min Chen, MD and Huishu Yuan, MD*

Purpose: To measure the porosity index (PI) by ultrashort echo-time magnetic resonance imaging (UTE MRI) of the femoral neck and tibia; assess its correlations with age, gender, and body mass index (BMI); and analyze the PI correlations between both sites to assess whether tibial PI can reflect changes of femoral neck PI.
Materials and Methods: In all, 68 healthy men and women (mean age, 45.7 ± 15.9 years) underwent 3D UTE MRI (3.0T) of the hip and mid-shaft tibia. PI of the inferior femoral neck cortex and the whole cortex of the tibia were analyzed. Associations between parameters and differences of PIs between men and women, pre- and postmenopausal women were tested.
Results: Femoral neck PI was negatively correlated with age (r = –0.385, P = 0.043) and curvilinearly correlated with BMI (R^2 = 0.225, P = 0.041) in men. Tibial PI was correlated with BMI (r = –0.477, P = 0.002) in women and age (r = 0.469, P = 0.043) in postmenopausal women, although P = 0.097 (r = 0.403) after adjustment for BMI. Femoral PI was significantly higher in men than in women ($P < 0.001$). No significant difference in femoral and tibial PI was observed between pre- and postmenopausal women. The femoral neck and tibial PIs were not significantly correlated in any group.
Conclusion: PIs had some correlations with age, gender, and BMI. Since femoral neck PI was not correlated with tibial PI, the tibia cannot substitute the femoral neck for estimating bone quality. Direct assessment of the femoral neck cortex is needed.
Level of Evidence: 3
Technical Efficacy Stage: 3

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Osteoporosis is a common skeletal disorder in the elderly and is characterized by low bone mass and microstructural deterioration of bone tissue, with an increased fracture risk.[1] Although bone mineral density (BMD) measured by dual X-ray absorptiometry is the standard for the diagnosis of osteoporosis (T score of ≤–2.5),[2] it has limitations in demonstrating changes in the bone microstructure. In addition, many patients with fragility fractures have normal or osteopenic BMD.[2]

Cortical bone plays an important role in human bone health. It accounts for nearly 80% of the skeleton,[3] and 70% of all the appendicular bone that is lost during aging is cortical.[4] Cortical porosity is a critical determinant of bone strength at the microstructural level,[5,6] and its in vivo assessment is important to understand bone deterioration in osteoporosis and better identify those at risk for fractures. High-resolution peripheral quantitative computed tomography (HR-pQCT) with a spatial resolution of 82 μm[7] allows evaluation of cortical porosity in vivo. However, a large part of cortical bone pores are as small as ~0.1 μm or 10–30 μm in diameter[8]; thus, HR-pQCT underestimates the porosity due to its limited resolution. Furthermore, it involves radiation exposure during examination and is limited to peripheral skeletal sites and cannot be applied in spine or proximal femur, which are also challenges of quantitative CT.[2]

With the evolution of magnetic resonance imaging (MRI) techniques, quantitative cortical porosity assessment is feasible in vivo using advanced MR sequences with ultrashort echo time (UTE) MRI.[9–12] Cortical bone contains

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*Address reprint requests to: HS.Y., Department of Radiology, Peking University Third Hospital, 49 North Garden Road, Haidian District, Beijing, P.R. China. E-mail: Huishuy@bjmu.edu.cn

From the Department of Radiology, Peking University Third Hospital, Beijing, P.R. China

~20% water by volume,[13] which consists of free water in pores and bound water connected to the collagen matrix.[14] The free-water fraction reflects the cortical porosity, whereas the bound-water fraction reflects the BMD.[10,15] With its ultrashort echo time, UTE MRI can detect the proton signal from cortical bone water and separately quantify pore water (T_2 values, 1 msec to 1 sec) and bound water (T_2 values, 0.3–0.4 msec)[12,15] with the help of adiabatic inversion pulses[11] or bicomponent analysis.[16] Although these methods provide indirect surrogates of cortical porosity, they are complicated and time-consuming and therefore have limited clinical application.

Recently, Rajapakse et al[12] proposed a two-point MRI method to assess cortical bone porosity using a double-echo UTE MR sequence. The porosity index (PI) was calculated as the ratio of the image intensities of the second echo (indicating signals mainly from pore water) and the first echo (indicating signals from all water), which represented the pore-water fraction and highly positively correlated with cortical porosity measured by micro-CT in vitro (R^2 = 0.79). In addition, this method demonstrated high reproducibility for the tibial PI measurements in vivo (with a between-days coefficient of variation of 2.2%). Therefore, this approach has potential for clinical use because it is time-saving and its postmeasurement processing is simple. The tibia is less susceptible to osteoporotic fracture than the proximal femur[17]; thus, it seems more clinically relevant to assess the porosity of the femoral neck. As the tibia and femoral neck are both part of the lower limb, we hypothesized that the assessment of the femoral neck porosity could be replaced by porosity measurement of the tibia, which is a more convenient location for MRI assessment. However, the relationship between the tibial PI and the femoral neck PI is currently unclear. Moreover, the correlations between PI and age, gender, and body mass index (BMI) have not been investigated thus far.

Therefore, this study aimed to 1) measure the PI using UTE MRI at the tibia and femoral neck of healthy men and women of different ages; 2) assess the correlations of PI with age, gender, and BMI; and 3) and analyze the correlations between PI of the tibia and femoral neck.

Materials and Methods

Subjects

The study was approved by the Institutional Medical Ethics Committee of the university hospital where the work was conducted, and written informed consent was obtained from all subjects after explaining the nature of the study. Healthy subjects were recruited from staff, students, and patients from the Outpatient Department within the institution. Exclusion criteria were as follows: histories of fragility fractures (fractures resulting from low impact trauma such as a fall from standing height); tibia or femoral neck fractures; recent immobilization (>3 months); medical history of diseases or treatments that may affect bone metabolism (such as hyperparathyroidism, hyperthyroidism, diabetes, chronic gastrointestinal disease, malignant tumors, etc., and treatments with glucocorticoids, estrogens, thyroid hormone, fluoride, bisphosphonate, calcitonin, barbiturates, and anticonvulsant medications).

UTE MRI Scanning

All participants were subjected to MRI of the nondominant hip (limb dominance was defined as the foot used for stair climbing, in a self-determined way) and the mid-shaft tibia on the same side by using a clinical 3.0T MRI scanner (MR750w; GE Healthcare, Milwaukee, WI). A dedicated, flexible, surface coil and a 3D double-echo UTE sequence ($TR/TE_1/TE_2$, 12.2/0.1/4.6 msec; matrix, 384 × 384; field of view [FOV], 17 cm; slice thickness, 2.4 mm; voxel volume, 0.196 × 0.196 × 2.4 mm^3; flip angle, 12°; bandwidth, 62.5 kHz; 10 axial images perpendicular to the femoral neck axis; and scan time, 6 min 30 sec) were used for hip imaging. An 8-channel knee coil and another 3D double-echo UTE sequence ($TR/TE_1/TE_2$, 12/0.1/4.0 msec; matrix, 256 × 256; FOV, 12 cm; slice thickness, 2.4 mm; voxel volume, 0.220 × 0.220 × 2.4 mm^3; flip angle, 12°; bandwidth, 62.5 kHz; 10 axial images; and scan time, 4 min 31 sec) were used to acquire tibial images. The tibial scan was centered on 38% of the tibial length proximal to the lateral malleolus (site of the thickest cortex). Notably, a TE of 0.1 msec was the shortest TE we could attain using our scanner.

Image Processing

The quality of the UTE images including motion artifacts and the contrast of the images were subjectively assessed by a musculoskeletal radiologist (M.C., 3 years of experience). All images were processed using a GE AW4.6 workstation (GE Healthcare). We obtained ratio images of the second echo and the first echo for the femoral neck and tibia, namely, the PI maps, on which cortical PIs of the two sites were measured. The region of interest (ROI) was restricted to compact-appearing cortex that excluded the trabecularized transition zone, as a large part of UTE signals in these areas are derived from fatty tissue, which might disturb the cortical water signal and therefore the PI measurements. The whole cortical bone region on the central axial slice of the tibia images was analyzed for the tibia, whereas the thick inferior region of the femoral neck cortex was analyzed, as the superior part was too thin for analysis. The analysis of the femoral neck PI was performed on the slice of the distal femoral neck (the site of insertion of the articular capsule at the femoral neck). Examples of ROIs are presented in Fig. 1. All ROIs were manually contoured on the second echo images, which were automatically matched on the PI maps. PIs were recorded as the average PI of the ROI.

Statistical Analysis

All statistical analyses were performed using SPSS software (v. 22.0; IBM, Armonk, NY). The correlations between PIs and age, PIs and BMI, and PIs of the tibia and the femoral neck were analyzed. PIs were also compared between men and women and between pre- and postmenopausal women. The normality of each continuous parameter was tested using the Shapiro–Wilk test. When parameters were normally distributed, the Pearson

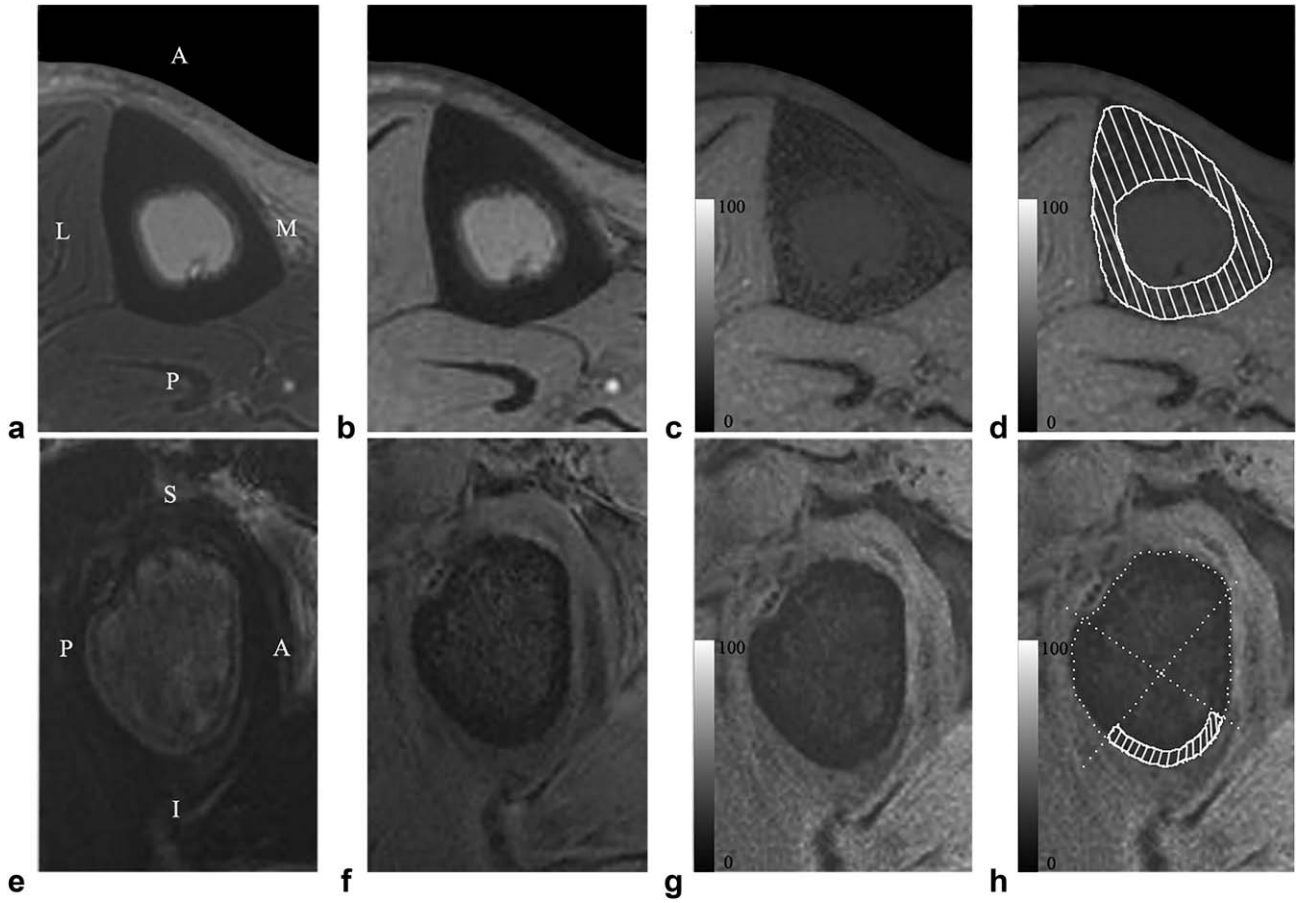

FIGURE 1: Representative ultrashort echo-time double-echo images, the corresponding porosity index maps, and ROIs of the tibia (a–d) and the femoral neck (e–h). (a,e): The first echo image; (b,f): the second echo image; (c,g): the porosity index map. (d,h): Examples of ROIs. A: anterior P: posterior M: medial L: lateral S: superior I: inferior.

correlation coefficient was computed. Otherwise, the Spearman correlation coefficient was used. Partial Pearson correlation coefficient was also calculated for adjustment of age or BMI. Curve estimation was applied when it displayed a possibility of curvilinear correlation instead of linear correlation on the scatterplot. The significance of the mean differences of parameters between participant groups were determined using two-sided *t*-tests or the nonparametric Mann–Whitney *U*-test for normally or abnormally distributed parameters. All P values < 0.05 were considered to indicate statistical significance.

Results

A total of 68 healthy subjects (28 men, 40 women including 19 postmenopausal women; mean age, 45.7 ± 15.9 [standard deviation] years; age range, 21–76 years) participated in the study. Representative double-echo UTE images of the femoral neck and tibia and PI maps calculated from the images are presented in Fig. 1. Cortical bones were well depicted on the tibial UTE images, but not so well depicted on the femoral neck UTE images due to the low signal-to-noise ratio resulting from the deep location of the femoral neck. Nevertheless, these images were considered acceptable for PI measurements.

Table 1 presents the descriptive characteristics and PI results of all 68 subjects. No significant differences in BMI were noted between men and women ($P = 0.611$) or pre- and postmenopausal women ($P = 0.260$, $t = 1.143$, 95% confidence interval [–1.113, 4.003]). In addition, the age of the men was statistically the same as that of women ($P = 0.118$), which allowed direct comparison of PI between the groups. The femoral neck PI had a wide range (27–95%). Men had significantly higher femoral neck PIs than women ($U = 229$, $P < 0.001$), whereas no significant difference was noted between different menopausal statuses ($P = 0.436$). In the tibia, the range of the PI was narrower (range, 28–57%) than that in the femoral neck. No difference was observed between men and women ($P = 0.859$), or pre- and postmenopausal women ($P = 0.871$).

Tables 2 and 3 present the correlation coefficients and partial correlation coefficients among parameters and the corresponding P values. Femoral neck PI demonstrated a negative correlation with age only in men ($r = –0.385$, $P = 0.043$, partial $r = –0.428$, $P = 0.026$ after adjustment for BMI), but no linear correlation with BMI in all groups. Interestingly, there was a statistically significant curvilinear correlation between BMI and femoral neck PI in men (y =

TABLE 1. General Characteristics and Porosity Indices of Men, Women, Premenopausal, and Postmenopausal Women

	Female	Male	Premenopausal women	Postmenopausal women
N	40	28	19	21
Age [years]	47.9 ± 15.3 50 [36,61.5]	42.5 ± 16.6 38 [27.25,56]	35.5 ± 8.5	61.7 ± 6.6
BMI [kg/m^2]	24.5 ± 4.0	24.1 ± 2.6	23.8 ± 4.2	25.3 ± 3.8
Tibia PI [%]	44 ± 6.3	43 ± 6.2	43 ± 7.6	44 ± 4.6
Femoral neck PI [%]	41 ± 10.2 41 [35,45]	56 ± 15.6	43 ± 12.7 41 [36,46]	39 ± 6.2

BMI, body mass index; PI, porosity index. All values are presented as means ± standard deviations. Values that are not normally distributed are also presented as median [IQR].

$-0.5283 + 0.484x - 0.010x^2$, $R^2 = 0.225$, $P = 0.041$). The femoral neck PI in men initially increased with BMI, but subsequently decreased. The associations between the tibial PI and the studied parameters were different: Tibial PI was significantly correlated with BMI in women and age in postmenopausal women ($r = -0.477$, $P = 0.002$ for BMI, $r = 0.469$, $P = 0.043$ for age), but not correlated with BMI or age in men. After adjustment for age, tibial PI was still significantly correlated with BMI in women (partial $r = -0.509$, $P = 0.001$). However, the significant correlation between tibial PI and age in postmenopausal women disappeared after adjusting for BMI (partial $r = 0.403$, $P = 0.097$). Furthermore, femoral neck PI and tibial PI were not correlated in all groups, although they displayed an association in premenopausal women ($r = -0.433$, $P = 0.050$). The scatterplots of all associations are depicted in Figs. 2 and 3.

Discussion

In our study, cortical PIs of the femoral neck and tibia were measured in the same cohort of subjects by using clinically practical double-echo UTE MRI sequences. We found that

TABLE 2. Correlations Between Porosity Index and Age or Body Mass Index

		Age [years]		BMI [kg/m^2]	
		r partial r	*P*	r partial r	*P*
Femoral neck PI [%]	Women	–0.097 (–0.378,0.236) –0.175 (–0.399,0.091)	0.553 0.286	0.185 (–0.154,0.486) 0.125 (–0.156,0.526)	0.254 0.449
	Men	**–0.385** (–0.657,0.003) **–0.428** (–0.650,–0.173)	0.043 0.026	0.027 (–0.311,0.390) 0.196 (–0.138,0.530)	0.890 0.327
	Premenopausal women	–0.034 (–0.497,0.469) –0.017 (–0.498,0.348)	0.883 0.944	0.146 (–0.327,0.588) 0.091 (–0.289,0.677)	0.529 0.702
	Postmenopausal women	0.073 (–0.487,0.236) 0.192 (–0.325,0.647)	0.766 0.445	0.298 (–0.224,0.754) 0.311 (–0.294,0.679)	0.215 0.209
Tibial PI [%]	Women	0.087 (–0.244,0.377) 0.234 (–0.067,0.477)	0.595 0.151	**–0.477** (–0.752,–0.108) **–0.509** (–0.745,–0.176)	0.002 0.001
	Men	0.060 (–0.314,0.424) 0.088 (–0.222,0.395)	0.762 0.662	0.148 (–0.214,0.539) 0.107 (–0.316,0.520)	0.453 0.595
	Premenopausal women	0.085 (–0.421,0.547) 0.212 (–0.286,0.676)	0.715 0.369	**–0.484** (–0.813,–0.023) **–0.514** (–0.856,0.076)	0.026 0.021
	Postmenopausal women	**0.469** (0.017,0.737) 0.403 (–0.061,0.728)	0.043 0.097	**–0.530** (–0.820,–0.013) **–0.478** (–0.816,–0.018)	0.020 0.045

BMI, body mass index; PI, porosity index; r, partial r (after adjustment for age or BMI) and *P* values are presented. Statistically significant r values are highlighted in bold font.
All r values are presented as *r* (95% confidence intervals).

TABLE 3. Correlations Between the Femoral Neck and Tibial Porosity Indices

	r	*P*
Women	–0.189 (–0.476,0.115)	0.242
Men	–0.285 (–0.572,0.103)	0.142
Premenopausal women	–0.433 (–0.759,0.001)	0.050
Postmenopausal women	0.158 (–0.340,0.593)	0.519

All r values are presented as *r* (95% confidence intervals).

the femoral neck PI was negatively correlated with age and curvilinearly correlated with BMI in men. In contrast, the tibial PI was inversely correlated with BMI in women and positively correlated with age in postmenopausal women. The femoral PI in men was significantly higher than that in women, but no difference was observed in the femoral and tibial PIs between pre- and postmenopausal women. Moreover, the PIs of the two sites were not correlated.

Although the role of cortical porosity in bone strength has been extensively investigated in many studies,[18–20] few of them assessed that of the femoral neck in vivo. Cortical porosity of the femoral neck was evaluated through PI measurements in our study, which may provide a new choice for clinical use.

The femoral neck PI varies widely among subjects, which is consistent with the high variation of the femoral neck cortical porosity observed in previous studies.[21] The tibial PI measured in our study ranged from 28–57% overall and 32–51% in the postmenopausal group; however, a previous study that measured the tibial PI of 34 menopausal women aged 55–80 years reported a PI of 15–31%.[12] As the shortest TE was limited to 0.1 msec in our study, which is higher than the value of 0.05 msec reported in the previous study,[12] the signal intensity acquired on our first echo images was lower and a part of the cortical water signal was lost according to the time–intensity curve,[12] which may have led to higher cortical PIs in our study as compared to those in the above-mentioned previous study.

In the present study, the femoral neck PI in men was significantly higher than that in women, which was close to those of the inferior femoral neck porosity measurements reported by Bell et al.[22] As bone structure adapts to habitual mechanical loading, which is known to be a key stimulus for osteogenesis,[23] the difference in the results between genders may be related to the differences in hip joint loads. Women have significantly greater hip flexion than men during walking, which may result in greater compression load on the inferior region of the femoral neck and reduction in cortical porosity.[22,24] However, contrasting results have also been reported in other studies of porosity measurements at the femoral neck or other bone sites[25,26]; thus, the gender difference in the PI values remains unclear. Furthermore, we did not observe any significant differences in the femoral neck and tibial PI between pre- and postmenopausal women, which contrasts the findings of previous studies.[7,27] This difference in the results could be attributed to the compact cortical region chosen for analysis. In our study, the ROIs of the cortical bones consisted of pure cortical bone tissue and the trabecularized transition areas were excluded. Therefore, the changes in the cortical-trabecular transitional area, which account for a considerable portion of the porosity changes after menopause,[25] were not included in the present study. This exclusion could have led to the similar PIs observed in pre- and postmenopausal women. In addition, the relatively small sample size (~20 subjects for each group) may have contributed to this result.[27]

The femoral neck PI demonstrated a negative correlation with age in men, which contradicts the findings of most previous studies.[27,28] However, significant individual variation exists in cortical bone porosity, especially in men: Low porosity has been noted in some elderly subjects, and high porosity has been observed in some young adults.[23,29] Similar results were reported by Tong et al,[30] who demonstrated that cortical porosity of the inferior femoral neck was higher in younger subjects than in older subjects. A positive correlation was observed between the tibial PI and age in postmenopausal women, which is in accordance with the effect of age on tibial porosity observed in previous studies.[7,27] As men and premenopausal women show slower deterioration in cortical porosity with age than postmenopausal women,[7,27] further study of PI measurements in a larger cohort may help identify any potential correlation between PI and age.

The effect of BMI on cortical porosity has not been extensively explored thus far. The negative correlation between BMI and female tibial cortical PI reported in our study was consistent with the findings of Evans et al,[31] who measured cortical porosity using HR-pQCT for comparison between obese and nonobese subjects. This result may suggest a protective role of BMI on tibial cortical bone strength. The underlying mechanisms may be that higher BMI brings an increase in the habitual loading on bone structure and the estrogen level.[32] Interestingly, there was a curvilinear correlation between BMI and the femoral neck PI in men: the PI initially increased with BMI and then decreased, indicating that BMI has a varied effect on femoral neck porosity. As fat distribution may affect associations between adiposity and bone microarchitecture,[33] and accumulation of local fat may have a negative effect on bone strength,[34] we believe that the femoral neck cortical PI is affected by BMI through both mechanical load and local fat status. Sundh et al[34] reported that high local subcutaneous fat was associated with high cortical porosity, possibly in a paracrine way.

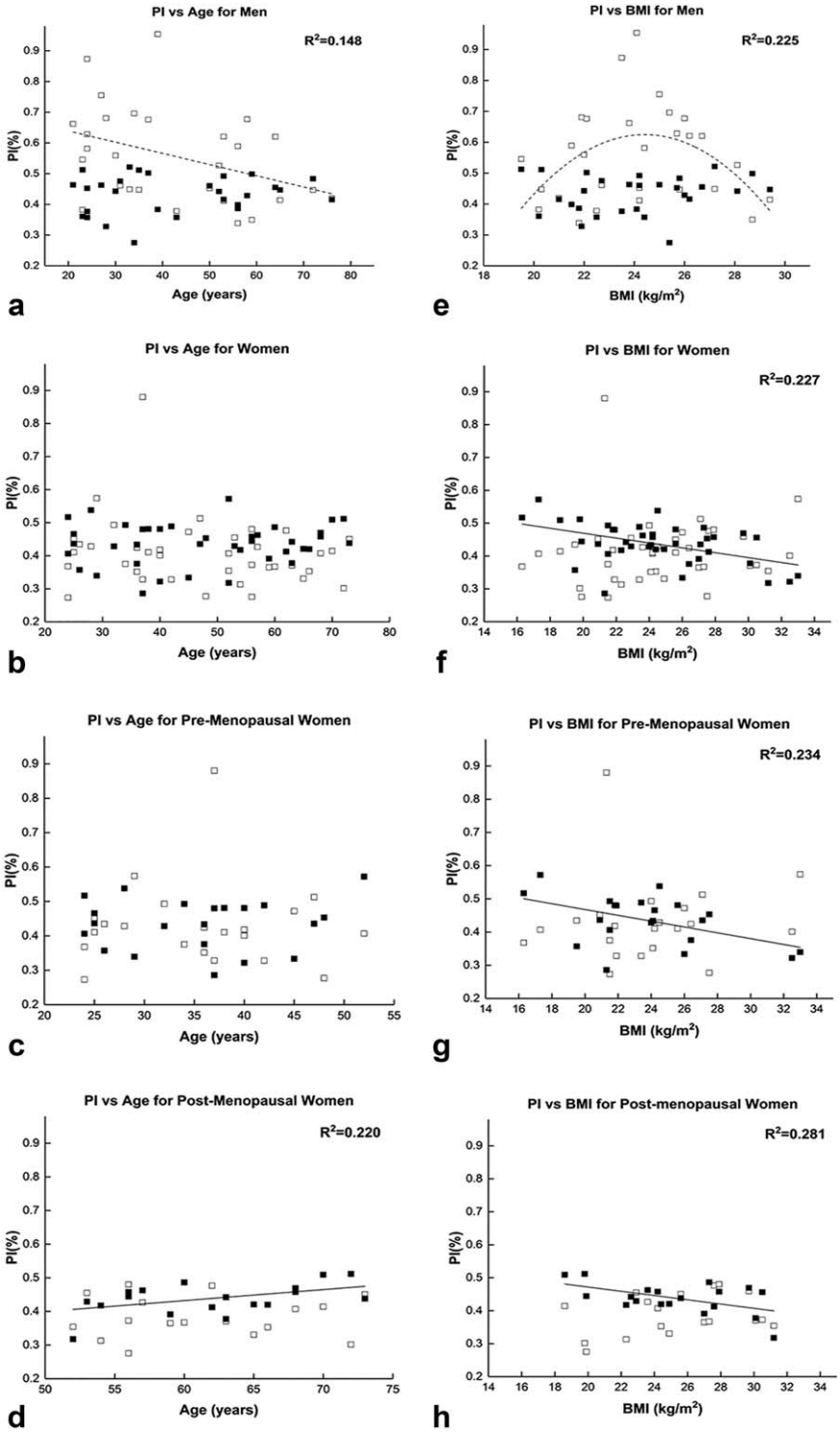

FIGURE 2: Scatterplots displaying the correlations between PI and age or BMI. Solid squares represent the tibial PI data and open squares represent the femoral neck PI data. Significant linear or curve fittings are marked with solid lines for the tibia and dashed lines for the femoral neck. PI, porosity index; BMI, body mass index.

Men with a low BMI may have less local subcutaneous fat, which may have yielded lower PI values than expected. Notably, lean mass and fat mass both contribute to body mass[35,36] and were reported to have different roles in the bone microarchitecture; further investigation is needed to clarify their effects on cortical PI.

We hypothesized that the assessment of the femoral neck porosity could be replaced by porosity measurement of the tibia; however, our data indicated a contrary conclusion, as evidenced by the differences in the relationships of femoral neck PI and tibial PI with age, gender, and BMI and the absence of a correlation between PIs of the two sites. These

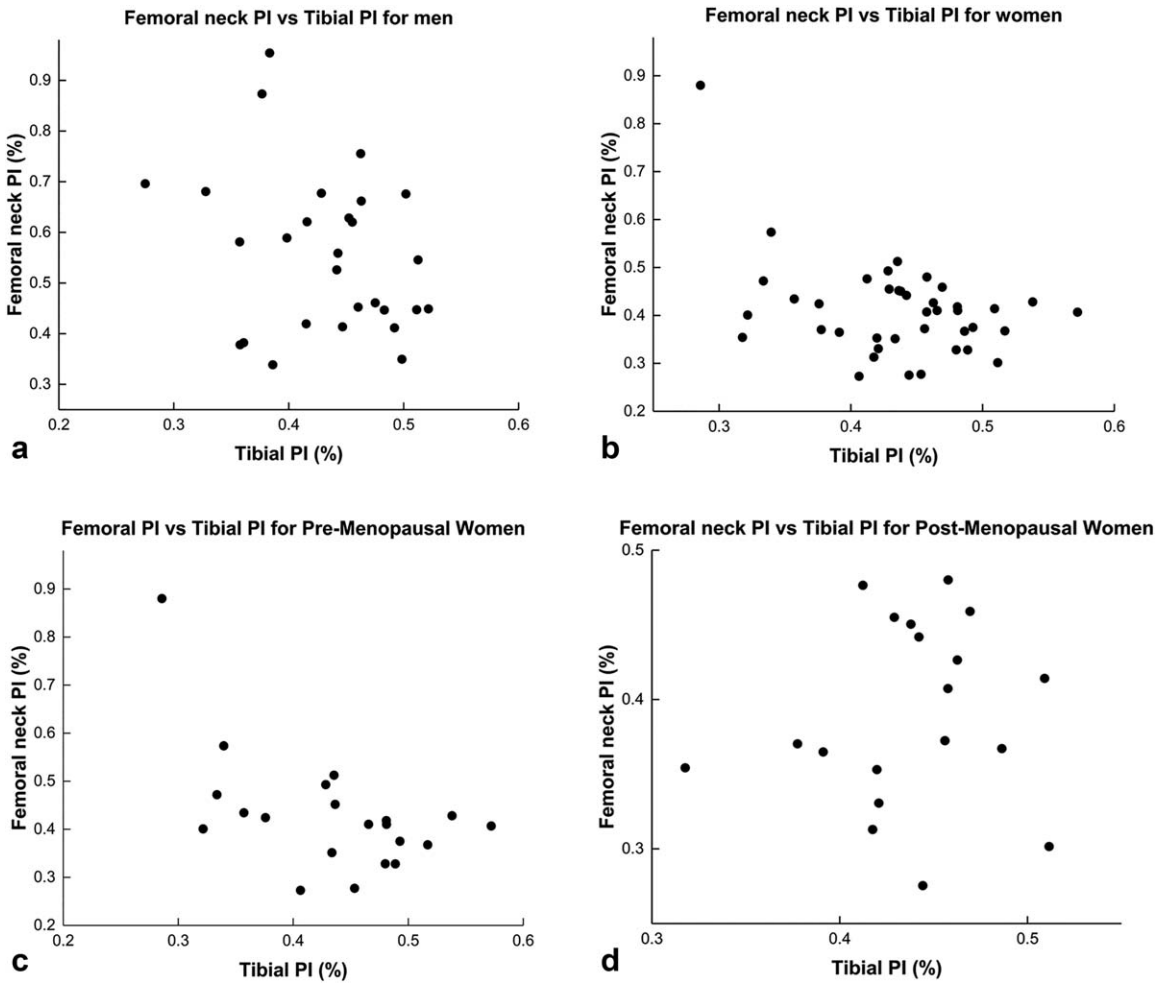

FIGURE 3: Scatterplots depicting the correlations between the femoral neck and tibial porosity indices. PI, porosity index.

results suggest that the assessment of tibial cortical porosity cannot substitute femoral neck cortical porosity measurement. The differences in the relationships mentioned above emphasize the importance of direct evaluation of femoral neck cortical porosity for fracture-risk prediction.

The present study has a few limitations that need to be addressed. First, the PI in our study was measured on the basis of a different approach from others' work.[12] As the shortest TE on our MR scanner was slightly longer than that from the existing approach (0.1 msec vs. 0.05 msec), some of the cortical water signals were not reflected in our PI, questioning whether it can still be an excellent surrogate of true cortical porosity. However, the cortical signal at 0.10 msec is very close to that at 0.05 msec, in terms of the UTE signal decay curve.[12] Therefore, we believe the measurement of PI using the first echo time of 0.1 msec can provide a good assessment of cortical porosity, but comparison of PIs with the values obtained from micro-CT imaging for validation may be the best choice. Second, as the ROI in the present study was selected by hand, the superior region of the femoral neck, which is more commonly affected during a fall, cannot be measured because it is too thin. Some automatic methods to help analyze this region should be developed. Third, the duration of scanning the femoral neck is relatively longer (6.5 min) than that of using clinical MRI sequences. Motion artifacts were observed on several images, which decreased the accuracy of identifying the cortical boundaries. Therefore, approaches to reduce motion artifacts such as the use of assistant straps to minimize the patient's mobility[37] or motion-correction techniques should be implemented in the future. Fourth, cortical porosity is not only regulated by age, gender, BMI, and menopause status, but also related to physical activity or exercise, diet, and other lifestyle factors,[38–40] which could be confounding factors when analyzing the correlations among parameters. All significant correlations noted in our study were mild to moderate, with $R^2 < 0.30$, which indicates that some other determinants for cortical PI exist; this should be considered in future studies. Finally, this study had a small cohort and lacked elderly subjects (age >76 years); therefore, studies with a larger cohort and wider age range are needed to investigate the determinants of cortical PI at different sites and to assess the role of PI in fracture-risk prediction and disease monitoring.

In conclusion, this study examined the application of cortical PI derived from double-echo UTE MRI sequences at the femoral neck and tibia of the same cohort. The femoral neck PI was negatively correlated with age and curvilinearly correlated with BMI in men, while the tibial PI was negatively correlated with BMI in women and showed a positive correlation with age in postmenopausal women. Femoral neck PI was not correlated with tibial PI, indicating the need for direct assessment of the femoral neck cortex for estimation of bone quality.

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