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Original Article

Development of a QUS Device to Evaluate Deterioration of Cortical Bone: Verification by HR-pQCT and Measurements in Healthy Individuals and Dialysis Patients

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Abstract

Introduction: The objectives of this study were to identify what is reflected in cortical speed of sound (cSOS) measured by a cortical quantitative ultrasound (cortical QUS) device we have developed, and to investigate cSOS measurements in healthy individuals and dialysis patients. *Methods:* The cSOS and the SOS were measured by cortical QUS and conventional QUS in 20 volunteers, and the correlations between these measurements and areal bone mineral density measured by dual-energy X-ray absorptiometry and bone microstructural parameters on high-resolution peripheral quantitative computed tomography were analyzed. The cSOS and the SOS were measured in 91 young adults (47 men, 44 women), 64 elderly people (30 men, 33 women), and 64 dialysis patients (33 men, 31 women). The period of hemodialysis and intact parathyroid hormoneevels were also investigated in the dialysis patients. *Results:* cSOS was correlated with cortical tissue mineral density (tibia: r = 0.74, radius: r = 0.72) on high-resolution peripheral quantitative computed tomography, reflecting the degree of minaralization and microporosity of cortical bone. There was no correlation with the thickness of cortical bone, suggesting that it measured the bone quality rather than bone mass. Elderly women had lower cSOS than young adults (3865 ± 74 vs 3971 ± 63 m/s, $p < 0.01$). Many of dialysis patients showed very low cSOS and it was related to higher intact parathyroid hormone levels (male: ß = −0.67, female: ß = −0.60). *Conclusions:* Our cortical QUS device is capable of evaluating the qualitative degradation of cortical bone, which cannot be assessed by conventional QUS, and its use in combination with conventional QUS may provide a better understanding of fracture risk.

Key Words: Cortical bone; Cortical speed of sound; Dialysis; High Resolution peripheral Quantitative CT (HR-pQCT); Quantitative ultrasound (QUS).

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RS, DC, TA, and TK have served on Research and Innovation Center, Furuno Electric Co., Ltd. The other authors declare that they have no conflicts of interest.

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Introduction

Osteoporosis is defined as a disease in which decreased bone strength leads to increased fracture risk. Osteoporotic fractures severely diminish the activities of daily living of elderly people, shorten their healthy lifespan, and greatly increase medical costs.

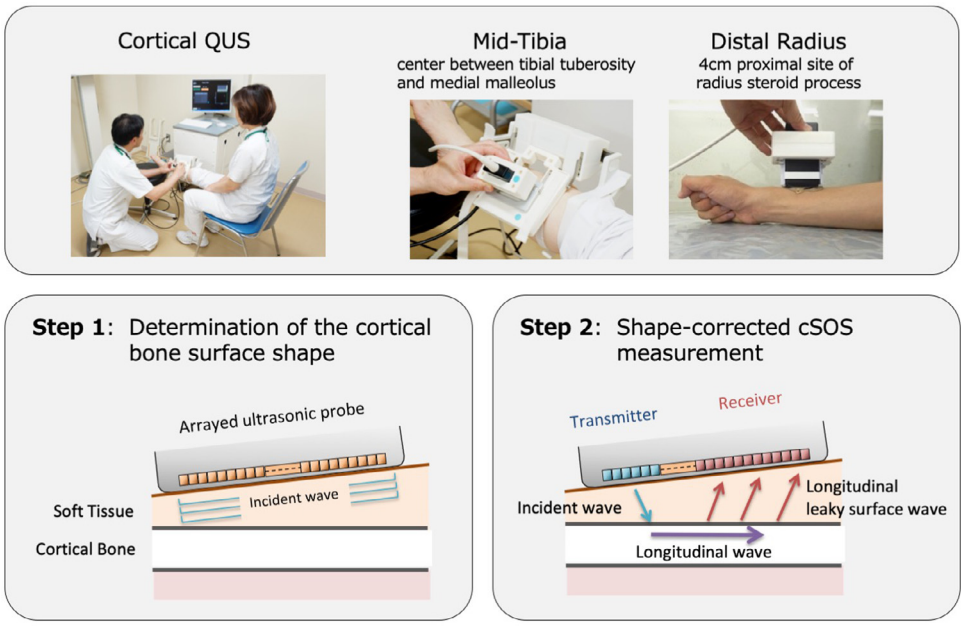

Fig. 1. Measurement of cortical speed of sound (cSOS) by cortical QUS: Measurement sites, process, and principle.

The gold standard for the evaluation of osteoporosis is bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry (DXA).[1,2] However, as DXA has yet to become widespread enough for extremely-numerous patients with osteoporosis, the fact that it is not used for many patients is an issue. Quantitative ultrasound (QUS) is a compact device that is simple to operate and does not involve radiation exposure. Previous studied have shown QUS has comparable ability of fracture prediction to DXA.[3] However, its reliability is generally not as high as that of DXA, and it is therefore regarded as more useful for screening for osteoporosis.[2] There is thus a need to add more functionality to QUS to improve its performance in evaluating fracture risk.

There are several types of QUS device that have been developed until now. The most common QUS devices measure the speed of ultrasound (SOS) propagated in the cancellous bone of the calcaneus using the facing transducers.[4–8] There are other QUS devices that measure the peripheral bone, such as the phalanges and radius.[9,10]

However, the structure that makes the greatest contribution to determining bone strength is cortical bone, and a technique known as the axial transmission (AT) method to evaluate ultrasound in cortical bone is thus currently the subject of research.[11–15]

Several AT methods have been developed, and all measure the cortical speed of sound (cSOS) propagating in the longitudinal direction of cortical bone. First, there is a method called first arriving signal (FAS) that calculates the speed from the FAS. The devices have used a frequency of 0.1 to 1.25 MHz, but the lower the frequency is, the more the result is affected by cortical bone thickness.[11–13] Recently, a method has been developed that performs multiple propagation mode using arrays of transducers and a wide range of time domain signals.[14,15] In this method, since the bone structure is modeled before analysis, errors may occur when the actual bone structure differs from the model. In particular, when cortical bone deteriorates and the back surface becomes spongy, there is a concern about the measurement accuracy. Therefore, Furuno Electric Co., Ltd. (Nishinomiya, Japan) has developed a device with a frequency of 3 MHz, a high frequency considering bone dimensions that analyses the FAS in order to eliminate the effect of bone thickness. As shown in Fig. 1, a probe is placed against the cortical bone of the central tibia or the distal radius, and transmits the ultrasound waves. The QUS device measures the speed of sound propagated through the cortical bone by detecting leaky surface waves from the cortical bone.

On the other hand, the imaging technique that currently enables the most detailed evaluation of cortical bone is high-resolution peripheral quantitative computed tomography (HR-pQCT).[16–18] HR-pQCT is a modality that provides high-resolution images and enables the in vivo analysis of a range of data, including the mineral density, thickness, and porosity of cortical bone. However, due to its high cost and complexity, it is not used in daily clinical practice.

It has not yet been established which aspects of cortical bone are actually evaluated by the cortical QUS device and how its measurements correlate with those of DXA and conventional calcaneal QUS. The measurements by this cortical QUS device in healthy individuals and populations at risk of fracture are also unknown.

The objectives of this study were to identify which aspects of cortical bone are reflected in measurements

with this cortical QUS device using HR-pQCT, a highest-resolution CT modality in clinical use, and to investigate how these are correlated with DXA and calcaneal QUS, the devices currently used to evaluate osteoporosis (Part 1), as well as to investigate the associations between measured values, age, and sex in a healthy population and to investigate measurements in dialysis patients as a population with abnormal bone metabolism that is at high risk of fractures (Part 2).

Methods

Cortical QUS Device

This device uses the AT method to measure the speed at which ultrasound waves are propagated in cortical bone (cortical speed of sound, cSOS).[11–15] As shown in Fig. 1, ultrasound waves are emitted obliquely from one end of the probe to the cortical bone. The incident waves are propagated in the cortical bone along the long axis of the bone, and waves known as longitudinal leaky surface waves are re-emitted on the soft tissue side. These waves are detected by multiple detectors, and the cSOS is calculated from the propagation distance and propagation time.

As shown in Fig. 1, a 2-step transmission and reception system is used to avoid errors occurring when the surface of the probe is not parallel with the surface of the bone. In Step 1, the shape of the bone surface is monitored, and the relative positions of the probe and the cortical bone surface are assessed, after which, in Step 2, ultrasound waves are emitted, propagated in cortical bone, and the longitudinal leaky surface waves are detected. The data on the surface of the cortical bone acquired in Step 1 are used to correct the ultrasound propagation path to ensure that the correct cSOS value is calculated.

In addition to the longitudinal leaky surface waves, the receiver array sensors also detect numerous unnecessary waves, including direct waves propagated from the transmitter to the receiver, and reflected waves from the periosteal and endosteal surface of the cortical bone. The narrower the thickness of the cortical bone, the more reflected waves from the endosteal surface are superimposed, and the cSOS becomes slower. To minimize the effect of cortical bone thickness, 3 MHz of the frequency, higher than that used in conventional AT, is used for this device. Because the use of a high frequency has the disadvantage such as scattering and absorption, a 32-channel array probe is used to obtain multichannel receiver data, enabling robust cSOS measurements even in noisy environments. cSOS measurements are made in the central tibia or distal radius, because soft tissue is comparatively thin, and both weight-bearing and non−weight-bearing cortical bone are to be evaluated. During tibial measurements, a measurement brace is attached to the leg. The use of a brace means that the probe can be placed at the same site in little time and with good reproducibility. The probe can be slid horizontally along the brace, which contains an internal encoder to measure the position of the probe. Because the values of tibial cSOS vary horizontally, the probe position and cSOS value are measured simultaneously and the mean cSOS per unit horizontal length is output, limiting the effect of the horizontal variation and increasing the reproducibility of measurements.

To verify reproducibility, cSOS values were measured 3 times on different days in 15 volunteer subjects (8 men, 7 women) with mean age of 44 ± 19 years (range 22−67 years). The root mean square coefficient of variance (RMS%CV) was 0.46% for the central tibia and 0.64% for the distal radius, indicating that the measurements were highly precise.

Table 1
Participants and Imaging Modalities Performed in Part 1 and 2 of This Study

		Age (years)	Gender (M/F)	Cortical QUS		QUS	DXA		HR-pQCT			
				Mid-tibia	Distal radius	Calcaneus	Spine	Hip	Mid-tibia	Distal radius	UD-tibia	UD-radius
Part 1	Volunteers (N = 20)	32-73	3/17	√	√	√	√	√	√	√	√	√
Part 2	Young adults (N = 91)	20-44	47/44	√		√						
	Elderly (N = 64)	60-84	30/33	√		√						
	Dialysis patients (N = 64)	37-75	33/31	√		√						

Abbr: UD-Radius, ultra distal radius; UD-Tibia, ultra distal tibia.
DXA Spine: average areal BMD of L1-4, DXA Hip: average areal BMD of bilateral total hips and femoral necks.
HR-pQCT Mid-Tibia and Distal Radius: cortical bone microstructure and mineral density, HR-pQCT UD-Tibia and UD-Radius: trabecular bone microstructure and mineral density.

Part 1: Validation Study by HR-pQCT

Subjects

The subjects were 20 volunteers (3 men, 17 women) with mean age of 56 ± 15 years (Table 1). To ensure that this group contained subjects with a wide variety of bone densities and qualities, they included individuals who varied widely in age (32–73 years), as well as one individual with rheumatoid arthritis and 3 dialysis patients. They were recruited in our office and hospital. Height of the subjects was 155 ± 8 cm (135–170 cm), weight was 53.2 ± 7.2 kg (42.0–69.0 kg), and body mass index (BMI) was 22.2 ± 4.0 kg/m^2 (15.4–33.5 kg/m^2).

Individuals taking antiosteoporosis drugs, pregnant women, and minors were excluded.

The study protocols were approved by the Ethics Committee, and informed consent was obtained from all subjects.

Cortical QUS

cSOS (m/s) was measured by cortical QUS in the right central tibia (center between tibial tuberosity and medial malleolus) and distal radius (4 cm proximal site of radius steroid process) (Fig. 1, Table 1).

Calcaneus QUS

SOS (m/s) was measured by conventional QUS in the right calcaneus (CM-200, Furuno, Hyogo, Japan) (Table 1).

DXA

The lumbar spine and proximal femur were scanned by DXA (Lunar Prodigy Advance, GE Lunar, Madison, WI). The lumbar spine was scanned at levels L1–4, and the mean areal BMD (aBMD, mg/cm^2) was calculated as the representative value, excluding vertebral bodies with fractures or severe osteoarthritic deformation. For the proximal femur, the aBMD of the total hip and femoral neck was taken as the representative value.

As to the reproducibility of aBMD measurements by DXA, the root mean square coefficient of variation (RMS%CV) of L1–4 was 1.00%, total hip 0.42%, femoral neck 0.76%.

HR-pQCT

The central tibia and distal radius, the same sites measured by cortical QUS, were scanned by HR-pQCT (XtremeCT II, Scanco Medical, Brüttisellen, Switzerland), and the microstructure of the cortical bone was evaluated. An aluminum ball 3 mm in diameter was applied as a marker to the site of cortical QUS scanning and used as a reference point to determine the scanning site in the HR-pQCT scout view (Fig. 2). The scanning range was 10.2 mm.

To evaluate the microstructure of trabecular bone, the ultra-distal radius and tibia of the right arm and leg were also scanned. The radius was scanned at a site 9.0 mm proximal to the wrist joint, and the tibia at a site 22.0 mm proximal to the ankle joint. The scanning range was 10.2 mm.

The scanning conditions were as follows: tube voltage 68 kVp, tube current 1470 μA, 100 W, integration time 4.3 ms, number of projections 900, FOV 140 mm, matrix 2304 × 2304, voxel size 60.7 μm, scanning range 10.2 mm, and number of scans 168. Scanning time was 2.0 minutes at each site, and the X-ray dose was volume computed tomography dose index (CTDI vol) 10.8 mGy and dose-length product 11.0 mGycm.

Bone microstructure and mineral density were measured following the standard analysis protocol for HR-pQCT. Cortical thickness (Ct.Th, mm), cortical porosity (Ct.Po, %), and cortical tissue mineral density (Ct.TMD, mg/cm^3) were measured for the central tibia and distal radius. Trabecular thickness (Tb.Th, mm), trabecular number (Tb.N, 1/mm), and trabecular BMD (Tb.BMD, mg/cm^3) were measured for the distal radius and tibia. Cortical TMD is the BMD of the cortical bone excluding areas of porosity, and reflects the mineralization and microporosity of cortical bone.[19–21]

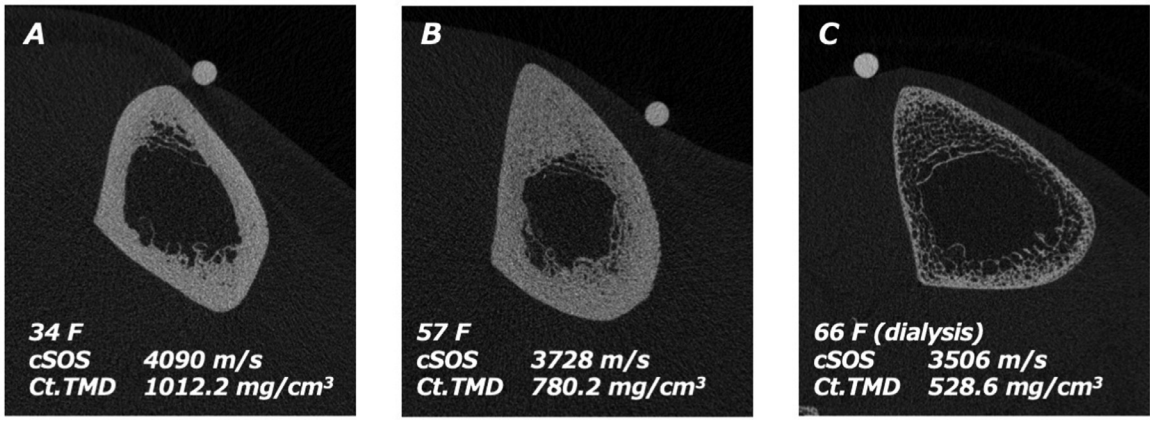

Fig. 2. HR-pQCT images of mid-tibia of young adults (A), elderly (B), and dialysis patient (C). A marker ball made of aluminum was used to correspond with the measurement site of cortical QUS.

As to reproducibility of the bone microstructure and mineral density measurements by HR-pQCT, the RMS%CV of Ct.Th was 1.17%, Ct.Po 13.28%, Ct.vTMD 0.56%, Tb.Th 1.00%, Tb.N 2.04%, Tb.vBMD 1.54%.

Statistical Analysis

Spearman's rank-correlation coefficient was used to test for correlations between cSOS and SOS measured by cortical and calcaneal QUS, aBMD measured by DXA, and bone microstructure and density parameters on HR-pQCT. In order to exclude the spurious correlation, partial rank-correlation coefficient corrected by age, height, and weight was also performed. For all tests, $p < 0.05$ was regarded as significant (IBM SPSS Statistics Version 21.0, IBM Corp, Armonk, NY).

Part 2: Measurements in Healthy Individuals and Dialysis Patients

Subjects

The subjects were 91 healthy young adults (47 men, 44 women, 20–44 years), 64 elderly people (30 men, 33 women, 60–84 years), and 64 dialysis patients as a fracture risk group with abnormal bone metabolism (33 men, 31 women, 37–75 years, mean years of hemodialysis 6.6 ± 8.3 years, range 0.2–36.3 years; Table 1). Individuals taking antiosteoporosis drugs, pregnant women, and minors were excluded.

Height of the healthy young adults was 167 ± 10 cm (145–188 cm), weight was 62.0 ± 12.4 kg (36.0–101.0 kg), and BMI was 22.1 ± 3.2 kg/m^2 (17.1–32.9 kg/m^2). There was no individual in healthy young adults who had a history of fragility fracture. Height of the elderly people was 157 ± 8 cm (135–175 cm), weight was 55.4 ± 10.5 kg (35.0–85.7 kg), and BMI was 22.5 ± 3.2 kg/m^2 (16.8–30.7 kg/m^2). There was no individual in elderly people who had a history of fragility fracture. Height of the dialysis patients was 162 ± 8 cm (148–178 cm), weight was 58.9 ± 14.0 kg (37.0–94.0 kg), and BMI was 22.1 ± 3.7 kg/m^2 (16.5–31.8 kg/m^2). There were 5 individuals in dialysis patients who had a history of fragility fracture.

The study protocols were approved by the Ethics Committee, and informed consent was obtained from all subjects.

Cortical QUS

cSOS (m/s) was measured by cortical QUS in the right central tibia (center between tibial tuberosity and medial malleolus) (Fig. 1, Table 1).

Calcaneus QUS

SOS (m/s) was measured by conventional QUS in the right calcaneus (CM-200, Furuno, Hyogo, Japan) (Table 1).

Blood Tests

The serum intact parathyroid hormone (iPTH) (pg/ml) levels of the dialysis patients were measured by electrochemiluminescence immunoassay.

Statistical Analysis

Bonferroni's test was used to test differences between the mean values of cSOS measured by cortical QUS (central tibia) and SOS measured by calcaneal QUS in young adults, elderly people, and dialysis patients. Spearman's rank-correlation coefficient was used to test for correlations between cSOS and SOS and age for all subjects, and for correlations between cSOS and SOS, years of hemodialysis, and iPTH for dialysis patients. Also, to know the factors that were most involved with cSOS and SOS, multiple regression analysis (stepwise) was performed with cSOS and SOS as the dependent variable and age, height, weight, fracture history, years of hemodialysis, and iPTH as the independent variable. For all tests, $p < 0.05$ was regarded as significant (IBM SPSS Statistics Version 21.0, IBM Corp, Armonk, NY).

Results

Part 1: Validation Study by HR-pQCT

Table 2 and 3 shows the correlations between cortical QUS, calcaneal QUS, DXA, and HR-pQCT.

Regarding cortical QUS, there was no correlation between cSOS and aBMD measured by DXA. With respect to cortical parameters on HR-pQCT, although cSOS was not correlated with cortical thickness and porosity, there was a strong correlation with cortical TMD (Figs. 2 and 3). There were no correlations between cSOS and trabecular parameters on HR-pQCT.

As to calcaneal QUS, SOS was correlated with cortical thickness and trabecular number of the tibia measured by HR-pQCT.

Part 2: Measurements in Healthy Individuals and Dialysis Patients

Table 4 shows the values of cortical QUS and calcaneal QUS measurements in healthy individuals and dialysis patients, and their correlations with age.

Among healthy individuals, cSOS measured by cortical QUS was lower in elderly people than in young adults only among women, showing a negative correlation with age ($r = -0.57$). SOS measured by calcaneal QUS was lower in elderly people compared with young adults, and this negative correlation with age was particularly strong for women (men: $r = -0.38$; women: $r = -0.70$). As shown in Fig. 4, although SOS decreased in almost all elderly people, cSOS had a broad distribution, decreasing in some elderly people but not in others.

Among dialysis patients, both cSOS and SOS were lower than the values seen in young adults (Table 4). As shown in Fig. 5, SOS (transverse axis) decreased in elderly people compared with young adults, but there was no significant difference between the values for dialysis patients and those for elderly people. In contrast, cSOS (longitudinal axis) decreased in elderly people compared with young adults, and it was very low in dialysis patients compared with the values seen in elderly people.

Table 2
Correlation Coefficients Between cSOS and SOS Measured by Cortical and Calcaneus QUS and Parameters Measured by DXA and HR-pQCT

(A) Cortical QUS at mid-tibia

	QUS	DXA			HR-pQCT			HR-pQCT		
	Calcaneus	L1-4L1-4	Total hip	Femoral neck	Mid-tibia Cortical bone			UD-tibia Trabecular bone		
	SOS	aBMD	aBMD	aBMD	Ct.Th	Ct.Po	Ct.TMD	Tb.Th	Tb.N	Tb.BMD
Cortical QUS (Mid-tibia) cSOS	0.46*	0.30	0.18	0.29	0.10	−0.31	0.83**	−0.17	0.22	0.30
Calcaneus QUS SOS	-	0.46 *	0.64 **	065**	0.68**	−0.43	0.41	−0.04	0.62**	0.66**

(B) Cortical QUS at distal-radius

	QUS	DXA			HR-pQCT			HR-pQCT		
	Calcaneus	L1−4	Total hip	Femoral neck	Distal radius Cortical bone			UD-radius Trabecular bone		
	SOS	aBMD	aBMD	aBMD	Ct.Th	Ct.Po	Ct.TMD	Tb.Th	Tb.N	Tb.BMD
Cortical QUS (Distal radius) cSOS	0.29	0.28	0.23	0.35	0.15	−0.53*	0.79**	−0.10	0.39	0.27
Calcaneus QUS SOS	-	0.46*	0.64**	0.65**	0.55*	−0.62**	0.41	0.26	0.67**	0.70**

Abbr: UD-Radius,ultra distal radius; UD-Tibia, ultra distal tibia.
Spearman's rank-correlation coefficient * $p < 0.05$, ** $p < 0.01$.

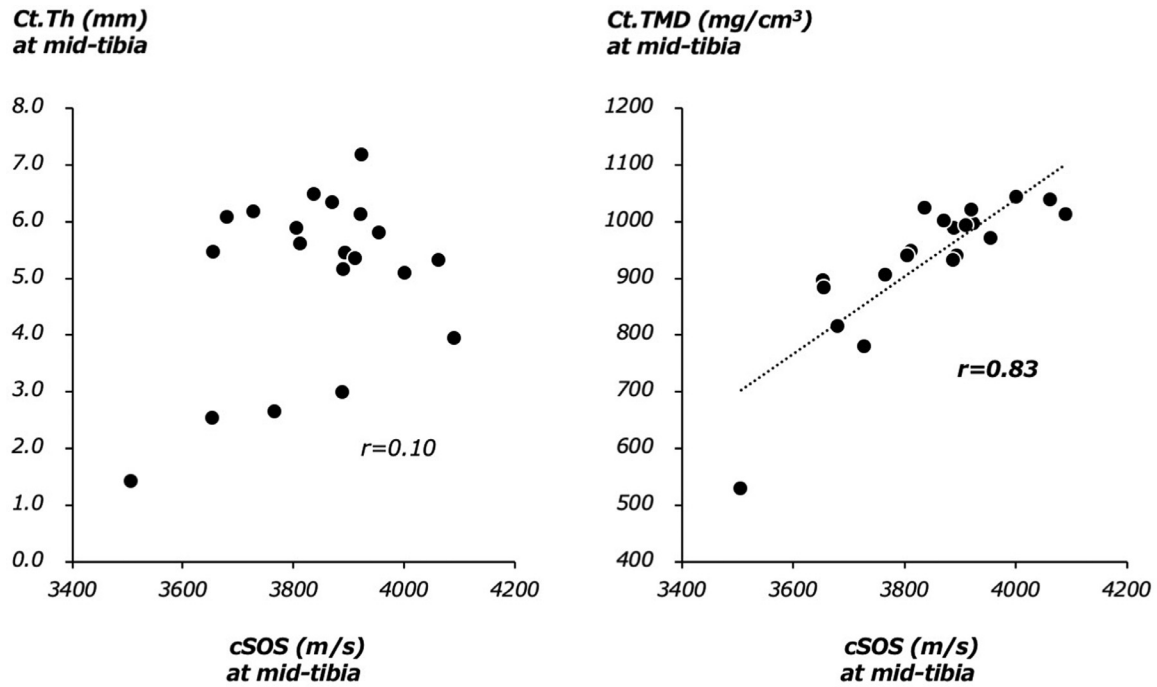

Fig. 3. Correlations between cSOS, cortical thickness (Ct.Th), and cortical tissue mineral density (Ct.TMD) at mid-tibia.

Table 3
Partial Correlation Coefficients Between cSOS and SOS Measured by Cortical and Calcaneus QUS and Parameters Measured by DXA and HR-pQCT Corrected by Age, Height, and Weight

(A) Cortical QUS at Mid-Tibia

	QUS	DXA			HR-pQCT			HR-pQCT		
	Calcaneus	L1−4	Total hip	Femoral neck	Mid-tibia Cortical bone			UD-tibia Trabecular bone		
	SOS	aBMD	aBMD	aBMD	Ct.Th	Ct.Po	Ct.TMD	Tb.Th	Tb.N	Tb.BMD
Cortical QUS (Mid-tibia) cSOS	0.08	−0.09	−0.18	−0.10	−0.23	0.06	0.74**	−0.08	0.02	0.13
Calcaneus QUS SOS	-	0.10	0.44	0.34	0.50*	−0.19	−0.09	−0.14	0.52 *	0.42

(B) Cortical QUS at Distal-Radius

	QUS	DXA			HR-pQCT			HR-pQCT		
	Calcaneus	L1−4	Total hip	Femoral neck	Distal radius Cortical bone			UD-radius Trabecular bone		
	SOS	aBMD	aBMD	aBMD	Ct.Th	Ct.Po	Ct.TMD	Tb.Th	Tb.N	Tb.BMD
Cortical QUS (Distal radius) cSOS	0.12	−0.06	−0.03	0.13	−0.17	−0.36	0.72**	−0.20	−0.05	−0.05
Calcaneus QUS SOS	-	0.10	0.44	0.34	0.24	-0.40	0.01	-0.19	0.43	0.31

Abbr: UD-Radius, ultra distal radius; UD-Tibia, ultra distal tibia.
Partial rank-correlation coefficient corrected by age, height, and weight * $p < 0.05$, ** $p < 0.01$.

Table 5 shows the results of the multiple regression analysis. The most related factor with cSOS in dialysis patients was serum iPTH (Fig. 6), but no such factor was evident for SOS.

Discussion

In these studies, HR-pQCT was used to identify which aspects of cortical bone are actually evaluated by the cortical QUS device (Part 1), and the distributions of measured values (cSOS) in healthy individuals and a dialysis patient population were investigated (Part 2).

Part 1. What Does Cortical QUS Assess?

As shown in Tables 2 and 3, cortical QUS was not correlated with DXA of the lumbar spine or femur. This indicates that cortical QUS assesses different bone elements than those measured by existing devices used to evaluate osteoporosis.

In terms of the correlation between cortical QUS and HR-pQCT, cSOS was not correlated with trabecular bone parameters, only with cortical bone parameters. This indicates that cortical QUS does in fact selectively evaluate cortical bone.

As shown in Figs. 2 and 3, cSOS was strongly correlated with Ct.TMD. Ct.TMD measured by HR-pQCT evaluates the cortical bone density excluding areas of porosity, and decreased Ct.TMD is caused by decreased calcification or increased microscopic cortical porosity undetectable by HR-pQCT.[22] Therefore, the strong correlation between cSOS and Ct.TMD indicates that cSOS reflects the state of microporosities or calcification in cortical bone (Fig. 7). A previous study also showed that the cortical QUS evaluated the apatite orientation in the human bone tissue.[23] cSOS was not correlated with Ct. Th. This indicates that it is not affected by the thickness of cortical bone, representing absolute bone mass.

In the fracture risk assessment, the importance of measuring bone quality, as well as bone mass, has recently been recognized.[24] The bone strength is determined by both its mass and quality, and poor-quality bone will be weaker even if bone mass is still high. The cortical QUS technique that we have developed measures microporosities and calcification, which are elements of bone quality.

When evaluating patients for fracture risk, it is known that, substantial amounts of patients fail to be diagnosed by conventional bone density measurement devices.[25−27] Cortical QUS is capable of selectively evaluating "the quality of cortical bone," which cannot be assessed by conventional devices, and it may thus be a complement to existing fracture risk assessment.

Table 4
Comparisons of cSOS and SOS Between Young Adults, Elderly, and Dialysis Patients in Male and Female, and the Correlation Coefficients With Age, Dialysis History, and Intact PTH

		Age (years)	Cortical QUS (Mid-Tibia)				Calcaneus QUS			
			cSOS (m/s)	Correlations with			SOS (m/s)	Correlations with		
				Age	Dialysis history	intact PTH		Age	Dialysis history	intact PTH
Male	Young adults	32 ± 6 (21-44)	3941 ± 60 (3787-4034)	−0.18	–	–	1537 ± 37 (1471-1642)	−0.44**	–	–
	Elderly	71 ± 7 (60-84)	3910 ± 73 (3784-4037)				1506 ± 37 (1448-1624)[a]			
	Dialysis patients	59 ± 9 (37-73)	3878 ± 108 (3631-4052)[a]	−0.24	−0.35*	−0.62**	1482 ± 23 (1449-1525)[a]	−0.25	−0.40*	0.27
Female	Young adults	31 ± 8 (20-44)	3971 ± 63 (3821-4087)	−0.54**	–	–	1546 ± 35 (1496-1613)	−0.73**	–	–
	Elderly	66 ± 5 (60-79)	3865 ± 74 (3690-4033)[a]				1493 ± 20 (1444-1543)[a]			
	Dialysis patients	64 ± 8 (47-75)	3805 ± 125 (3566-3995)[a]	−0.06	−0.52**	−0.38*	1477 ± 27 (1432-1550)[a]	−0.25	−0.06	0.21

Spearman's rank-correlation coefficient *$p < 0.05$, **$p < 0.01$.
Bonferroni test vs young adults [a]$p < 0.01$.

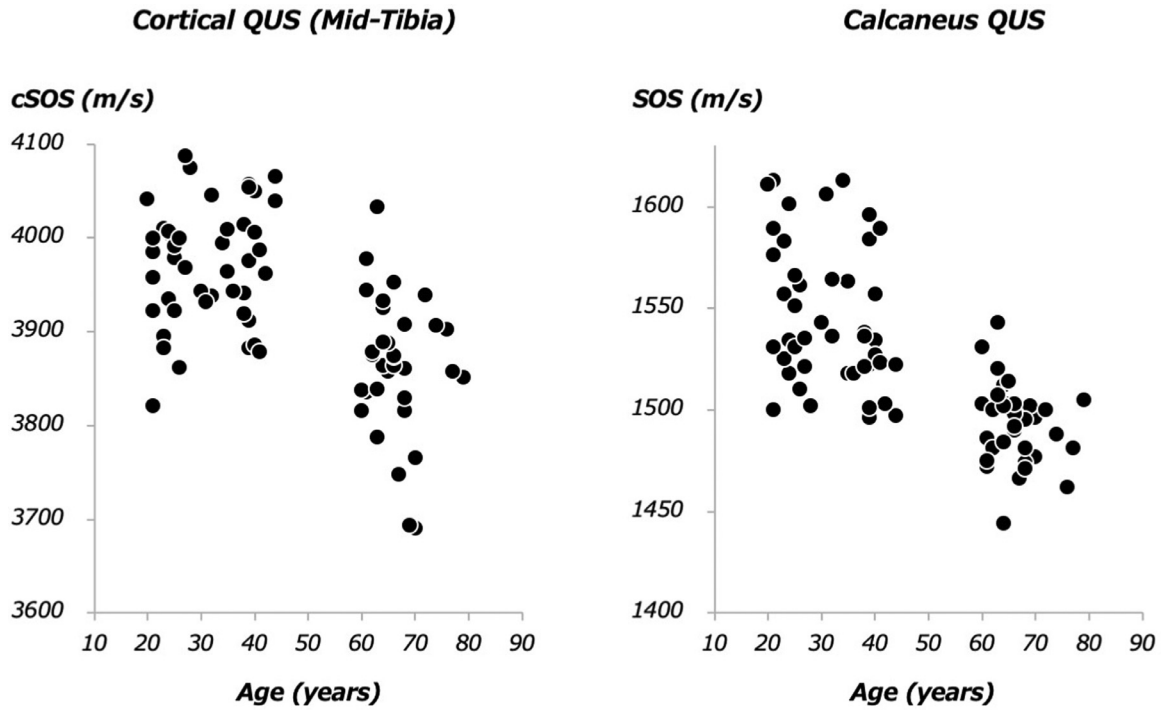

Fig. 4. Age-related differences of cSOS at mid-tibia and SOS at the calcaneus in healthy female volunteers (young adults and elderly).

Table 5
Multiple Regression Analysis Between cSOS, SOS, and Age, Height, Weight, Fracture History, Dialysis History, and Intact PTH in Male and Female Dialysis Patients

	Cortical QUS (Mid-Tibia) cSOS				Calcaneus QUS SOS			
		r	ß	*p*		r	ß	p
Male	model	0.67		<0.01	model	-		-
	iPTH		−0.67	<0.01	none		-	-
Female	model	0.80		<0.01	model	-		-
	height		0.61	<0.01	none		-	-
	iPTH		-0.60	<0.01				

Multiple regression analysis (stepwise): dependent variable; cSOS, SOS. independent variables; age, height, weight, fracture history, dialysis history, and intact PTH.
There was no model with a *p*-value <0.05 between SOS measured by calcaneus QUS and independent variables.

Part 2. Measured Values in Healthy Individuals and Dialysis Patients

As shown in Fig. 4, both cSOS measured by cortical QUS and SOS measured by calcaneal QUS decreased with age in healthy women. Unlike the decrease in SOS, the decrease in cSOS showed different patterns with wide variation. As shown by Part 1, a decrease in cSOS indicates degradation in the quality of cortical bone due to microporosity or diminished calcification, whereas a decrease in SOS is mainly due to a reduction in the amount of cancellous bone. Therefore, the results in Fig. 4 means that bone mass declines with age and menopause in most women, and in some women, the quality of cortical bone is deteriorated with increased microporosity or diminished calcification.

In this study, dialysis patients were also investigated as a population with abnormal bone metabolism and high risk of fractures. As shown in Table 4, as anticipated, both SOS and cSOS decreased in dialysis patients. This suggested not only that dialysis patient may lose bone

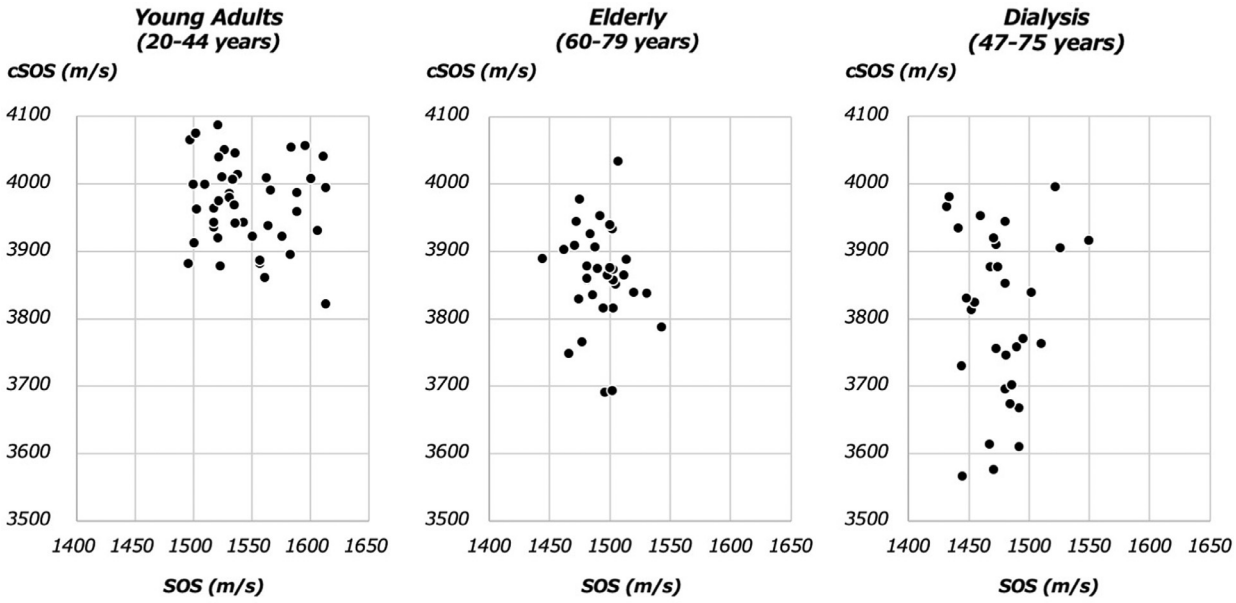

Fig. 5. Distributions of cSOS at mid-tibia and SOS at the calcaneus in female young adults, elderly, and dialysis patients.

mass but also that increased microporosity and diminished calcification may occur.

As shown in Fig. 5, SOS measured by calcaneal QUS (transverse axis) showed the same pattern of decline as a result of both aging and dialysis, but cSOS measured by cortical QUS (longitudinal axis) decreased in some subjects as a result of aging, but it decreased in a higher proportion of patients as a result of dialysis. This indicates that bone mass decreases by the same amount in both elderly and dialysis patients, but that there is a marked decrease in the quality of cortical bone in dialysis patients.

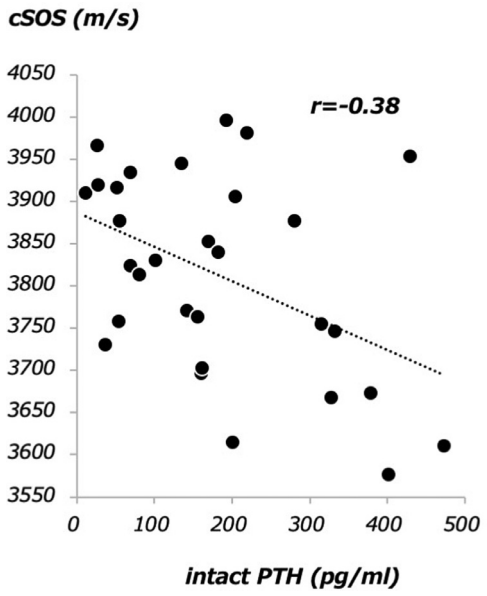

Fig. 6. Correlations between cSOS at mid-tibia and intact PTH in female dialysis patients.

There are some previous studies that evaluated dialysis patients using conventional calcaneus QUS and phalangeal QUS devices.[28,29] They also showed that significantly lower QUS parameters in dialysis patients than in controls.

As shown in Table 5 and Fig. 6, the decrease in cSOS was greater in patients with poorly controlled serum PTH. The longer that abnormal bone metabolism continues, the more the quality of cortical bone may be further degraded.

The degradation of cortical bone quality seen in some elderly women and dialysis patients in this study cannot be picked up by screening with conventional calcaneal QUS alone, and the combination of calcaneal and cortical QUS may thus improve the evaluation of bone fragility and fracture risk that may be overlooked with current methods.

Compared with DXA, this device is a compact, portable, simple, inexpensive, noninvasive ultrasound device that does not involve radiation exposure, and, as such, it can be widely used in clinics and screening. The use of QUS to establish a more effective system of screening for patients at high risk of fracture may help prevent many fragility fractures.

Limitations

This study had a number of limitations. First, measurements were made in the central tibia, which is not a common site of fragility fracture, leaving doubts as to how well it evaluates the risk of fracture of the spine or femur.

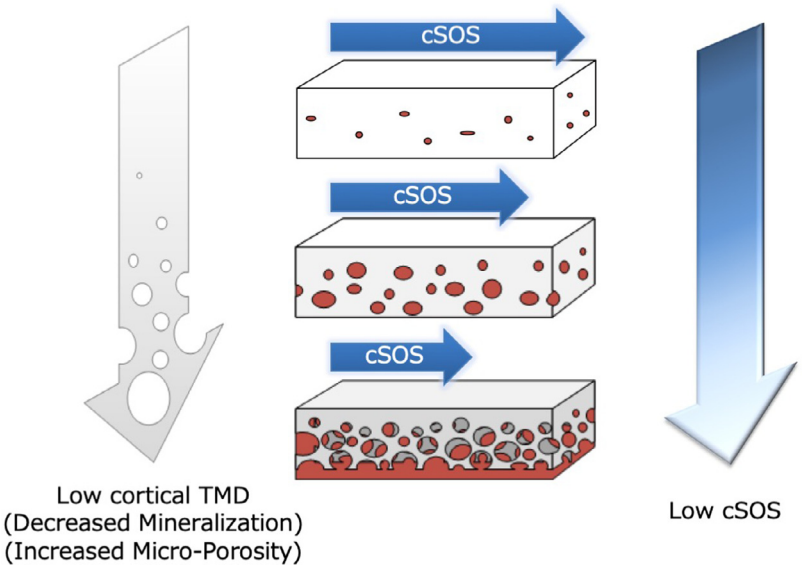

Fig. 7. Low cSOS represents low-mineralized cortical bone with increased micro-cortical porosity.

We also analyzed the correlation between cSOS measured at the central tibia and the distal radius, found 0.77 of correlation coefficient ($p < 0.001$), suggesting that an assessment of central tibia may to some extent reflect the condition of cortical bone elsewhere, including the femur. Further studies are nevertheless required to investigate the extent to which cortical QUS actually evaluates fracture risk.

Cortical QUS measurement requires somewhat more work to perform than calcaneal QUS. We have produced a support device for use in central tibial measurement, which enables measurements to be made simply by moving the probe along the device. However, there is still scope for further improvement.

Limited number of the participants is also the limitation of this study. We regarded this study as a pilot study, and further study is needed to clarify the usefulness of this device in the clinical medicine.

There was lack of information about subjects' background data such as menopausal status, parents' fracture history, smoking, drinking, underlying illness and medication. The relationship between these factors and cortical QUS has not been fully investigated.

In conclusion, cSOS measured by cortical QUS was considered to reflect the microporosity and the degree of calcification of cortical bone. Cortical QUS may be capable of selectively evaluating the "bone quality" rather than "bone mass" of cortical bone, something that cannot be assessed by conventional calcaneal QUS. cSOS was very low in some elderly women and dialysis patients, and this could not be picked up by conventional calcaneal QUS. The combination of calcaneal and cortical QUS may thus improve the evaluation of bone fragility and fracture risk that may be overlooked with current methods.

Further studies are required to ascertain the actual association with fracture risk.

Author Contributions

Development of the device (RS, DC, TA, and TK); Study design (RS, KC, and KY); Data acquisition (RS, TA, TK, KC, NO, AO, ST, and KY); Data analysis (KC); Drafting the manuscript (KC); Revision of manuscript content (RS); Approval of the final version of the manuscript (MO and KY)

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