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Original article

Differences in the effects of BMI on bone microstructure between loaded and unloaded bones assessed by HR-pQCT in Japanese postmenopausal women

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ABSTRACT

Objectives: The relationship between weight-related load and bone mineral density (BMD)/bone microstructure under normal load conditions using high-resolution peripheral quantitative computed tomography (HR-pQCT) remains unconfirmed. The study aims to investigate the differences in effect of body mass index (BMI) on BMD/bone microstructure of loaded and unloaded bones, respectively, in Japanese postmenopausal women.

Methods: Fifty-seven postmenopausal women underwent HR-pQCT on the tibia and radius. Correlation analysis, principal component (PC) analysis, and hierarchical multiple regression were performed to examine the relationship between BMI and HR-pQCT parameters.

Results: Several microstructural parameters of the tibia and radius correlated with BMI through a simple correlation analysis, and these relationships remained unchanged even with an age-adjusted partial correlation analysis. PC analysis was conducted using seven bone microstructure parameters. The first PC (PC1) reflected all parameters of trabecular and cortical bone microstructures, except for cortical porosity, whereas the second PC (PC2) reflected only cortical bone microstructure. Hierarchical multiple regression analysis indicated that BMI was more strongly related to BMD/bone microstructure in the tibia than in the radius. Furthermore, BMI was associated with trabecular/cortical BMD, and PC1 (not PC2) of the tibia and radius. Thus, BMI was strongly related to the trabecular bone microstructure rather than the cortical bone microstructure.

Conclusions: Our data confirmed that BMI is associated with volumetric BMD and trabecular bone microstructure parameters in the tibia and radius. However, although BMI may be more related to HR-pQCT parameters in the tibia than in the radius, the magnitude of association is modest.

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1. Introduction

Mechanical stress on bone caused by physical activity is important for maintaining bone mass and bone strength. Bone strength is determined by bone mineral density (BMD) and bone quality, accounting for 70% and 30%, respectively. Bone microstructure is

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generally one of the determinants of bone quality [1], and bone histomorphometry in animals has been extensively studied [2,3]. Bone microstructure is influenced by mechanical stress, and it alters under unloaded conditions, as well as during exercise loading, as confirmed in animal models [4,5].

BMD, which is another determinant of bone strength, can be evaluated by dual-energy X-ray absorptiometry (DXA). Mechanical stress also influences changes in BMD. Felson et al [6] indicated that weight affects BMD in weight-bearing bones, such as the femoral neck or Ward's triangle, but this effect is not observed in the radius. They added that weight-related load is an important factor in determining BMD; however, this phenomenon has only been recognized in men and not in postmenopausal women.

Although DXA is useful for assessing bone strength, it possesses several limitations. DXA is a 2D analysis and provides insufficient information about bone quality. In addition, the microstructural parameters in the cortical and trabecular bone are difficult to be separately analyzed using DXA [7].

In the 2000s, high-resolution peripheral quantitative computed tomography (HR-pQCT) was introduced [8]. HR-pQCT noninvasively evaluates the human bone microstructure, which can be divided into the trabecular and cortical bones [9]. Countries such as Australia and USA have used HR-pQCT in healthy individuals, and HR-pQCT has been more useful in detecting bone fracture risk than DXA [10]. HR-pQCT was introduced in Japan in 2015, and it has been utilized for conducting survey results on various pathological conditions and drug effects [11–13].

Limited studies have used HR-pQCT to investigate whether mechanical stress is related to bone microstructure. Under specific conditions, such as long-term space flight and bed rest, tibial BMD and bone microstructure are markedly worse than radial BMD and bone microstructure [14,15]. Thus, mechanical stress may be an important factor in maintaining homeostasis in weight-bearing bones. In addition, several recent studies have investigated the relationship between mechanical stress and BMD/bone microstructure by using HR-pQCT. Although the loading conditions differ in each study, the response to loading seems to be different between trabecular and cortical BMD/bone microstructure [14,16,17]. Therefore, the effect of weight-related mechanical stress on BMD/bone microstructure parameters of the trabecular or cortical bone is not clear.

No surveys have used HR-pQCT to examine the relationship between weight-related load and BMD/bone microstructure parameters under normal load conditions. We used body mass index (BMI) as a measure of weight-related mechanical stress on bones. In general, as the BMI value increases, the mechanical stress on the bones increases. The first hypothesis was that BMD/bone microstructure in loading sites, such as the lower limbs, which are exposed to mechanical stress in daily life, may have a stronger relationship with BMI than in nonloading sites. In addition, our second hypothesis was that weight-related mechanical stress affects the microstructure of trabecular and cortical bone differently. Therefore, the purpose of this study is to investigate the differences in effect of BMI on bone strength (BMD + bone microstructure) of loaded and unloaded bones, respectively, in Japanese postmenopausal women.

2. Methods

2.1. Subjects

The present retrospective observational study conducted at a single institution (Shimura Hospital) was approved by the Ethics Review Committee for Clinical Research at Shimura Hospital (approval number: 2019-2) and Hiroshima International University (approval number: C19-011). All subject consent forms were processed using an opt-out system. Patients over 60 years of age who were diagnosed with postmenopausal osteoporosis who visited Shimura Hospital as outpatients between January 2017 and December 2019 were considered eligible to participate. These patients were diagnosed with postmenopausal osteoporosis based on criteria defined by the Japanese Society for Bone and Mineral Research. The inclusion criteria were as follows: (1) women over 60 years of age with postmenopausal osteoporosis; (2) patients who had not received osteoporosis treatment in the past; (3) patients who can walk without a walking aid such as a cane. All subjects underwent blood tests, spinal radiography, DXA, and HR-pQCT. Patients who met any of the following criteria were excluded from the study: (1) central nervous system disease; (2) secondary osteoporosis; (3) severe renal dysfunction (eGFR < 30 mL/min); (4) severe liver or heart dysfunction; (5) malignancy; (6) a history of osteoporosis treatment. All survey items were based on data obtained from medical records. Our study enrolled 94 patients, but 37 were excluded from the study due to central nervous system diseases (n = 1), malignant tumor (n = 1), and history of osteoporosis treatments (n = 35). Therefore, we used the data of 57 subjects for the analysis.

2.2. Blood tests

Since the serum albumin level, which indicates the nutritional status of the whole body, has been shown to be associated with osteoporosis [18], the following data were used for this study: total protein (TP), albumin (ALB), and estimated glomerular filtration rate (eGFR). To evaluate bone turnover, we used a bone formation marker, type I procollagen N-terminal propeptide (via electrochemiluminescence immunoassay; BML, Inc., Tokyo, Japan), and a bone resorption marker, tartrate-resistant acid phosphatase 5b (via enzyme immunoassay; BML, Inc., Tokyo, Japan).

2.3. Radiographic assessment

Information of previous history of hip fracture was obtained by each investigator. Radiography was performed on the thoracic and lumbar spines. The vertebral fractures of T4 to L4 were independently measured by 3 investigators (T.Y., Y.I., and N.O.). Vertebral fractures were defined according to Genant et al. [19]. Fractures were classified as mild, moderate, or severe deformities. We counted the number of vertebral fractures that had a deformity classification above mild.

2.4. DXA

The areal BMDs of the lumbar vertebrae, femoral neck, and total hip were measured using DXA (Hologic, Bedford, MA, USA). The osteoporosis diagnosis was based on the lowest % young adult mean (YAM) of the 3 measured locations and defined according to the Japanese Society for Bone and Mineral Research.

2.5. High-resolution peripheral quantitative computed tomography

Each subject's nondominant distal radius and tibia were scanned by second-generation HR-pQCT (Xtreme CT II, Scanco Medical AG, Brüttisellen, Switzerland) to assess bone microstructure. The opposite limb was scanned if a previous implant, such as a screw or plate, was present in the nondominant limb. The reference line was placed at the endplates of the distal radius and tibia in all participants.

The HR-pQCT imaging protocol and settings were as reported by Chiba et al [20]. The scan region was 10.2 mm in width at the distal

radius and 9.0 mm proximal to the wrist joint, and 10.2 mm in width at the distal tibia and 22.0 mm proximal to the subchondral endplate of the ankle joint.

The measured parameters were as follows: total volumetric BMD (Tt.vBMD; mg/cm^3), trabecular volumetric BMD (Tb.vBMD; mg/cm^3), trabecular bone volume to tissue volume (BV/TV; %), trabecular thickness (Tb.Th; mm), trabecular number (Tb.N; mm^{-1}), trabecular separation (Tb.Sp; mm), cortical volumetric BMD (Ct.vBMD; mg/cm^3), cortical thickness (Ct.Th; mm), cortical area (Ct.Ar; mm^2), and cortical porosity (Ct.Po; %).

2.6. Statistical analysis

A priori, power analysis was performed with a power of 0.8, effect size of 0.5, and a significance level of 5%, and the number of subjects required (n = 30) was confirmed by correlation analysis. The effect size values were based on Cohen's report [21]. However, during the course of the study, there was concern that when the number of subjects was 30, the power was less than 0.8. Therefore, the number of subjects needed for our study was increased and data of 57 subjects were analyzed. The power was analyzed on the basis of the correlation coefficients of Tt.vBMD, Tb.vBMD, and Ct.vBMD using the post hoc tests (significance level = 5%) of 57 subjects, with the values of 0.984, 0.959, and 0.931, respectively. Based on these results, we considered the number of subjects reasonable for conducting a correlation analysis.

Pearson's correlation coefficient was performed to investigate the relationship among demographic data, biochemical data, and HR-pQCT parameters. Furthermore, a partial correlation analysis was performed to adjust for the effect of age and to investigate the relationship between height, weight, BMI, biochemical data, and HR-pQCT.

To investigate the effect of BMI on the tibia and radius HR-pQCT parameters, a hierarchical multiple regression analysis was performed. The hierarchical multiple regression analysis can investigate the influence of the independent variable on the dependent variable by inputting the independent variable step by step [22].

Before performing hierarchical multiple regression analysis, we conducted principal component (PC) analysis on the microstructural parameters of the tibia and radius evaluated by HR-pQCT. PC analysis is a type of multivariate statistical technique that uses orthogonal transformation to extract important information from multiple variables in a data set and convert it to a set of linear decorrelated variables called PCs [23]. An advantage of the PC analysis is that the variance of the data set can be captured with a small number of PC. The PC scores of the first PC (PC1) and the second PC (PC2) of the tibial and radius HR-pQCT parameters were used as the dependent variables in the hierarchical multiple regression analysis. The PC1 of the tibia and radius reflected the bone microstructure parameters of all trabecular and cortical bones except Ct.Po. Furthermore, the PC2 of the tibia and radius reflected the bone microstructure parameters of cortical bone. However, in the third PC (PC3), the parameter showing a factor loading of 0.5 or more was only Tb.Th of the tibia, and we did not use PC3 as a dependent variable.

To determine the independent variables used in the hierarchical multiple regression analysis, we used the variable inflation factor to confirm the multicollinearity. The number of subjects required for multiple regression analysis is reportedly 10 times the number of independent variables [24]. In our study, a minimum of 30 patients were required because we supposed that 3 independent variables, namely, age, TRACP-5b, and BMI, would be selected. The correlation between the height and weight of the subjects was weak in our study ($r = 0.360$, $P = 0.003$). In other words, even if they have the same body height, they have different body weights, and even if they have the same body weight, they have different body heights. Both body height and weight are parameters that reflect the skeletal morphology of subjects, and BMI is an index that integrates both the parameters. For these reasons, we used BMI as the independent variable. We have set the subjects in our study to postmenopausal women with osteoporosis. The bone metabolic dynamics of postmenopausal osteoporosis showed high bone turnover with the increase of bone resorption, and ovariectomy (OVX) model animals showed bone loss due to increased bone resorption. The high bone turnover leads to cortical bone porosity and increased Ct. Po. Since the increased serum TRACP-5b suggests increased bone resorption or high bone turnover, the serum TRACP-5b levels were factors that could be strongly associated with bone microstructure. Thus, we set serum TRACP-5b as one of the independent variables. These independent variables were subsequently chosen and entered according to the following procedure: Model 1: age; Model 2: age, TRACP-5b; Model 3: age, TRACP-5b, and BMI. The fit of the model was evaluated using R^2. The relative importance of the variables obtained in the final multiple regression model was evaluated using the standard variable regression coefficient (β), and the change in the R^2 value (ΔR^2), the effect of BMI on Tb.vBMD and Ct.vBMD, and each PC were investigated.

A P-value of < 0.05 was considered to be statistically significant. SPSS for Windows (version 22, IBM Corp., Armonk, NY, USA) was used for the PC analysis and hierarchical multiple regression analysis, and R version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/) was used for all the other statistical analyses.

3. Results

3.1. Patient characteristics

All quantitative variables are expressed as mean ± standard deviation (SD), and patient characteristics are shown in Table 1. The average T-scores at the femoral neck, total hip, and lumbar vertebra in 57 subjects were −3.06 ± 1.11, −2.52 ± 1.06, and −2.05 ± 1.72, respectively. All subjects were diagnosed with postmenopausal osteoporosis based on their histories of fragile fractures and their T-scores.

3.2. Simple correlation analysis

The results of the Pearson's correlation coefficient are shown in Table 2. A number of the microstructural parameters obtained by HR-pQCT in the distal tibia (Table 2A) and distal radius (Table 2B) correlated with age, weight, and BMI. In particular, BMI correlated with all the microstructural parameters except for Tb.Sp and Ct.Ar in the distal tibia. The relationship between BMI and tibial/radial HR-pQCT, which showed a significant correlation, is shown in Fig. 1.

3.3. Age-adjusted partial correlation analysis

The results of the age-adjusted partial correlation analysis are shown in Supplementary Table 1. A number of the microstructural parameters obtained by HR-pQCT in the distal tibia (Supplementary Table 1A) and distal radius (Supplementary Table 1B) correlated with BMI, similar to the simple correlation analysis. In the simple correlation and partial correlation analyses, the HR-pQCT parameters of the distal tibia tended to have a strong correlation (|r |: distal tibia, 0.266–0.606; distal radius, 0.273–0.487) with BMI compared with the HR-pQCT parameters of the distal radius.

Table 1
Patient characteristics.

Variables		Value (mean ± SD)	Range (minimum ~ maximum)
Demographic parameters			
N		57	
Age, yr		73.51 ± 7.97	60–88
Height, m		1.50 ± 0.06	1.29–1.63
Weight, kg		49.53 ± 8.45	35.00–71.10
BMI, kg/m^2		22.10 ± 3.58	16.57–31.32
Biochemical parameters			
TP, g/dL		7.00 ± 0.43	6.20–8.70
ALB, g/dL		4.11 ± 0.31	2.90–4.90
eGFR, mL/min		69.60 ± 16.43	40.30–123.20
TRACP-5b, mU/dL		458.56 ± 220.53	156.00–1219.00
P1NP, μg/L		63.47 ± 51.39	13.8–307.6
DXA parameters			
T-score	Femur neck	−3.06 ± 1.11	−5.60~−0.60
	Total hip	−2.52 ± 1.06	−4.90~−1.00
	Lumbar spine	−2.05 ± 1.72	−4.80–2.90
Fragility fracture			
Hip fracture	One side, n (%)	7 (12.3)	
	Both sides, n (%)	1 (1.8)	
Number of vertebral fractures	1, n (%)	19 (33.3)	
	2, n (%)	10 (17.5)	
	≥ 3, n (%)	15 (26.3)	

Values given as mean ± standard deviation (SD) or n (%).
BMI, body mass index; TP, total protein; ALB, albumin; eGFR, estimated glomerular filtration rate; TRACP-5b, tartrate-resistant acid phosphatase 5b; P1NP, procollagen type I N-terminal propeptide; DXA, dual-energy X-ray absorptiometry.

3.4. PC analysis

The results of the PC analysis are shown in Table 3. Seven microstructural parameters (BV/TV, Tb.N, Tb.Th, Tb.Sp, Ct.Ar, Ct.Th, and Ct.Po) were used for PC analysis. The PC loadings of PC1 in tibia and radius were high for all trabecular and cortical bone microstructural parameters except Ct.Po. In other words, PC1 reflected the overall microstructural parameters of trabecular and cortical bone. On the other hand, the PC loadings of PC2 in tibia and radius were high in cortical bone microstructural parameters such as Ct.Ar, Ct.Th, and Ct.Po. Therefore, the PC2 reflected the information of microstructural parameters on the cortical bone side.

3.5. Hierarchical multiple regression analysis

Table 4 presents the results of the hierarchical multiple regression analysis with Tb.vBMD, Ct.vBMD, PC1, and PC2 of the tibia/radius as dependent variables. In this analysis, the independent variables were those that correlated with the HR-pQCT parameters of either the distal tibia or the radius in the partial correlation analysis. This study identified that BMI was an independent factor contributing to Tb.vBMD, Ct.vBMD, and PC1 of the tibia and radius. Table 4 presents each R^2, and their representative data are shown below. Regarding the tibia, the R^2 values in Model 3 were 0.386 ($\Delta R^2 = 0.289$, $P < 0.001$), 0.466 ($\Delta R^2 = 0.269$, $P < 0.001$), and 0.329 ($\Delta R^2 = 0.255$, $P < 0.001$) for Tb.vBMD, Ct.vBMD, and PC1, respectively. Regarding the radius, the R^2 values in Model 3 were 0.257 ($\Delta R^2 = 0.152$, $P = 0.002$), 0.442 ($\Delta R^2 = 0.121$, $P = 0.001$), and 0.198 ($\Delta R^2 = 0.115$, $P = 0.008$) for Tb.vBMD, Ct.vBMD, and PC1, respectively. Thus, the ΔR^2 values at Model 3 for Tb.vBMD, Ct.vBMD, and PC1 were higher in the tibia than in the radius. However, BMI was not related to PC2 in both the tibia and radius.

We identified that serum TRACP-5b was an independent factor contributing to Ct.vBMD of the tibia and radius. In Model 2, the R^2 for the tibia was 0.198 ($\Delta R^2 = 0.151$, $P = 0.002$), whereas that for the radius was 0.321 ($\Delta R^2 = 0.143$, $P = 0.001$). Meanwhile, serum TRACP-5b was not related to Tb.vBMD/PC1/PC2 in both the tibia and radius.

4. Discussion

The study results yielded 2 important findings based on the 2 abovementioned hypotheses. (1) We confirmed that BMI is related to BMD and bone microstructural parameters in the tibia and radius, which did not change after age-adjusted partial correlation analysis. Moreover, hierarchical multiple regression analysis indicated that BMI had a stronger effect on BMD and bone microstructure in the tibia than in the radius. (2) Although BMI was related to PC1 reflecting all microstructural parameters, except for Ct.Po, no relationship was found between BMI and PC2 reflecting the cortical bone microstructural parameters. Therefore, it is suggested that BMI is relatively more strongly related to the microstructure of trabecular bone than cortical bone. Our consideration is described below.

In analyzing the relationship between each factor and each HR-pQCT parameter in our study, age was the most important confounding factor. According to a simple correlation analysis, most of the bone microstructural parameters of the tibia and radius measured by HR-pQCT correlated with age, weight, and BMI. In particular, BMI was associated with all of the bone microstructural parameters, except for Tb.Sp and Ct.Ar, in the tibia (Table 2 and Fig. 1). In general, age had the strongest influence on bone microstructure parameters. Various findings showing bone microstructure deterioration with age were observed in healthy subjects, and the microstructural change was greater in women than in men [25–27]. Age may have a considerable effect on bone microstructure because our subjects were postmenopausal women; therefore, we performed an age-adjusted partial correlation analysis. This analysis showed that several HR-pQCT parameters were correlated in both the tibia and radius (Supplementary Table 1) and that BMI was an independent related factor that affected the bone microstructure independent of age (Table 4).

The present study demonstrated differences in the effects of BMI on the microstructure of loaded and unloaded bone in postmenopausal women. The results of the simple correlation and partial correlation analyses show that the HR-pQCT parameters of the distal tibia tended to strongly correlate with BMI compared with the HR-pQCT parameters of the distal radius (tibia, |r

Table 2
Results of simple correlation analysis.

A. Demographic data, biochemical parameters vs HR-pQCT parameters (distal tibia)

	HR−pQCT parameters (distal tibia)								
	Tt.vBMD	Trabecular bone parameters					Cortical bone parameters			
		Tb.vBMD	BV/TV	Tb.N	Tb.Th	Tb.Sp	Ct.vBMD	Ct.Ar	Ct.Th	Ct.Po
Age	**−0.297**	**−0.310**	**−0.262**	**−0.417**	0.110	**0.425**	−0.217	0.034	−0.005	−0.061
	0.025	***0.019***	***0.049***	***0.001***	*0.415*	***0.001***	*0.105*	*0.799*	*0.969*	*0.653*
Height	−0.005	0.221	0.220	0.255	−0.008	−0.226	0.027	−0.047	−0.207	−0.112
	0.971	*0.098*	*0.100*	*0.056*	*0.954*	*0.090*	*0.840*	*0.728*	*0.123*	*0.409*
Weight	**0.464**	**0.544**	**0.570**	**0.395**	**0.477**	−0.248	**0.417**	0.174	0.172	**−0.356**
	< 0.001	***< 0.001***	***< 0.001***	***0.002***	***< 0.001***	*0.063*	***0.001***	*0.196*	*0.200*	***0.007***
BMI	**0.507**	**0.465**	**0.493**	**0.296**	**0.514**	−0.151	**0.437**	0.214	**0.301**	**−0.319**
	< 0.001	***< 0.001***	***< 0.001***	***0.025***	***< 0.001***	*0.262*	***0.001***	*0.111*	***0.023***	***0.016***
TP	0.090	0.141	0.155	0.091	0.027	−0.120	−0.034	0.049	0.000	0.182
	0.505	*0.296*	*0.250*	*0.502*	*0.844*	*0.376*	*0.803*	*0.716*	*0.999*	*0.176*
ALB	0.037	0.087	0.095	0.088	−0.128	−0.106	−0.027	0.070	−0.017	0.134
	0.787	*0.520*	*0.482*	*0.517*	*0.343*	*0.432*	*0.840*	*0.604*	*0.902*	*0.321*
eGFR	−0.157	−0.030	−0.063	0.044	−0.104	−0.007	**−0.275**	−0.216	−0.222	0.254
	0.245	*0.824*	*0.643*	*0.743*	*0.443*	*0.959*	***0.038***	*0.107*	*0.098*	*0.057*
TRACP−5b	−0.113	0.031	0.027	0.041	0.002	−0.028	**−0.340**	−0.073	−0.101	0.074
	0.404	*0.816*	*0.844*	*0.764*	*0.988*	*0.838*	***0.003***	*0.588*	*0.456*	*0.584*
P1NP	−0.050	0.050	0.038	0.067	0.018	−0.132	**−0.330**	0.011	0.056	−0.003
	0.711	*0.713*	*0.777*	*0.622*	*0.897*	*0.327*	***0.012***	*0.936*	*0.678*	*0.982*

B. Demographic data, biochemical parameters vs HR-pQCT parameters (distal radius)

	HR−pQCT parameters (distal radius)								
	Tt.vBMD	Trabecular bone parameters					Cortical bone parameters			
		Tb.vBMD	BV/TV	Tb.N	Tb.Th	Tb.Sp	Ct.vBMD	Ct.Ar	Ct.Th	Ct.Po
Age	**−0.362**	**−0.320**	−0.245	**−0.319**	−0.026	**0.323**	**−0.421**	−0.200	−0.226	0.215
	0.006	***0.015***	*0.066*	***0.016***	*0.846*	***0.014***	***0.001***	*0.135*	*0.091*	*0.107*
Height	0.023	0.184	0.173	0.175	0.056	−0.150	0.111	0.249	−0.019	**−0.423**
	0.863	*0.172*	*0.198*	*0.193*	*0.680*	*0.265*	*0.411*	*0.062*	*0.890*	***0.001***
Weight	**0.349**	**0.384**	**0.394**	**0.361**	0.085	−0.172	**0.263**	**0.342**	0.210	**−0.270**
	0.008	***0.003***	***0.002***	***0.006***	*0.528*	*0.200*	***0.048***	***0.009***	*0.117*	***0.042***
BMI	**0.372**	**0.315**	**0.332**	**0.297**	0.063	−0.102	0.230	0.222	0.239	−0.063
	0.004	***0.017***	***0.012***	***0.025***	*0.643*	*0.451*	*0.085*	*0.097*	*0.074*	*0.642*
TP	0.023	0.190	0.228	0.141	**0.269**	−0.140	−0.105	0.079	0.002	0.113
	0.867	*0.156*	*0.087*	*0.297*	***0.043***	*0.298*	*0.436*	*0.561*	*0.986*	*0.402*
ALB	0.024	0.140	0.148	0.126	0.139	−0.060	−0.014	0.166	0.070	−0.009
	0.859	*0.301*	*0.271*	*0.350*	*0.303*	*0.657*	*0.917*	*0.218*	*0.605*	*0.954*
eGFR	−0.075	−0.033	−0.082	−0.028	−0.066	0.023	−0.080	−0.1494	−0.122	−0.140
	0.580	*0.807*	*0.547*	*0.834*	*0.625*	*0.863*	*0.553*	*0.267*	*0.367*	*0.299*
TRACP−5b	−0.195	−0.044	−0.082	0.010	−0.053	−0.079	**−0.381**	−0.090	−0.190	0.064
	0.145	*0.745*	*0.547*	*0.940*	*0.698*	*0.560*	***0.004***	*0.505*	*0.157*	*0.638*
P1NP	−0.125	0.033	0.005	0.114	−0.072	−0.178	**−0.334**	−0.067	−0.131	−0.009
	0.353	*0.809*	*0.971*	*0.398*	*0.594*	*0.185*	***0.011***	*0.623*	*0.330*	*0.950*

The correlation coefficient *r* is shown in the upper part of each cell, and the P-value (in italics) is shown in the lower part.
The data for $P < 0.05$ is shown in bold.
HR-pQCT, high-resolution peripheral quantitative computed tomography; BMI, body mass index; TP, total protein; ALB, albumin; eGFR, estimated glomerular filtration rate; TRACP-5b, tartrate-resistant acid phosphatase 5b; P1NP, procollagen type I N-terminal propeptide; Tt.vBMD, total volumetric bone mineral density; Tb.vBMD, trabecular volumetric bone mineral density; BV/TV, trabecular bone volume to tissue volume; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; Ct.vBMD, cortical volumetric bone mineral density; Ct.Ar, cortical area; Ct.Th, cortical thickness; Ct.Po, cortical porosity.

| = 0.296−0.514; radius, |r | = 0.297−0.372) (Table 2 and Fig. 1). In addition, the hierarchical multiple regression analysis indicated that BMI had a stronger effect on BMD and bone microstructure in the tibia than in the radius (Table 4). Felson et al [6] showed that BMI was strongly associated with BMD in women, whereas no differences were observed in the effects of BMI on unloaded (radius) and loaded (spine and proximal femur) bone in women. Although Felson et al measured BMD using DXA, we measured BMD and bone microstructure using HR-pQCT. The factors that enabled us to indicate this differential effect were the measuring equipment and evaluation items used in our study. To the best of our knowledge, the differential effect of BMI on the BMD/bone microstructure of loaded and unloaded bones has remained unreported, and our study investigating postmenopausal women with osteoporosis is probably the first report to demonstrate that BMI affects the tibia more than the radius.

In addition, we analyzed the differences in the effects of BMI on the bone strength of trabecular and cortical bones. BMI was related to BMD and bone microstructure in the trabecular bone area in the distal tibia and radius (Table 4). In the cortical bone area, BMI was an independent factor contributing to BMD and was not related to PC2, which reflects the bone microstructure of the cortical bone (Table 4). The metabolic turnover of the trabecular and cortical bones is generally different, ie, the metabolic turnover of the trabecular bone is reportedly higher than that of the cortical bone [28]. In animal models of unloading and exercise loading, changes in the trabecular bone mass are followed by changes in the cortical bone mass [29]. In humans, prolonged bed rest results in bone loss from the trabecular compartment rather than from the cortical compartment in the tibia [30]. Considering that BMI was not a factor of extreme loading, it was found to be an important factor that especially determined the trabecular bone mass in the lower

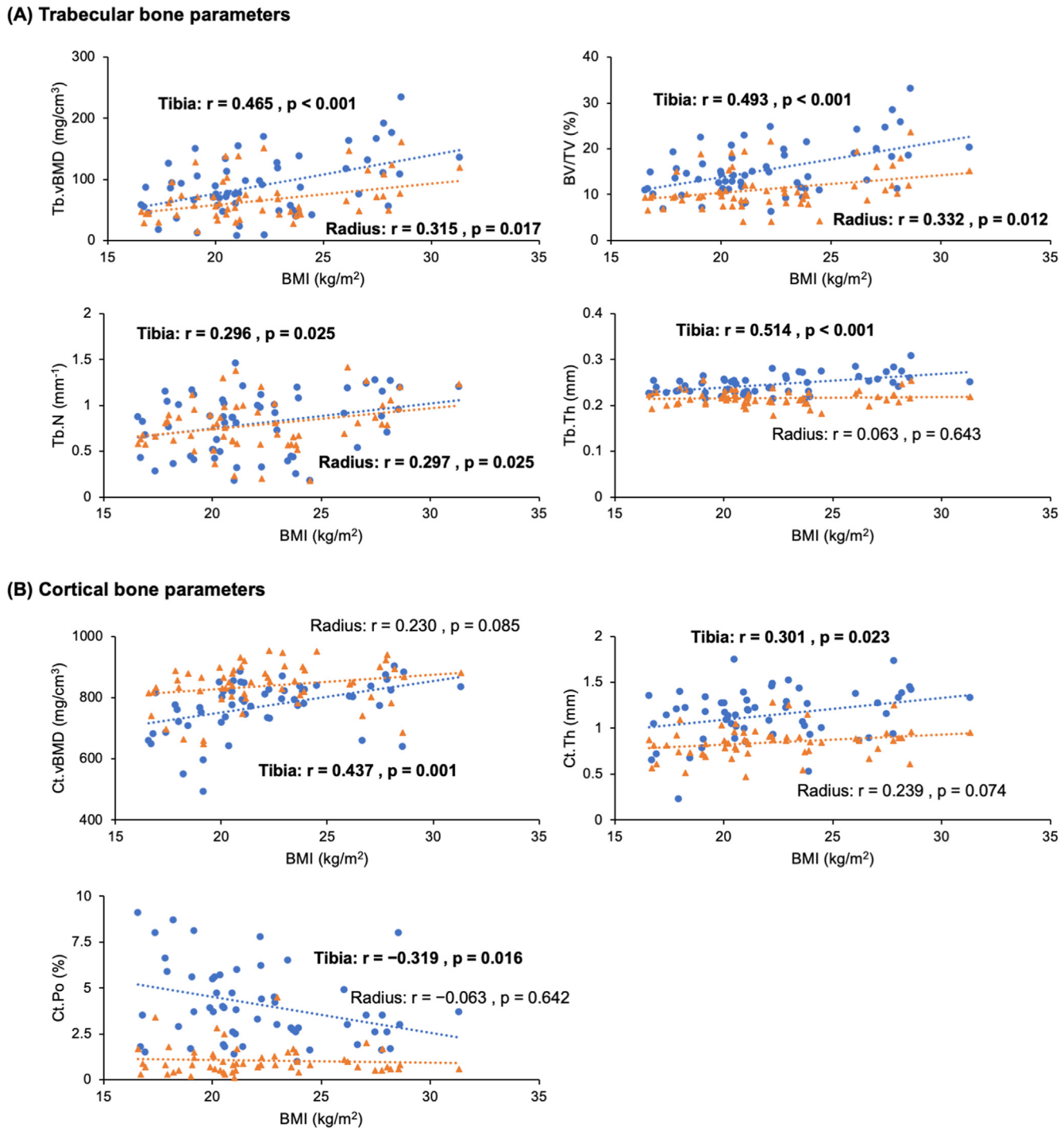

Fig. 1. Scatter plots showing the correlation between BMI and HR-pQCT parameters Scatter plots demonstrated the relationships between BMI. and (A) trabecular bone parameters or (B) cortical bone parameters in the tibia and radius. The blue-round plots show the values for the tibia and the orange-triangular plots show the values for the radius. The *r* value indicates the correlation coefficient. The regression line is shown by a dotted line.

limbs, without affecting the cortical bone microstructure.

Although different from the study purpose, the serum TRACP-5b was also a factor contributing to the Ct.vBMD of distal tibia/radius independent of BMI (Table 4). The increased bone remodeling generally affects cortical BMD more than trabecular BMD. The bone turnover of postmenopausal women is high not only in the trabecular bone but also in the cortical bone, with an increase in cortical bone porosity [31]. The increased bone remodeling also occurs in the cortical bone of an ovariectomized cynomolgus monkey, and the effect of denosumab (Dmab), which is a bone resorption inhibitor, on cortical BMD is caused by the closure of remodeling space in the cortical bone [32]. A recent study demonstrated the effects of parathyroid hormone (PTH) and Dmab on the cortical bone using HR-pQCT. Compared with PTH that promotes bone remodeling, Dmab, which suppresses bone remodeling, decreases Co.Po in the cortical bone and significantly

Table 3
Principal component analysis for HR-pQCT parameters in the distal tibia and radius.

			Distal tibia			Distal radius	
			PC 1	PC 2	PC 3	PC 1	PC 2
HR-pQCT parameters	Trabecular bone parameters	BV/TV	**0.873**	−0.338	0.246	**0.894**	−0.278
		Tb.N	**0.812**	−0.467	−0.271	**0.858**	−0.333
		Tb.Th	**0.542**	0.033	**0.766**	**0.705**	−0.278
		Tb.Sp	**−0.727**	0.410	0.477	**−0.794**	0.307
	Cortical bone parameters	Ct.Ar	**0.580**	**0.725**	−0.027	**0.644**	**0.612**
		Ct.Th	**0.611**	**0.691**	0.055	**0.610**	**0.715**
		Ct.Po	0.179	**0.627**	−0.452	0.224	**0.639**
Eigenvalue			2.984	1.898	1.157	3.500	1.652
Total explained variance (%)			42.630	27.112	16.523	50.004	23.599

The values in the table are principal component loadings.
Principal component loadings >0.5 are in bold.
HR-pQCT, high-resolution peripheral quantitative computed tomography; BV/TV, trabecular bone volume to tissue volume; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; Ct.Ar, cortical area; Ct.Th, cortical thickness; Ct.Po, cortical porosity; PC, principal component.

Table 4
Hierarchical multiple regression analysis to investigate the effects of BMI.

	Distal tibia			Distal radius		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Dependent variable: Tb.vBMD						
Age	**−0.310**	**−0.310**	**−0.420**	**−0.320**	**−0.320**	**−0.400**
	0.019	***0.020***	***< 0.001***	***0.015***	***0.016***	***0.002***
TRACP-5b		0.033	−0.004		−0.042	−0.069
		0.799	*0.972*		*0.744*	*0.563*
BMI			**0.550**			**0.399**
			< 0.001			***0.002***
R^2	**0.096**	0.097	**0.386**	**0.102**	0.104	**0.257**
	0.019	*0.063*	***< 0.001***	***0.015***	*0.051*	***0.001***
ΔR^2	**0.096**	0.001	**0.289**	**0.102**	0.002	**0.152**
	0.019	*0.799*	***< 0.001***	***0.015***	*0.744*	***0.002***
Dependent variable: Ct.vBMD						
Age	−0.217	−0.215	**−0.321**	**−0.421**	**−0.419**	**−0.490**
	0.105	*0.084*	***0.003***	***0.001***	***< 0.001***	***< 0.001***
TRACP-5b		**−0.388**	**−0.424**		**−0.379**	**−0.403**
		0.002	***< 0.001***		***0.001***	***< 0.001***
BMI			**0.530**			**0.356**
			< 0.001			***0.001***
R^2	0.047	**0.198**	**0.466**	**0.177**	**0.321**	**0.442**
	0.105	***0.003***	***< 0.001***	***0.001***	***< 0.001***	***< 0.001***
ΔR^2	0.047	**0.151**	**0.269**	**0.177**	**0.143**	**0.121**
	0.105	***0.002***	***< 0.001***	***0.001***	***0.001***	***0.001***
Dependent variable: PC1						
Age	**−0.272**	**−0.272**	**−0.375**	**−0.282**	**−0.281**	**−0.351**
	0.041	***0.043***	***0.002***	***0.034***	***0.035***	***0.007***
TRACP-5b		−0.003	−0.038		−0.055	−0.079
		0.982	*0.739*		*0.674*	*0.527*
BMI			**0.517**			**0.347**
			< 0.001			***0.008***
R^2	**0.074**	0.074	**0.329**	**0.079**	0.082	**0.198**
	0.041	*0.126*	***< 0.001***	***0.034***	*0.098*	***0.008***
ΔR^2	**0.074**	0.000	**0.255**	**0.079**	0.003	**0.115**
	0.041	*0.982*	***< 0.001***	***0.034***	*0.674*	***0.008***
Dependent variable: PC2						
Age	0.234	0.235	0.264	0.081	0.082	0.080
	0.079	*0.081*	*0.055*	*0.548*	*0.548*	*0.566*
TRACP-5b		−0.062	−0.052		−0.086	−0.086
		0.640	*0.694*		*0.530*	*0.533*
BMI			−0.148			0.006
			0.276			*0.968*
R^2	0.055	0.059	0.080	0.007	0.014	0.014
	0.079	*0.195*	*0.217*	*0.548*	*0.685*	*0.861*
ΔR^2	0.055	0.004	0.021	0.007	0.007	0.000
	0.079	*0.640*	*0.276*	*0.548*	*0.530*	*0.968*

Model 1: age; Model 2: age, TRACP-5b; Model 3: age, TRACP-5b, BMI.
Values in the table are standardized β coefficients.
The values are shown in italics to indicate the p-value.
The data for $P < 0.05$ is shown in bold.
TRACP-5b, tartrate-resistant acid phosphatase 5b; BMI, body mass index; Tb.vBMD, trabecular volumetric bone mineral density; Ct.vBMD, cortical volumetric bone mineral density; PC, principal component.

increases Ct.vBMD [33]. The average serum TRACP-5b levels were high (Table 1), considering that all of our subjects were postmenopausal women with primary osteoporosis, and many of them may have had high bone turnover. In subjects with higher serum TRACP-5b levels, the Haversian canal area may be larger; however, serum TRACP-5b and Ct.Po had no correlation, and unfortunately, cortical bone porosity caused by BMI may be undetected despite using HR-pQCT. Nevertheless, we believe that the present findings, which revealed the relationship between serum TRACP-5b and cortical BMD in untreated postmenopausal women with osteoporosis, are important and support previous reports.

However, this study has several limitations. Our study was a retrospective cross-sectional design and not longitudinal. Although we investigated the relationship between BMI, which is an indicator of physique, and BMD/bone microstructure parameters, it may be appropriate to focus on weight rather than BMI as an indicator of weight-related load. We concluded that BMI is more strongly related to the trabecular/cortical BMD and trabecular bone microstructure in the tibia than in the radius; however, we did not directly compare the tibia and radius. Furthermore, since the subjects were limited to postmenopausal women with osteoporosis, the results of this study should be applied with caution to premenopausal women and men. Moreover, given that the sample size in our study was small (57 patients), only 3 parameters, which were regarded as independent factors, were used, and the effects of other confounding factors could not be adjusted. In addition, the physical activity of the subjects in this study was not investigated, and these differences may affect the results. The strain on the bones caused by physical activity can increase local or systemic bone metabolic turnover, resulting in net bone apposition [34]. A recent study revealed a relationship between differences in physical activity and BMD/bone microstructure assessed using HR-pQCT. Ng et al [35] reported that time spent performing moderate to vigorous physical activity showed a relationship with cortical bone side parameters of the tibia. Furthermore, using The Bone-specific Physical Activity Questionnaire, they found that past physical activity scores were related to the cortical bone parameters of the tibia, while current physical activity scores were related to the trabecular bone parameters, such as Tb.Th of the tibia. These results suggest that the amount of current and past physical activity affects the trabecular and cortical bones differently, and physical activity should be investigated in detail in future studies. We used a PC analysis for bone microstructure parameters to determine the dependent variable in a hierarchical multiple regression analysis. However, the PCs calculated using a PC analysis is a synthetic variable and therefore does not directly reflect the original variable. In addition, we entered independent variables in the order of age, TRACP-5b,

and BMI in a hierarchical multiple regression analysis conducted using SPSS. However, we may need to investigate the relative importance of the independent variables based on previous reports [36]. Therefore, further research is required to thoroughly understand the influence of mechanical stress on BMD and bone microstructure, as well as the effect of serum TRACP-5b on cortical BMD.

5. Conclusions

Our data confirmed that BMI is associated with volumetric BMD and trabecular bone microstructure parameters at the tibia and radius. In correlation analysis, the majority of the correlation coefficients between BMI and HR-pQCT parameters in the tibia were higher than those in the radius, and it was shown that BMI may be more related to HR-pQCT parameters in the tibia than in the radius. However, the difference in the relevance of BMI to the HR-pQCT parameters between the tibia and radius was modest.

CRediT author statement

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Conflicts of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afos.2021.05.002.

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