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Novel ultrasonic bone densitometry based on two longitudinal waves: Significant correlation with pQCT measurement values, and age-related changes in trabecular bone density, cortical thickness, and elastic modulus of trabecular bone in a normal Japanese population

新方式二波検出型骨密度測定：pQCT法との相関および、正常日本人海綿骨密度、皮質骨厚、海綿骨弾性定数における経年変化

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Key words: Trabecular bone density (TbD), Cortical thickness (CoTh), Elastic modulus of trabecular bone (EMTb), Ultrasonic bone densitometry, Fast and slow waves, pQCT

**Novel ultrasonic bone densitometry based on two longitudinal waves:
Significant correlation with pQCT measurement values and age-related changes
in trabecular bone density, cortical thickness, and elastic modulus of trabecular
bone in a normal Japanese population**

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Mini-Abstract

A reference database for trabecular bone density, cortical thickness, and elastic
modulus of trabecular bone for a novel ultrasonic bone densitometry system
(LD-100) based on two longitudinal waves (fast and slow) was determined over a
wide age range in a normal Japanese population.

ABSTRACT

Introduction: A novel ultrasonic bone densitometry system (LD-100 system) was applied to create a reference database for trabecular bone density (TBD), cortical thickness (CoTh), and elastic modulus of trabecular bone (EMTb) for this device over a wide age range in a normal Japanese population.

Methods: In a comparative study between LD-100 and peripheral quantitative computed tomography (pQCT) systems, 52 individuals were examined by both systems at the same radius simultaneously. To create a reference database, a total of 2380 healthy subjects (1179 men, 1201 women), ages 18-99 years, were examined using the LD-100 system.

Results: Highly significant correlations between the LD-100 and pQCT systems were found in TBD ($r=0.877$, $p<0.001$) and CoTh ($r=0.723$, $p<0.001$). For the reference database, peak values of TBD, CoTh and EMTb were observed at 30-34 years (255.09 mg/cm^3), 20-24 years (5.23 mm) and 20-24 years (4.09 GPa) in men, and at 25-29 years (209.24 mg/cm^3), 25-29 years (3.98 mm), and 20-24 years (3.33 GPa) in women, respectively. The TBD fell significantly ($p<0.05$) beginning at 55-59 years in both sexes, with a relatively rapid decrease in women. The CoTh showed a significant decrease beginning at 40-44 years in men and 50-54 years in women. The EMTb showed a significant decrease beginning at 40-44 years in men and 55-59

years in women.

Conclusions: The LD-100 system is a useful bone densitometry device and the database of age-related changes in TBD, CoTh and EMTb established in this study will provide fundamental data for future studies related to bone status.

KEYWORDS: trabecular bone density (TBD); cortical thickness (CoTh); elastic modulus of trabecular bone (EMTb); ultrasonic bone densitometry; fast and slow waves; pQCT

INTRODUCTION

Early identification of risks for deteriorating bone status is one of the most important approaches to preventing osteoporosis. For this reason, establishing a simple, non-invasive technique for mass-screening of bone status is necessary. In the non-invasive assessment of skeletal status, dual photon X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) are relatively widely used X-ray-based methods. Dual photon X-ray absorptiometry is the most widely used method for bone densitometry, with excellent precision and accuracy, and has been used as a gold standard for fracture risk assessment (1-3), although drawbacks have recently been pointed out, such as two-dimensional projectional density measurements precluding separation of cortical and trabecular bone with entirely different properties (4, 5). Another X-ray-based method, pQCT is a three-dimensional bone mass measurement technique that separately determines the trabecular and cortical bone mineral density of the forearm volumetrically (6).

On the other hand, the quantitative ultrasound (QUS) method, free from the exposure to ionizing radiation, has been applied to the assessment of bone status for almost two decades, opening the further possibility of measuring bone quality in addition to bone density (7-9). Quantitative ultrasound, a non-radiation method, has the advantage of avoiding the limiting factor for preventive studies, particularly

for those involving children, adolescents, and pregnant women, and for medical check-ups performed at non-X-ray-shielded sites. Additionally, QUS is generally inexpensive, portable, and highly acceptable/repeatable to the subjects.

Presently available QUS devices can be classified mostly into three groups related to the type of ultrasound transmission (trabecular transverse transmission, cortical transverse transmission, and cortical axial transmission) (10). Trabecular transverse transmission is the best for measuring the heel; cortical transverse transmission is used in phalanx contact devices; and cortical axial transmission presently is being investigated for use in multiple sites, such as phalanges, the radius, and the tibia (11).

Recently, an ultrasonic wave propagation phenomenon described as Biot's theory that focuses on two longitudinal waves (fast and slow waves) has been actively studied (12-18). Cancellous bone is a poroelastic and biphasic medium composed of an elastic network (trabecular network) filled with a viscous fluid (bone marrow). According to the Biot theory, the fast wave is related to a propagation mode mainly involving the solid phase (trabecular network), whereas the slow wave is related to the fluid phase (bone marrow), and the arrival time of the fast wave is simply determined by the speed and the distance of propagation in bone tissue (19). It has been shown that both fast and slow longitudinal waves propagate through trabecular bone as predicted by Biot's theory and that

experimentally observed propagation speeds for fast and slow waves coincided well with the theoretically calculated ones (12-14). The propagation speeds and amplitudes of the fast and slow waves are significantly affected by the trabecular micro- and macro-structures, the trabecular orientation to the propagation direction, and the visco-elastic properties of bone marrow (12-15).

The LD-100 system (Oyo Electric, Kyoto, Japan) is a newly developed ultrasonic apparatus to apply the ultrasonic parameters based on two longitudinal waves (fast and slow waves) (20-22). The ultrasonic parameters obtained by LD-100 system are trabecular bone density (TBD, mg/cm^3), cortical thickness (CoTh, mm), and elastic modulus of trabecular bone (EMTb, GPa) calculated from the propagation speed (m/s) and the attenuation (dB) of both fast and slow waves. The measurement site used for LD-100 system is the distal radius, where echo waves are technically easily accessible and also one of the most common fracture sites in osteoporosis.

The aim of this study is to indicate the reliability and capability of the new QUS device, the LD-100 system. The present study first showed the high correlation between the TBD and CoTh values of the LD-100 and pQCT systems, adopting the distal radius of the same forearm as a measurement site, and then created a reference database for TBD, CoTh, and EMTb in a normal population using this new QUS method, as the first step for the clinical application of this apparatus.

MATERIALS AND METHODS

Subjects

To compare LD-100 and pQCT systems, measurements by both systems were performed in the same 52 volunteers (age range, 36-85 years) on the same day. Subsequently, to create a reference database for the LD-100 system, a total of 2380 healthy Japanese volunteers (1179 men and 1201 women; age range 18-99 years) were examined using the LD-100 system. This study was approved by the Ethics Review Board at Kobe University Graduate School of Medicine and was performed between April 2007 and April 2009. Following provision of informed consent, an extensive and accurate clinical history was obtained. For the purpose of determining the reference database, subjects with a history of disease and/or pharmacotherapy known to affect bone metabolism, other than smoking, diet, and alcohol, were excluded.

LD-100 measurements

Calibration of the LD-100 system was performed individually according to the instructions from the manufacturer. The LD-100 system was applied to the forearm, specifically the distal radius of the subjects. To ensure adequate acoustic contact, ultrasound gel was applied to the skin at the measurement site.

As described in the previous literature (23), in the transmission mode for the measurement of transmitted ultrasound through the measurement site (distal site of the radius), one of the transducers was the ultrasonic transmitter and the other acted as a receiver. Both transducers were coaxially aligned and moved simultaneously for scanning. The amplitudes and propagation times of both the fast and slow waves were obtained in the transmission mode.

In the echo mode, both transducers were driven by a short signal voltage and acted as transmitters. After the transmission of a pulse wave, both transducers were switched to act as receivers to receive echo signals from the acoustical boundaries. Echo signals were analyzed to obtain the thicknesses of soft tissue, cortical bone, and trabecular bone of the measurement site.

For the measurement of transmitted ultrasound through the measurement site in the transmission mode, the ultrasound beam scanned in a raster pattern through the measurement site using a two-axis scanning mechanism.

The ultrasonic measurement involved two scans. In the first scan, transmitted signals were taken and recorded at intervals of 2 mm over a scanning area in both X and Y directions ($28 \times 28 \text{ mm}^2$). The overall amplitude of transmitted signals, including both the fast and slow waves, was analyzed to obtain a local attenuation distribution of the measurement site. The local attenuation distribution was

displayed as a two-dimensional image of the distal end of the forearm. This two-dimensional image was used to confirm the bone geometry of the measurement site and to determine the position (distal 5.5% portion of the radius) for the second scan. The second scanning area ($4 \times 4 \text{ mm}^2$) was automatically selected by a specially developed measurement algorithm at the nearest point to the distal 5.5% point and also at a site with a good likelihood for fast and slow wave transmission in trabecular bone. The waveforms and amplitudes of both the fast and slow waves were analyzed automatically both for the time and frequency domains during the first scanning to select a perpendicular incidence site for the ultrasonic beam and to avoid interference waves overlapping with the transmitted signal.

During the second scan, the measurements were executed at intervals of 1 mm both in the transmission and echo modes. Transmitted signals were recorded at intervals of 1 mm and analyzed in the transmission mode to obtain the amplitudes and propagation times (time-of-flight) of both the fast and slow waves. Echo signals were analyzed in the echo mode to obtain the thicknesses of soft tissue, cortical bone, and trabecular bone of the measurement site. The CoTh is expressed as the sum of the thicknesses of the cortical bone at the inlet and outlet sides of the ultrasonic beam.

The ultrasonic parameters used to derive the trabecular density are given in the literature (20-22) and expressed for the slow wave as:

$$e^{-\alpha'_4 x_4} T'_{34} T'_{45} = \left(\frac{B_0}{AT} \right) \frac{E'_2}{E_0}$$

where E_0 is the received signal voltage without the measurement subject (propagation through only water as a reference medium); E'_2 , received signal voltage for the slow wave; α'_4 , attenuation constant of the slow wave in trabecular bone; A , total attenuation excluding trabecular bone; B_0 , attenuation in water (without the measurement subject); x_4 , thickness of the trabecular bone; and $T'_{34} T'_{45}$, the product of the transmission coefficients of both sides of the trabecular bone for the slow wave. Then, the apparent density, ρ_4 , of trabecular bone was evaluated using the equation. The propagation speed, c_4 , of the fast wave in trabecular bone is given by:

$$c_4 = \frac{x_4}{t_4}$$

where t_4 is the propagation time in trabecular bone and x_4 and t_4 were obtained using measured signals during the second scan in both the transmission and echo modes.

The elastic modulus of trabecular bone with bone marrow *in situ* for the longitudinal wave was evaluated using c_4 and as:

$$\begin{aligned}
EMTb &= E_4 + E'_4(1 - V_f) \\
&= \rho_4 c_4^2 + \rho'_4 c'^2_4(1 - V_f)
\end{aligned}$$

where E_4 is the elasticity of the trabecular structure; E'_4 , the elasticity of the bone marrow; ρ_4 , the bone mass density of trabecular bone; c_4 , the propagation speed of the fast wave in the trabecular structure, ρ'_4 , the bone marrow density; c'_4 , the propagation speed of the slow wave in bone marrow; and V_f , the bone volume fraction (bone volumetric density)(BV/TV) (24).

The short term of reproducibility (percent coefficient of variation: %CV) of all parameters was obtained by measurements of 10 normal subjects (5 men and 5 women) performed once a day for 10 consecutive days.

pQCT measurements

Peripheral quantitative computed tomography measurements were performed in 52 subjects ages 36-85 years, on the non-dominant forearm at a distance 4% of the forearm length proximal to the distal end of the radius for TBD and at the mid-radial 20% site for CoTh (25), using single 2.5-mm thick slice pQCT (XCT-960 Stratec, Medizintechnik, Pforzheim, Germany).

Statistical analysis

Data management and analysis were performed using SPSS v15.0 software (Statistical Package for Social Sciences; SPSS, Chicago, IL, USA). All data are expressed as mean \pm standard deviation (SD). For the reference database for TBD, CoTh, and EMTb of the LD-100 system, all subjects were divided into 5-year age groups and data were shown by age groups for both sexes. Parameters in each age group were compared using Tukey's method after analysis of variance (ANOVA). Pearson's correlations between the LD-100 and pQCT measurement values in TBD and CoTh were expressed by linear regression. Correlations were considered statistically significant for values of $p < 0.05$.

The T-scores, criteria for assessing bone status and determining the risk of fracture (26), were calculated as:

$$T - \text{score} = \frac{(\text{Mean}_{\text{subject}} - \text{Mean}_{\text{young-reference}})}{\text{SD}_{\text{young-reference}}}$$

The age range of 20 to 39 years, where no significant differences from the peak value were observed in all three parameters (TBD, CoTh, and EMTb), for men and women, was used for the young reference range.

RESULTS

In the comparative study between the LD-100 and pQCT systems, a highly significant correlation was found between the LD-100 and pQCT measurement values in TBD ($r=0.877$; $p<0.001$) (Fig. 1A) and CoTh ($r=0.723$; $p<0.001$) (Fig. 1B).

Anthropometric features of the population used to create a reference database for the LD-100 system are summarized in Table 1. Fundamental data of TBD, CoTh, and EMTb for the LD-100 system are summarized in Tables 2A and 2B, and graphically described in Figures 2A, 2B, and 2C, respectively.

Peak TBD in men (255.09 mg/cm^3) was found at 30-34 years (Table 2A), and in women (209.24 mg/cm^3) at 25-29 years (Table 2B). In men, TBD was maintained at a plateau from 25-29 years to 35-39 years, then started to decrease thereafter in a linear manner with age, with a significant decrease ($p<0.05$) beginning from 55-59 years (Fig. 2A). On the other hand, TBD in women was maintained at a plateau from 20-24 years to 45-49 years, then started to decrease thereafter with a significant decrease from 55-59 years (Fig. 2A).

Regarding the CoTh, the peak value was found at 20-24 years in men (5.23 mm) and at 25-29 years in women (3.98 mm) (Tables 2A, 2B). In men, CoTh was maintained at a plateau from 20-24 to 35-39 years, then significantly decreased ($p<0.05$) thereafter in a linear manner with age, particularly after 60-64 years (Fig.

2B). In contrast, CoTh in women was maintained at a plateau from 20-24 to 45-49 years, then decreased significantly thereafter in a linear manner with age (Fig. 2B).

The EMTb showed a peak in the age group of 20-24 years in both sexes (4.09 GPa in men and 3.33 GPa in women) (Tables 2A, 2B). In men, EMTb started to decrease after the peak value and showed a significant decrease ($p < 0.05$) beginning at 40-44 years (Fig. 2C). In contrast, EMTb in women was maintained at a plateau until 45-49 years, then decreased thereafter with a significant decrease from 55-59 years (Fig. 2C). The age-dependent change of EMTb was much larger in men than in women. Additionally, under 65-69 years, the standard deviation of EMTb in men was much larger than that in women (Fig. 2C).

The %CVs of the three parameters were 1.96% (range, 0.99 - 2.42%) for TBD, 1.87% (range, 0.89- 2.61%) for CoTh, and 1.48% (range, 0.62- 2.41%) for EMTb.

DISCUSSION

The new QUS system LD-100 has been developed to evaluate TBD, CoTh, and EMTb, which cannot be evaluated by the previously developed QUS instruments, by applying the ultrasonic parameters based on two longitudinal waves, fast and slow waves.

We first showed a highly significant correlation between the LD-100 and pQCT

measurement values, not only in TBD ($r=0.877$, $p<0.001$), but also in CoTh ($r=0.723$; $p<0.001$), using 52 individuals measured at the same radius simultaneously, suggesting that this new QUS apparatus, LD-100, can be used for the evaluation of bone status with similar reliability to pQCT. The percent coefficient of variation of TBD with the LD-100 system was also similar to that with pQCT reported in the literature (4, 25).

The measurement sites adopted by the LD-100 and pQCT systems were slightly different, although on the same radius of the subjects. As mentioned in *MATERIALS AND METHODS*, the measurement site for the LD-100 system (the nearest point to the distal 5.5% point of the radius for both TBD and CoTh) was chosen to select a perpendicular incidence site for the ultrasonic beam and to avoid interference waves overlapping with the transmitted signal. On the other hand, the measurement site used for the pQCT system is well-accepted as 4% of the forearm length proximal to the distal end of the radius for TBD and the mid-radial 20% site for CoTh, adopting the area of high mineral content and trabecular bone percentage for the former and the area with a relatively round shape of the cross-section of the radius, permitting the application of the circular ring model, for the latter (25, 27-31). In the present study, a highly significant correlation was found between the LD-100 and pQCT measurement values in TBD and CoTh, suggesting that evaluation of the bone status,

at least the bone status of the forearm, can be similarly evaluated at positions used by both systems.

In the present study, the peak TBD was observed in men 30-34 years of age and in women 25-29 years of age, while plateaus were found in men from 25-29 to 35-39 years and in women from 20-24 to 45-49 years. Similar findings have been reported in Japanese women using a pQCT system, showing the peak TBD at 25-29 years and a plateau of TBD from 20-24 to 40-44 years (28). The difference in the pattern of decrease in TBD after the plateau between men and women seen in our study is probably related to the well-known estrogen effect on maintaining bone mass in women (32, 33).

Very few studies have examined cortical thickness, particularly in terms of a reference database showing age-related changes in cortical thickness in a normative population. In the present study, CoTh deduced from the propagation time (the time-of-flight) between the transmitting and the receiving transducers for the fast and slow waves showed a similar age range of plateau (from 20-24 to 35-39 years in men and from 20-24 to 45-49 years in women) to that in TBD (from 25-29 to 35-39 years in men and from 20-24 to 45-49 years in women), indicating that the pattern of age-related changes in CoTh resembles that in TBD. The CoTh reportedly decreased about 50% in the 70-79 year age group compared to the 20-29 year age group in

Japanese women using a pQCT system (34). Similarly, CoTh measured by the LD-100 system decreased 48% in the 75-79 year group compared to the 25-29 year group in women, while decreasing 36% during the same age interval in men. Reports have shown that biomechanical failure force of the long bone is correlated with cortical thickness, as well as cross-sectional area and principal area moments of inertia, but not with TBD (35, 36). Indeed, CoTh measured by the LD-100 system showed a good correlation ($r=0.612$, $p<0.001$) with strength-strain index, another parameter in the pQCT system reflecting bone strength (data not shown).

Furthermore, we presented a reference database for EMTb for the first time, using the LD-100 system based on two longitudinal transmitted waves (fast and slow waves). The EMTb deduced from the measured bone density and propagation speed of the fast wave is directly related to the mechanical strength of bone, which has never been assessed in a non-invasive manner (24). In the present study, the age group showing peak EMTb (20-24 years in both sexes) was younger than that showing peak TBD (30-34 years in men and 25-29 years in women), suggesting that decreases in bone elasticity might start earlier than decreases in bone density. In men, EMTb showed a significant decrease beginning at 40-44 years. In contrast, EMTb in women maintained a plateau until 45-49 years, then decreased thereafter with a significant decrease from 55-59 years. The pattern of decrease in EMTb

after the plateau in women resembled that in TBD, suggesting that estrogen also participates in maintaining the elasticity of bone in women.

Our results also showed that, the standard deviation of EMTb at ages below 65-69 years and the age-dependent change of EMTb were much larger in men than in women (Fig. 2C). In the relationship analysis between TBD and EMTb (Figs. 3A, 3B), both EMTb and the divergence of EMTb were increased at higher TBD, especially after a TBD value of 200 mg/cm³. As shown in Figure 2A, TBD is relatively higher in men than in women and the mean value of TBD is consistently higher than 200 mg/cm³ in men under 65-69 years. These things suggested that the higher standard deviation of EMTb at ages below 65-69 years and the larger age-dependent change in EMTb in men than in women (Fig. 2C) might result from the relatively higher TBD in men than in women. As previously described, EMTb is given by:

$$\begin{aligned}
 EMTb &= E_4 + E'_4(1 - V_f) \\
 &= \rho_4 c_4^2 + \rho'_4 c_4'^2(1 - V_f)
 \end{aligned}$$

In this equation, bone volume fraction (bone volumetric density) (V_f) changes from 0 to 1 and EMTb approaches $\rho_4 c_4^2$ along with the increase of V_f . A previous study indicated that c_4 and the divergence of c_4 increased along with the increase of V_f (24). The increased divergence of EMTb at higher TBD might be principally explained by

this increased divergence of c_4 at higher V_f . It has been shown that c_4 and EMTb mostly depend on the orientation of the trabeculae (23). The increased divergence of c_4 at higher V_f and the resulting increased divergence of EMTb at higher TBD might be caused by the increased multiplicity of the trabecular structure at higher bone densities (23, 24, 37).

The novel LD-100 ultrasound bone densitometry system based on two longitudinal waves (fast and slow waves) is thus very useful for multi-sided evaluation of bone status. Furthermore, the LD-100 system has advantages of ready portability and no use of radiation (particularly beneficial for children, adolescents, and pregnant women requiring early detection of bone risk and for medical check-ups performed at non-X-ray-shielded sites), as well as a simple handling process and relatively low price.

The World Health Organization recommended the use of T scores (established using central DXA) to interpret data from densitometry devices and a threshold of -2.5 standard deviation to diagnose osteoporosis (26). However, there is increasing evidence that the current T score definition of osteoporosis cannot be universally applied to different densitometry techniques or sites and particularly to peripheral devices (38, 39). Indeed, mean values in the present study with T scores under -2.5 were observed only in CoTh in women 75-79 years of age or older, but not in TBD or

EMTb even in the oldest age group (85-89 years in men and 95-99 years in women). There is increasing interest in device-specific thresholds for interpreting peripheral bone measurements in clinical practice and in the management of osteoporosis (40, 41). It could be appropriate to apply this concept to this new QUS device, the LD-100 system, to define specific thresholds for identifying patients at high or low risk of having osteoporosis and for confirming patients with low bone mass by comparison to normative data.

Because the LD-100 and pQCT systems adopt the radius of the same forearm for the measuring site and a highly significant correlation was found between both systems in TBD and CoTh, the LD-100 system seems as useful as pQCT for evaluating bone status, especially of the forearm. Precise evaluation of the distal radius itself seems important, because fracture of the distal radius (Colles' fracture) has been thought a sentinel for future increased risk of other osteoporotic fractures (42, 43). Furthermore, in the pQCT studies, it has been reported that the index of volumetric bone mineral density and CoTh as well as the bone strength index at the forearm are useful for predicting vertebral fractures as well as Colles' fractures (35, 44). Recently, it has been shown that TBD measured by the LD-100 system shows a closer relationship with TBD measured by the pQCT system than bone mineral density measured by DXA at the ultra distal radius and that TBD and EMTb

measured by the LD-100 system are able to predict vertebral fractures as well as TBD measured by the pQCT system (23). Although, adequately designed prospective studies using the LD-100 system are needed to evaluate which parameter (TBD, CoTh, and/or EMTb) in this apparatus is most correlated to actual fractures or changes in biochemical markers of bone status (45) and to define the specific thresholds of these parameters for identifying patients with high risk of bone fractures, this novel ultrasound bone densitometry system will be a useful device not only for evaluating bone status in individuals, but also for mass screening studies of bone status or population-based screening programs of bone. The LD-100 system is now close upon the commercial use. The database of age-related changes in TBD, CoTh, and EMTb for the LD-100 system established in the present study provides fundamental data for such evaluations as well as future mass screening studies of bone status.

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FIGURE LEGENDS

Figure 1:

A) Correlation of trabecular bone density (TBD) measured by the LD-100 and pQCT systems, using the following regression equation: $Y = 1.116X - 12.574$ ($r=0.877$, $p<0.001$). X: pQCT; Y: LD-100.

B) Correlation of cortical thickness (CoTh) measured by the LD-100 and pQCT systems, using the following regression equation: $Y = 2.553X - 1.556$ ($r=0.723$, $p<0.001$). X: pQCT; Y: LD-100.

Figure 2:

A) Changes in TBD (mg/cm^3) with age and sex. Open circle, men; closed circle, women. *Significant decrease from peak value ($p<0.05$); **Significant decrease from peak value ($p<0.01$).

B) Changes in CoTh (mm) with age and sex. Open circle, men; closed circle, women. *Significant decrease from peak value ($p<0.05$); **Significant decrease from peak value ($p<0.01$).

C) Changes in EMTb (GPa) with age and sex. Open circle, men; closed circle, women. *Significant decrease from peak value ($p<0.05$); **Significant decrease from peak value ($p<0.01$).

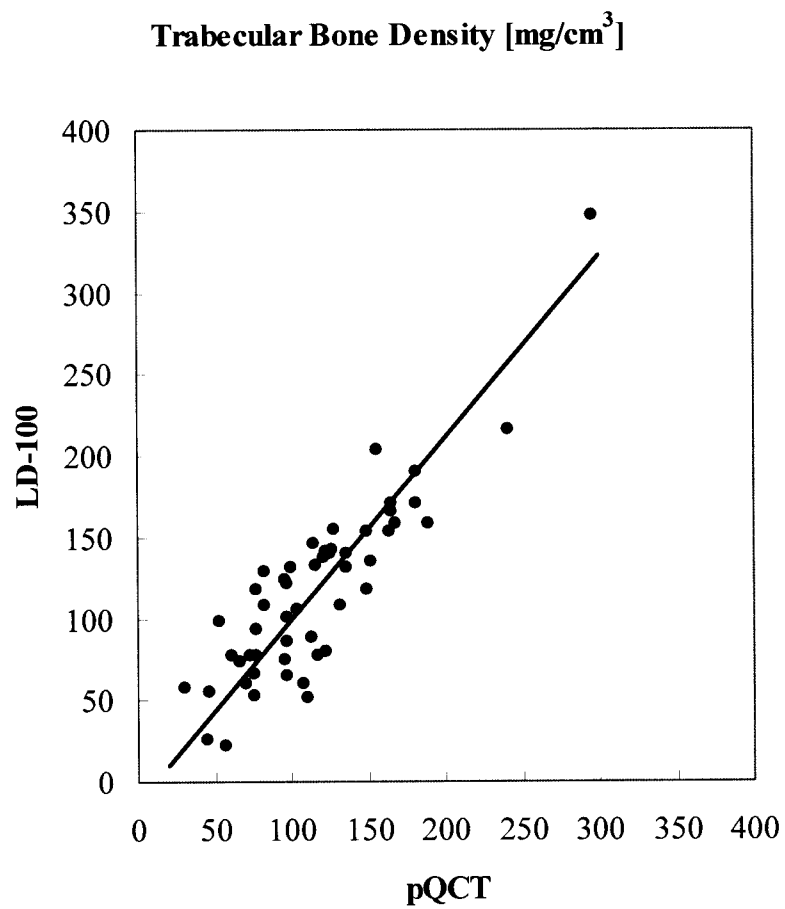
Figure 3:

A) Elastic modulus of trabecular bone (EMTb) values plotted versus trabecular bone density (TbD) values in men. ----- theoretically deduced relation.

B) Elastic modulus of trabecular bone (EMTb) values plotted versus trabecular bone density (TbD) values in women. ----- theoretically deduced relation.

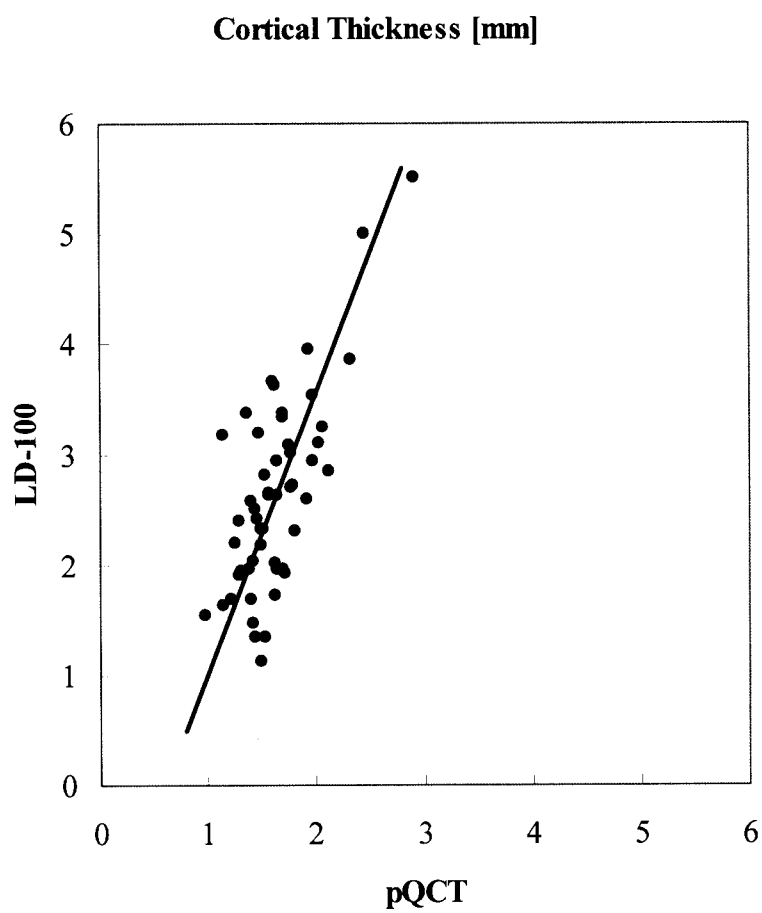
FIGURES

Figure 1A



$$Y = 1.116X - 12.574, \quad X: \text{pQCT}, \quad Y: \text{LD-100}.$$
$$r = 0.877, \quad p < 0.001$$

Figure 1B



$Y = 2.553X - 1.556$, X: pQCT, Y: LD-100.
 $r = 0.723$, $p < 0.001$

Figure 2A

Age - related Changes of TBD in Both Genders

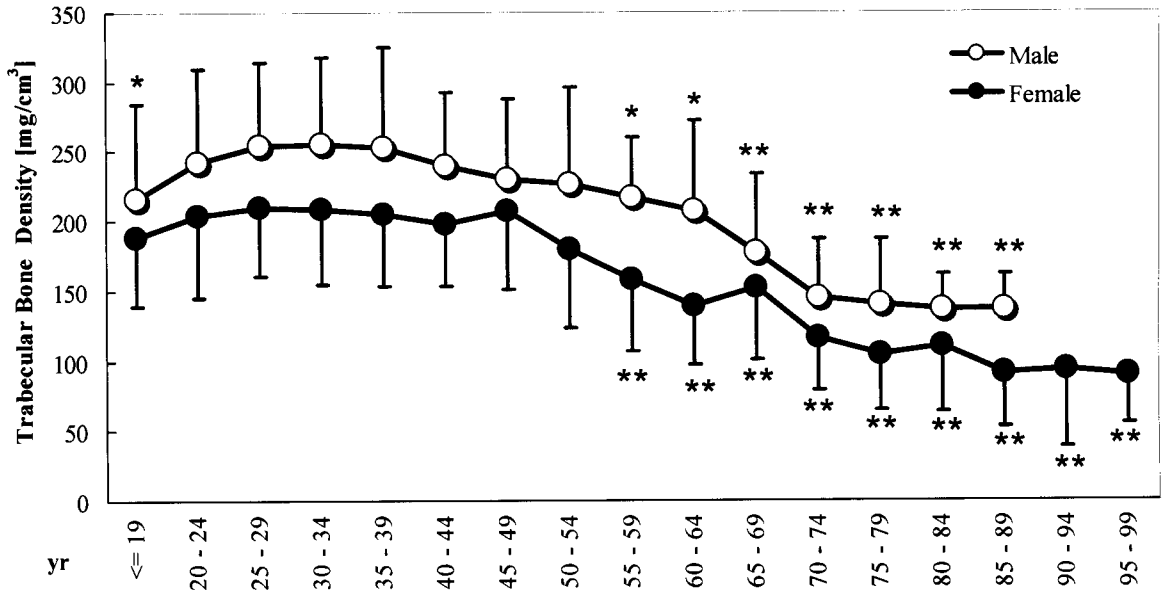


Figure 2B

Age - related Changes of CoTh in Both Genders

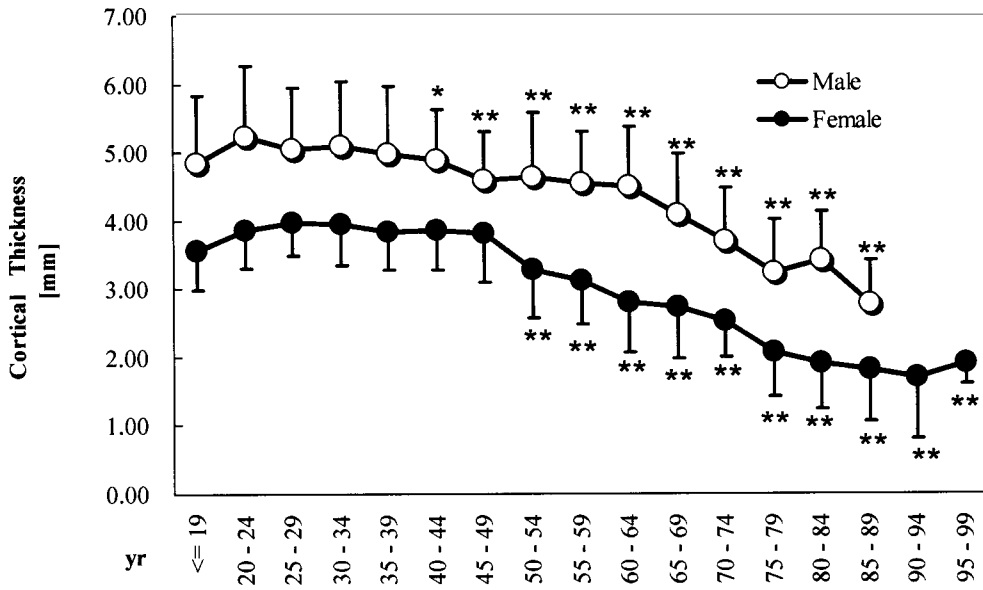


Figure 2C

Age - related Changes of EMTb in Both Genders

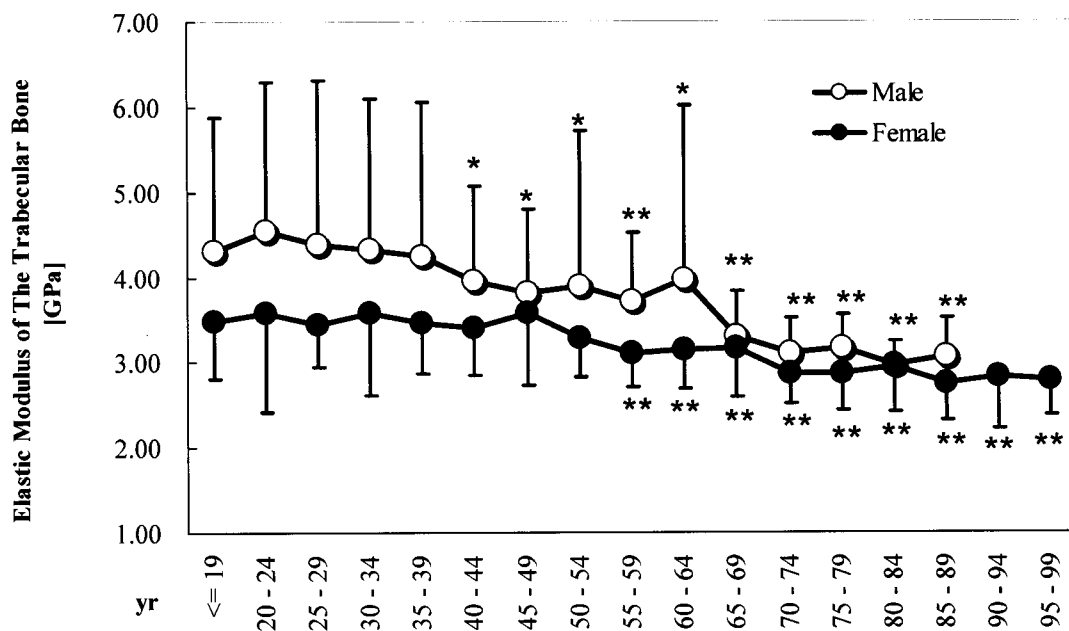


Figure 3A

In Men

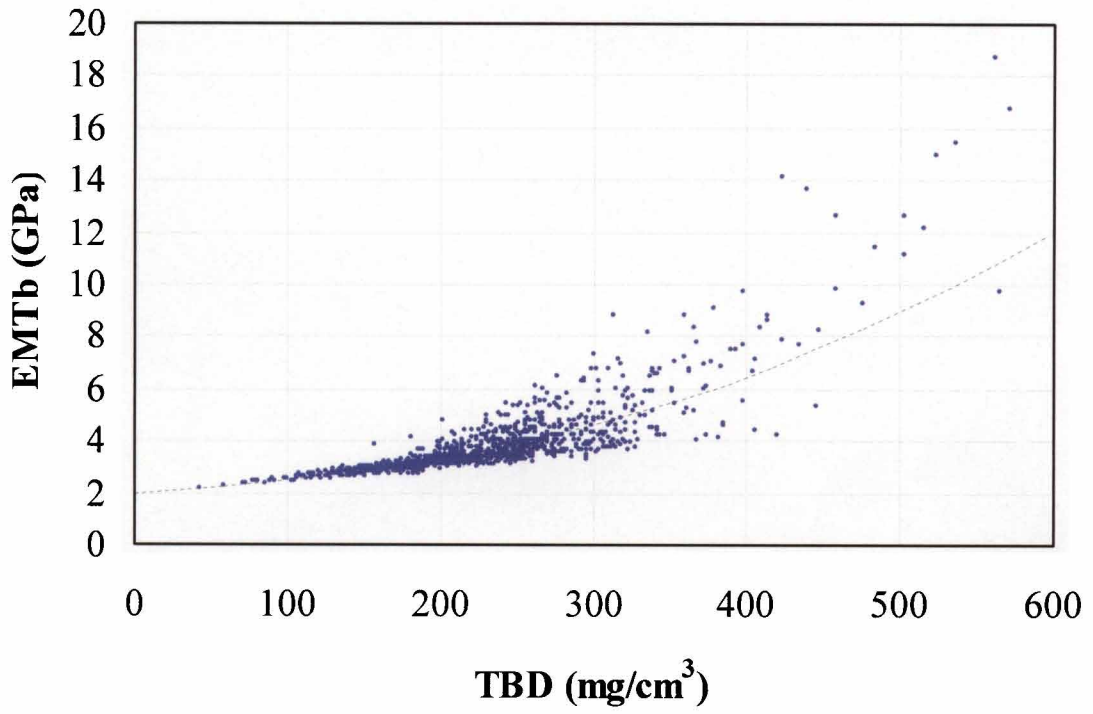
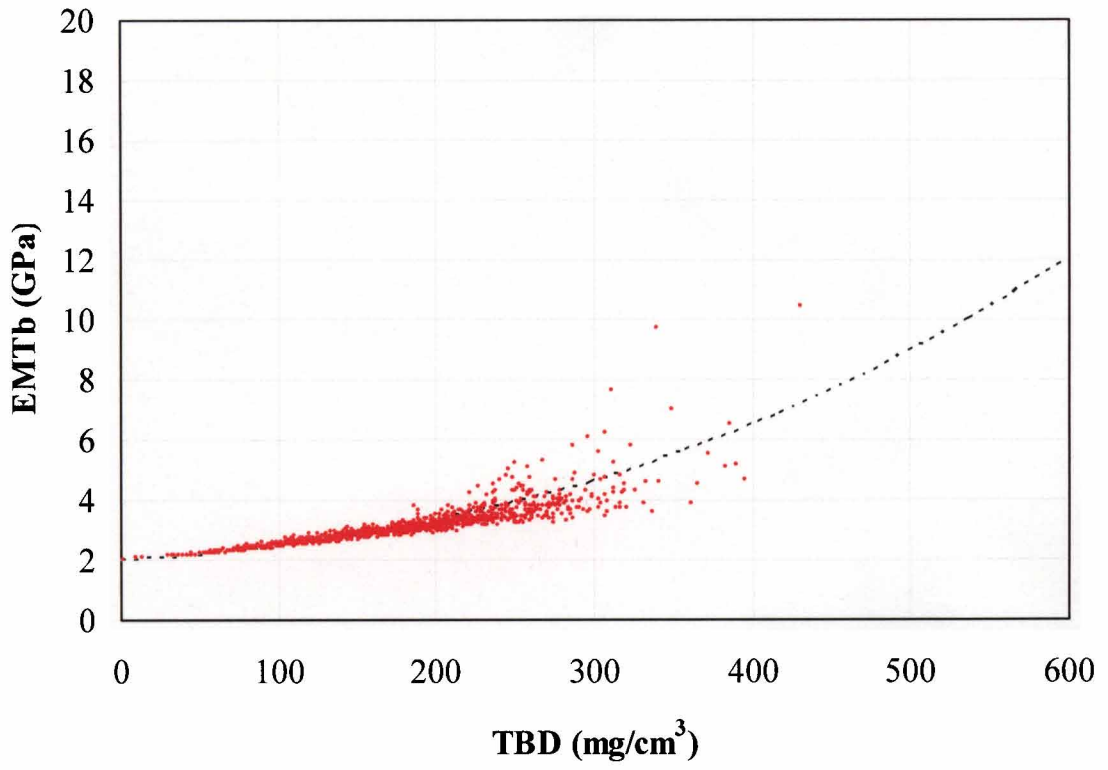


Figure 3B

In Women



Tables

Table 1. Anthropometric characteristics of subjects for a reference database of the LD-100 system

Variable	Total (n=2380)	Male (n=1179)	Female (n=1201)
	Mean ± SD	Mean ± SD	Mean ± SD
Age [years]	39.00 ± 19.27	36.00 ± 16.55	41.00 ± 21.32
Weight [kg]	57.94 ± 12.37	65.33 ± 10.28	50.54 ± 9.54
Height [cm]	162.65 ± 19.01	170.95 ± 9.58	154.35 ± 22.21
BMI [kg/m ²]	21.54 ± 3.08	22.32 ± 3.37	20.58 ± 2.35

n, number of subjects; BMI, body mass index.

All data are expressed as mean ± SD for each value.

Table 2A. LD-100 ultrasound indices in healthy Japanese men

		TBD (mg/cm ³)			CoTh (mm)			EMTb (GPa)		
	n	Mean	SD	T-score	Mean	SD	T-score	Mean	SD	T-score
≤19	185	215.46 *	68.43	-0.50	4.85	0.97	-0.28	3.79	1.41	-0.17
20 - 24	250	241.75	67.76	-0.10	5.23	1.04	0.10	4.09	1.52	0.02
25 - 29	77	254.19	59.89	0.09	5.06	0.88	-0.07	4.06	1.59	0.00
30 - 34	110	255.09	62.75	0.10	5.10	0.93	-0.03	4.05	1.57	-0.01
35 - 39	109	253.37	71.06	0.07	4.99	0.98	-0.14	4.01	1.83	0.01
40 - 44	87	240.15	51.80	-0.13	4.89 *	0.74	-0.24	3.70 *	0.92	-0.23
45 - 49	81	230.02	57.20	-0.28	4.59 **	0.71	-0.55	3.58 *	0.86	-0.30
50 - 54	78	226.07	70.31	-0.34	4.65 **	0.93	-0.48	3.68 *	1.89	-0.24
55 - 59	94	216.91 *	43.58	-0.48	4.55 **	0.74	-0.59	3.44 **	0.59	-0.39
60 - 64	50	207.43 *	64.48	-0.62	4.50 **	0.86	-0.64	3.60 **	1.84	-0.29
65 - 69	16	176.81 **	57.44	-1.08	4.09 **	0.88	-1.05	3.06 **	0.51	-0.63
70 - 74	12	145.49 **	41.51	-1.55	3.70 **	0.77	-1.44	2.82 **	0.29	-0.78
75 - 79	12	140.32 **	46.56	-1.63	3.24 **	0.79	-1.91	2.79 **	0.31	-0.79
80 - 84	12	136.20 **	25.55	-1.69	3.42 **	0.71	-1.73	2.71 **	0.18	-0.84
85 - 89	6	136.73 **	25.23	-1.68	2.79 **	0.64	-2.36	2.75 **	0.25	-0.82
Total	1179	230.86	67.02	-0.27	4.85	0.99	-0.28	3.81	1.45	-0.16

n, number of subjects.

TBD, trabecular bone density; CoTh, cortical bone thickness.

EMTb, elastic modulus of trabecular bone;

* Significant decrease from peak value (p<0.05)

**Significant decrease from peak value (p<0.01)

T-score = (Mean subject – Mean young-reference) / SD young-reference. The age range of 20 to 39 years was

used for the young-reference range.

Table 2B. LD-100 ultrasound indices in healthy Japanese women

		TBD (mg/ cm ³)			CoTh (mm)			EMTb (GPa)		
	n	Mean	SD	T-score	Mean	SD	T-score	Mean	SD	T-score
≤19	130	187.68	48.96	-0.34	3.56	0.57	-0.62	3.17	0.51	-0.18
20 - 24	214	203.35	58.23	-0.05	3.85	0.56	-0.09	3.33	0.92	0.04
25 - 29	115	209.24	48.76	0.06	3.98	0.49	0.15	3.26	0.45	-0.06
30 - 34	139	208.66	53.62	0.05	3.94	0.58	0.07	3.33	0.68	0.04
35 - 39	99	204.86	51.99	-0.02	3.82	0.55	-0.15	3.26	0.51	-0.06
40 - 44	80	197.58	43.64	-0.16	3.87	0.59	-0.05	3.18	0.42	-0.17
45 - 49	71	207.12	56.12	0.02	3.82	0.73	-0.15	3.33	0.65	0.04
50 - 54	44	179.74	55.80	-0.49	3.28	** 0.71	-1.13	3.04	0.45	-0.36
55 - 59	49	159.85	** 51.91	-0.85	3.13	** 0.65	-1.40	2.87	** 0.36	-0.58
60 - 64	35	138.77	** 41.96	-1.24	2.81	** 0.74	-1.98	2.79	** 0.33	-0.71
65 - 69	44	150.34	** 51.19	-1.03	2.73	** 0.75	-2.13	2.88	** 0.46	-0.61
70 - 74	33	115.68	** 37.12	-1.67	2.53	** 0.54	-2.49	2.60	** 0.25	-0.97
75 - 79	56	104.58	** 39.25	-1.88	2.06	** 0.64	-3.35	2.55	** 0.29	-1.04
80 - 84	37	109.68	** 45.84	-1.78	1.90	** 0.66	-3.64	2.61	** 0.35	-0.96
85 - 89	36	90.99	** 38.81	-2.13	1.81	** 0.76	-3.80	2.46	** 0.27	-1.17
90 - 94	14	93.23	** 55.01	-2.08	1.71	** 0.9	-3.98	2.52	** 0.46	-1.08
95 - 99	5	90.17	** 35.41	-2.14	1.91	** 0.31	-3.62	2.46	** 0.26	-1.17
Total	1201	181.32	62.80	-0.46	3.44	0.91	-0.84	3.11	0.65	-0.26

n, number of subjects.

TBD, trabecular bone density; CoTh, cortical bone thickness.

EMTb, elastic modulus of trabecular bone;

* Significant decrease from peak value (p<0.05)

**Significant decrease from peak value (p<0.01)

T-score = (Mean subject – Mean young-reference) / SD young-reference. The age range of 20 to 39 years was

used for the young-reference range.