Endocrine Journal 2005, **52** (6), 659–666

Effects of Age, Grip Strength and Smoking on Forearm Volumetric Bone Mineral Density and Bone Geometry by Peripheral Quantitative Computed Tomography: Comparisons between Female and Male

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Abstract. Peripheral quantitative computed tomography (pQCT) is useful to measure volumetric bone mineral density (vBMD) distinguishing trabecular from cortical bones as well as quantity of bone geometry. In the present study, we examined the effects of age, grip strength and smoking on vBMD, bone geometry and bone strength index (polar strength strain index (SSIp)), and then compared with the differences between female and male by employing pQCT in Japanese 252 female and 230 male subjects. Age was negatively correlated with vBMD, cortical area (Ct.Ar) and cortical thickness (Ct.Th) as well as SSIp in both sexes, and the correlation coefficients were higher in female, compared with those in male. Although age was correlated with endocortical circumferences (En.Le) in both sexes, periosteal circumferences (Ex.Le) were correlated with age only in male. Volumetric BMD, Ct.Ar, Ct.Th and SSIp were significantly lower in the group with vertebral fractures, although En.Le and Ex.Le were similar between subjects with and without vertebral fractures. Grip strength was positively correlated with vBMD, Ct.Ar, Ct.Th as well as SSIp. The extent of correlation was much higher in female, compared with that in male. Ct.vBMD, Ct.Ar, Ct.Th and SSIp, but not trabecular vBMD, were significantly lower in the group with high Brinkman index (number of cigarettes smoked per day) × (duration of smoking (years)) in female. These parameters were not significantly different between groups with high and low Brinkman index in male. In conclusion, the present study demonstrated that age, grip strength and smoking affected forearm vBMD, bone geometry and bone strength index by pQCT. These effects were greater in female, compared with those in male.

Key words: Bone mineral density, Bone geometry, Sex difference, Grip strength, Smoking
(*Endocrine Journal* **52**: 659–666, 2005)

BONE mineral density (BMD) is useful to evaluate osteopenia and predict osteoporotic fractures. Dual-energy X-ray absorptiometry (DXA) is used to estimate areal BMD of individual bones. However, the areal BMD measured by DXA is different from true volumetric bone mineral density (vBMD). Bone strength is affected by BMD as well as bone quality, including bone structure, the accumulation of micro damage, bone turnover state, bone matrix protein and degree of mineralization [1]. Moreover, the change of bone geometry also affects bone strength. Peripheral quantitative computed tomography (pQCT) has a potential to measure vBMD and the advantage of distinguishing trabecular from cortical bones. It is also

Received: June 6, 2005
Accepted: August 4, 2005
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useful to quantify geometric properties of long bone, because it can be used to estimate area and circumferences of total bone as well as cortical area (Ct.Ar) and cortical thickness (Ct.Th) [2]. Moreover, pQCT helps to estimate bone strength by calculating polar strength strain index (SSIp), which has recently been elaborated to predict bone strength noninvasively [3]. Bone size increases with aging [4]. Increased bone loss after menopause is associated with increased periosteal apposition rate [5]. Our previous study revealed that an excess and a deficiency of endogenous parathyroid hormone (PTH) affect bone geometry determined by pQCT [6]. These findings suggest that the evaluation of bone geometry change is useful to estimate the bone fragility.

Riggs *et al.* recently reported in a population-based study that the cross-sectional area of the vertebrae and proximal femur increased in both sexes over life, although vBMD at those sites decreased by 39–55% and 34–46%, respectively, with greater decreases in female than in male [7]. On the other hand, the increased muscle strength elevates BMD [8–11], and smoking enhances the risk of fractures [12, 13]. However, no reports have been available about the sex difference in the effects of muscle strength and smoking on vBMD and bone geometry by using pQCT.

In the present study, we examined the effects of age, grip strength and smoking on vBMD, bone geometry and bone strength index, and then compared the differences between female and male by employing pQCT in Japanese 252 female and 230 male subjects to quantify the amount of smoking for the patient, who have smoking history.

Materials and Methods

Subjects

Subjects were 250 Japanese women (65.0 ± 15.5 years, aged 26–86 years) and 230 Japanese men (63.9 ± 12.6 years, aged 30–84 years), who visited Kuno Hospital. The subjects included both those with normal BMD and osteoporotic patients. The protocol of this study was approved by the Institutional Review Board of the institution. All subjects agreed to participate in the study and gave their informed consent. Subjects were interviewed about the details of age at menopause and smoking history. None had hepatic or renal dysfunction, thyroid diseases or systemic diseases, which might affect bone metabolism. All subjects were free of drugs known to influence bone metabolism until the time of the present study. Brinkman index (BI) was calculated as (number of cigarettes smoked per day) × (duration of smoking (years)).

Radiography

Lateral radiographs of the thoracic and lumbar spine were taken. The anterior, central and posterior heights of each of the 13 vertebral bodies from T_4 to L_4 were measured using an electronic caliper. Vertebral fractures were diagnosed to be present if at least one of three height measurements taken from along the length of the same vertebra were decreased by more than 20% compared with the height of the nearest uncompressed vertebral body. Defining vertebral fractures from radiographs of the spine is difficult, because there is no gold standard for what types of deformities of vertebral shape are the results of breakage of bone. Definitions of vertebral fractures with high true positive rates and low false positive rates are clinically useful in identifying women who may have vertebral fractures. The criterion in the present study (>20%) was considered to be good for defining spinal fractures, because it had a relatively high true positive rate and low false positive rate based on qualitative classifications from a previous report [14].

BMD measurements by pQCT

pQCT analysis was performed at the nondominant forearm using an XCT-960 device (Stratec, Pforzheim, Germany) with a single energy X-ray source, as previously described [15]. All computed tomography scans had a slice thickness of 2.5 mm and a vortex size of 0.59 mm. The scanner was positioned at the site of the forearm whose distance from the ulnar styloid process corresponded to 4% and 20% of forearm length, for distal radius and midradius, respectively. To calculate the structural properties of the cortical shell, trabecular and cortical bone had to be separated. To separate the cortical bone, all voxels (0.295 mm × 0.295 mm × 1 mm) of the scanned image with a BMD lower than the threshold (267 mg/cm^3) were eliminated [16]. To separate trabecular bone, 55% of the cross-sectional area of bone was peeled off from the outer area. BMD was calculated for the cortical bone and the trabecular

bone separately. Ct.Ar is the region with linear attenuation. Ct.Th was defined as the mean distance between inner and outer edge of the cortical shell. Endocortical and periosteal circumferences were expressed as En.Le and Ex.Le, respectively. SSIp lies within the theory of stability of mechanical structures against bending or torsion. SSIp was calculated by: $(r^2 \times A \times CD/1200)/rmax$, where A is the area of a voxel (mm^2), r is its distance from the center of gravity, CD is the cortical density (mg/mm^3) and is divided by the normal physiological density of cortical bone (1,200 mg/mm^3), and rmax is the maximum distance of a voxel from the center of gravity [17]. The coefficient of variation was under 1%.

Statistical analysis

Regression analysis was performed using the statistical computer program StatView (Abacus Concepts, Berkeley, CA). Simple regression analysis was used to assess the linear relationship between study parameters, and the Pearson's correlation coefficients were calculated. All data were expressed as the mean ± SD for each index. Comparisons between two groups were made with unpaired t-test. P values<0.05 were considered significant. Univariate or multiple logistic regression analyses were performed to evaluate association between various indices and gender or vertebral fractures.

Results

Background data

Baseline indices for female and male subjects in the present study are shown in Table 1. Age and BMI were similar between male and female groups. Height, weight, grip strength and BI were higher in male than in female, as expected. Volumetric BMD and all bone geometric parameters as well as SSIp were higher in male, compared with those in female.

A multiple logistic analysis was performed with the gender as a dependent variable. Gender was significantly related to all parameters obtained by pQCT in the presence and absence of age adjustment (data not shown).

Table 1. Background data in female and male subjects

	Female	Male	*p*
No. of subjects	252	230	
Age (years)	65.0 ± 15.5	63.9 ± 12.6	N.S.
Body height (cm)	150.2 ± 6.2	163.5 ± 6.3	<0.0001
Body weight (kg)	50.2 ± 9.2	59.4 ± 10.2	<0.0001
BMI (kg/m^2)	22.23 ± 3.49	22.21 ± 3.50	N.S.
Hand grip strength (kg)	20.5 ± 7.8	32.7 ± 10.2	<0.0001
BI	57.6 ± 180.6	775.8 ± 600.7	<0.0001
Tt.vBMD (mg/cm^3)	295.58 ± 79.77	369.21 ± 86.90	<0.0001
Tb.vBMD (mg/cm^3)	133.92 ± 50.62	192.82 ± 51.31	<0.0001
Ct.vBMD (mg/cm^3)	828.75 ± 68.89	880.38 ± 71.17	<0.0001
Ct.Ar (mm^2)	26.44 ± 19.70	53.55 ± 28.43	<0.0001
Ct.Th (mm)	0.461 ± 0.363	0.820 ± 0.480	<0.0001
En.Le (mm)	58.63 ± 6.72	66.16 ± 9.40	<0.0001
Ex.Le (mm)	61.52 ± 5.43	71.31 ± 7.27	<0.0001
SSIp (mm^3)	192.5 ± 102.7	388.7 ± 162.2	<0.0001

Table 2. Correlations between age and pQCT parameters

	Female	*p*	Male	*p*
Tt.vBMD	–0.702	<0.001	–0.44	<0.001
Tb.vBMD	–0.577	<0.001	–0.301	<0.001
Ct.vBMD	–0.67	<0.001	–0.41	<0.001
Ct.Ar	–0.671	<0.001	–0.401	<0.001
Ct.Th	–0.657	<0.001	–0.414	<0.001
En.Le	0.3	<0.001	0.326	<0.001
Ex.Le	0.094	0.13	0.25	<0.001
SSIp	–0.62	<0.001	–0.368	<0.001

Effects of aging on vBMD, bone geometric parameters and bone strength index

The correlation coefficients between age and the parameters obtained by pQCT are shown in Table 2. Age was negatively correlated with vBMD in both sexes, and the correlation coefficients were higher in female, compared with those in male. As for Ct.Ar and Ct.Th as well as SSIp, similar results were obtained. Although age was correlated with En.Le in both sexes, Ex.Le were correlated with age only in male.

The strong relationship between age and pQCT parameters in female suggests that menopause affects vBMD, bone geometric parameters and bone strength index. We, therefore, compared various indices between pre- and postmenopausal women aged 45–55 years to examine the effects of menopause on pQCT parameters. As shown in Table 3, vBMD, Ct.Ar, Ct.Th and SSIp were significantly lower in postmenopausal group, compared with those in premenopausal group.

However, the bone geometric indices, such as En.Le and Ex.Le, were not significantly different between the two groups.

Comparison of vBMD, bone geometric parameters and bone strength index between subjects with and without vertebral fractures

In order to investigate whether various parameters by pQCT would affect bone fragility, we compared various indices between subjects with and without vertebral fractures (Table 4). 75/202 female and 21/198 male had vertebral fractures by X-ray analysis. Volumetric BMD, Ct.Ar, Ct.Th and SSIp were significantly lower in fracture group, although En.Le and Ex.Le were similar between subjects with and without vertebral fractures. The sex differences were not observed in the comparison of pQCT parameters between groups with and without vertebral fractures.

Since age might affect various parameters by pQCT, a multiple logistic analysis was performed with the presence of vertebral fractures as a dependent variable. In male, vBMD, Ct.Ar and Ct.Th as well as SSIp were significantly related to vertebral fractures, when age was adjusted. However, in female, Ct.vBMD, Ct.Ar and Ct.Th as well as SSIp were not significantly related to vertebral fractures when age was adjusted, although Tt.vBMD and Tb.vBMD were significantly related to vertebral fractures, suggesting that age might affect the difference of Ct.vBMD, Ct.Ar and Ct.Th as well as SSIp between groups in the presence and absence of vertebral fractures.

Correlations between grip strength and pQCT parameters

The correlation coefficients between grip strength and the parameters obtained by pQCT were shown in Table 5. Grip strength was positively correlated with vBMD, Ct.Ar, and Ct.Th as well as SSIp. The correlations of grip strength and vBMD, Ct.Ar, and Ct.Th as well as SSIp were much higher in female, compared with those in male.

Table 3. Comparison of various indices between pre- and postmenopausal women aged 45–55 years

	Premenopause	Postmenopause	*p*
No. of subjects	10	21	0.0181
Age (years)	48.9 ± 2.0	51.2 ± 2.5	
Tt.vBMD (mg/cm^3)	420.97 ± 49.89	347.65 ± 69.86	0.006
Tb.vBMD (mg/cm^3)	204.70 ± 42.87	163.87 ± 43.75	0.0208
Ct.vBMD (mg/cm^3)	922.20 ± 56.74	863.11 ± 66.62	0.0223
Ct.Ar (mm^2)	56.32 ± 13.18	38.72 ± 18.33	0.0112
Ct.Th (mm)	1.007 ± 0.272	0.673 ± 0.331	0.0097
En.Le (mm)	53.91 ± 6.22	57.87 ± 7.94	N.S.
Ex.Le (mm)	60.23 ± 4.78	62.10 ± 6.42	N.S.
SSIp (mm^3)	335.6 ± 54.8	260.7 ± 87.3	0.0192

Table 5. Correlations between grip strength and pQCT parameters

	Female	*p*	Male	*p*
Tt.vBMD	0.41	<0.001	0.189	<0.001
Tb.vBMD	0.321	<0.001	0.157	0.03
Ct.vBMD	0.258	<0.001	0.167	0.02
Ct.Ar	0.433	<0.001	0.225	0.002
Ct.Th	0.405	<0.001	0.183	0.012
SSIp	0.447	<0.001	0.305	<0.001

Table 4. Comparison of various indices between subjects with and without vertebral fracture

	Female		*p*	Male		*p*
	fracture (–)	fracture (+)		fracture (–)	fracture (+)	
No. of subjects	127	75		177	21	
Age (years)	64.9 ± 9.7	77.5 ± 8.4	<0.0001	66.9 ± 8.7	73.1 ± 9.0	0.0023
Tt.vBMD (mg/cm^3)	298.0 ± 62.4	236.8 ± 43.5	<0.0001	367.5 ± 82.7	278.9 ± 60.7	<0.0001
Tb.vBMD (mg/cm^3)	141.8 ± 38.4	92.1 ± 34.0	0.0024	193.7 ± 47.9	132.6 ± 34.1	<0.0001
Ct.vBMD (mg/cm^3)	823.6 ± 60.5	798.1 ± 51.0	<0.0001	878.7 ± 71.6	828.6 ± 54.0	0.0022
Ct.Ar (mm^2)	25.89 ± 17.07	14.97 ± 11.74	<0.0001	53.17 ± 28.49	29.46 ± 19.98	0.0003
Ct.Th (mm)	0.446 ± 0.306	0.256 ± 0.221	<0.0001	0.807 ± 0.479	0.432 ± 0.309	0.0006
En.Le (mm)	58.94 ± 6.40	60.59 ± 6.63	N.S.	66.86 ± 9.52	69.42 ± 7.75	N.S.
Ex.Le (mm)	61.74 ± 5.32	62.20 ± 5.90	N.S.	71.93 ± 7.40	72.13 ± 6.73	N.S.
SSIp (mm^3)	192.8 ± 84.2	136.7 ± 79.6	<0.0001	390.1 ± 164.2	252.4 ± 112.7	0.0002

Comparison of vBMD, bone geometric parameters and bone strength index between subjects with high and low BI

Next, we examined the effects of smoking on vBMD, bone geometric parameters and bone strength index. High BI group was defined by 400 and more than from low BI group. Body height was similar in groups with high and low BI. As shown in Table 6, Ct.vBMD, Ct.Ar, Ct.Th and SSIp, but not trabecular (Tb) vBMD, were significantly lower in the group with high BI in female. These parameters were not significantly different between groups with high and low BI in male. On the other hand, En.Le were significantly higher in the group with high BI in both sexes, although Ex.Le was higher in the group with high BI only in male.

Discussion

Aging is an important risk factor for decreased BMD and osteoporotic fracture [12, 18]. There were no age-dependent changes in radial total and trabecular BMD by pQCT in premenopausal female [19]. In contrast, age and years since menopause were negatively correlated with BMD in postmenopausal female [19]. The annual bone loss rates at predominantly trabecular bone sites were accelerated in radial pQCT in Japanese female [20]. Moreover, Riggs *et al.* [7] recently reported by employing pQCT that bone cross-sectional area increased in both sexes, whereas vBMD decreased with greater extent in female than in male at the vertebrae and proximal femur. The present study revealed that vBMD, bone geometry index and bone strength index were all higher in male, compared with those in female. In the comparisons between male and female, the relationship between age and vBMD was higher in female. The age-dependent changes of bone geometry indices were also greater in female, compared with those in male. These findings were partly in contrast with those by Riggs *et al.* [7]. Namely, they reported that the age-related decreases of trabecular vBMD were similar in both sexes, although cortical vBMD decreased more in female than in male at radius. These discrepancies might be partly due to the background of subjects or racial differences.

Age-related periosteal apposition is considered to occur in male [21, 22] and, to a lesser extent in female [21, 23–25]. Ahlborg *et al.* [5] reported that the medullary bone diameter increased annually by 1.1%, and the periosteal diameter by 0.7% after menopause. Moreover, serum estradiol levels were correlated with changes in the periosteal diameter and changes in BMD. Our data of pre- and postmenopause women were compatible with their evidence. Taken together, the great change in vBMD and bone geometry as well as bone strength index in female might be explained by the influence of estrogen deficiency by menopause. In a previous study, the rates of metacarpal cortical loss were very similar in both male and female, but periosteal apposition was somewhat greater in male (and endocortical loss somewhat less), mitigating the loss of thickness and overall mass [26]. Another study also supported those findings in long bones [27]. These evidence were compatible with our findings that age was correlated with Ex.Le only in male.

In Japanese female, radial pQCT showed a higher

Table 6. Influence of smoking on vBMD, bone geometric parameters and bone strength indice

	Female		*p*	Male		*p*
	BI<400	BI≥400		BI<400	BI≥400	
No. of subjects	182	13		48	145	
Age (years)	69.2 ± 11.0	70.5 ± 10.7	N.S.	69.1 ± 9.5	67.2 ± 8.7	N.S.
Tt.vBMD (mg/cm^3)	278.7 ± 64.7	236.2 ± 42.6	0.0212	372.9 ± 91.8	352.0 ± 81.9	N.S.
Tb.vBMD (mg/cm^3)	123.6 ± 44.0	117.8 ± 46.5	N.S.	190.8 ± 53.7	185.4 ± 48.7	N.S.
Ct.vBMD (mg/cm^3)	816.7 ± 59.6	783.7 ± 27.0	0.0488	805.2 ± 68.4	868.7 ± 72.7	N.S.
Ct.Ar (mm^2)	22.74 ± 16.64	11.89 ± 6.27	0.0206	54.65 ± 27.61	49.14 ± 29.0	N.S.
Ct.Th (mm)	0.392 ± 0.300	0.190 ± 0.105	0.0168	0.847 ± 0.477	0.736 ± 0.476	N.S.
En.Le (mm)	59.18 ± 6.48	63.19 ± 4.84	0.0303	64.49 ± 8.06	68.21 ± 9.60	0.0168
Ex.Le (mm)	61.65 ± 5.47	64.39 ± 4.48	N.S.	69.82 ± 6.02	72.83 ± 7.57	0.0131
SSIp (mm^3)	177.2 ± 88.4	111.7 ± 52.5	0.009	384.6 ± 152.9	372.2 ± 169.8	N.S.

odds ratio of fracture risk (4.4) than radial DXA, and cortical area ratio seemed to be a good predictor of fracture risk (odds ratio: 5.2) [20]. Moreover, in a study using 126 human cadavers, radial pQCT, spine QCT and femoral DXA showed similar capability of predicting a combined index of mechanical strength at the hip, spine and radius [28]. The present study revealed that vBMD was lower in both cortical and trabecular bones in the group with vertebral fractures in both sexes. Moreover, cortical thickness and area as well as bone strength index were significantly lower in the fracture group, although En.Le and Ex.Le were not significantly different in either group. These findings indicate that the index of vBMD and cortical thickness as well as bone strength index are useful to predict vertebral fractures. However, whether bone geometry measurements would be useful for the prediction of fracture risk still remains unknown. A large scale study increasing the number of subjects to assess radial or femoral fractures is necessary to clarify these issues.

Muscle strength is related to BMD [10, 11]. Several studies [8, 9] suggested that grip strength was correlated with BMD. Wapniarz *et al.* [19] reported that bone mineral content and bone area at distal radius by pQCT were significantly correlated with grip strength. However, they speculated that grip strength was related to bone mass and not to volumetric density. In the present study, grip strength was significantly correlated with vBMD, Ct.Ar, Ct.Th and bone strength index. However, Boonen *et al.* reported that grip strength was significantly related to cortical, but not to trabecular density in 129 community based women by radial pQCT [29]. These discrepancies might be caused by the relatively small number of subjects in their study. Moreover, the correlations between grip strength and pQCT parameters were higher in female, compared with those in male in the present data. Several studies suggested that the impact of mechanical stress on osteoblast was affected by estrogen [30, 31]. These findings suggest that muscle strength and/or mechanical stress affect BMD and bone strength dependent on the state of estrogen.

Smoking is related to decreased BMD in several studies [32–35]. Slemenda *et al.* [36] reported that the rates of bone loss from the radius were significantly greater in subjects with smoking. Moreover, smoking is linked to an increased prevalence of vertebral and hip fractures [12, 13, 37]. In the present study, smoking was related to cortical vBMD, Ct.Th, Ct.Ar and bone strength index only in female, not in male. A study by Szulc *et al.* [38] suggested that secondary hyperparathyroidism might be related to bone loss in moderate smokers. Therefore, secondary hyperparathyroidism might affect cortical bone more potently in female, possibly dependent on the state of estrogen. Actually, we previously demonstrated that estrogen antagonizes osteoclast formation induced by PTH in mouse [39, 40]. Moreover, estrogen was effective to prevent bone loss in patients with primary hyperparathyroidism [41, 42]. These findings suggest that estrogen protects the bone from the catabolic effects of PTH induced by smoking. However, since the differences of pQCT parameters for cortical bone were slight between groups with high and low BI, a large scale study is necessary to clarify the effects of smoking on the cortical bone.

In conclusion, the present study demonstrated that age, grip strength and smoking affected vBMD, bone geometry and bone strength index by pQCT, and that the extent of these effects was greater in female, compared with male.

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