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Bone mineral measurement in Japan

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Various methods for evaluating bone mineral in appendicular, and axial bone or in the whole skeleton have recently become available. As bone mineral is one of the major determinants of bone strength, its exact measurement should be useful for the diagnosis of osteoporosis, as well as for the prediction of fracture risk and monitoring of therapeutical response.

The aims of this paper are to review the fundamental performance of bone mineral measurements, the improvements in DXA systems, and the progress in site-specific bone mineral instruments for the radius and calcaneus used in Japan, and to introduce diagnostic criteria for primary osteoporosis, and report on annual rates of bone loss in Japanese females.

Key words: bone mineral measurement, osteoporosis, fundamental performance, DXA, diagnostic criteria

INTRODUCTION

THE AVERAGE LIFE SPAN of the Japanese, which is the longest in the world, is 76 years for males and 82 years for females.[1] The elderly population, persons age 65 years and over, is increasing, and it is expected to be 25% of the total population in 2,020.

Osteoporosis is the most common metabolic disorder of bone, resulting in an insidious bone loss primarily evident in fractures. It affects more than five million elderly Japanese. Recently, it has been widely recognized as a major health issue by both the medical field and the general public. The currently accepted conceptual definition of osteoporosis is that it is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.[2] Since bone mass is one of the major determinants of bone strength, fracture will occur more easily if there is substantial bone loss. Bone mineral measurements have become tools for a rational approach to the diagnosis and treatment of abnormal bone loss. During the past few decades much effort has been made to develop methods of quantitative assessment of bone mass for the early detection of bone loss, monitoring of response to treatment, and prediction of the fracture risk.

In Japan, several methods such as microdensitometry (MD)[3] or radiographic absorptiometry (RA), and its improved analytic methods, computed X-ray densitometry (CXD)[4] and digital image processing (DIP),[5] single-energy X-ray absorptiometry (SXA),[6] dual-energy X-ray absorptiometry (DXA),[7] quantitative computed tomography for lumbar spine (QCT),[8] QCT for peripheral bone (pQCT)[9] and quantitative ultrasound (QUS)[10] are available for the non-invasive measurement of bone mass (Table 1). Each method differs in the principle of measurement, the skeletal sites that can be scanned, performance specifications such as precision, and radiation dose. More than 6,000 bone densitometry instruments have been used in the screening of osteopenia and diagnosis of osteoporosis. The distribution of bone mineral measurement systems in Japan is as follows; 350 for MD, 100 for SXA, 1,100 for axial DXA, 4,400 for peripheral DXA, 50 for pQCT, and 900 for QUS. The development and application of these methods have contributed to the rapidly increasing knowledge of the epidemiology, pathogenesis, prevention and

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treatment of osteoporosis. In this paper, the present state of bone mineral measurement in Japan will be reviewed.

Fundamental Performance of Bone Mineral Measurements

A number of techniques are available to evaluate bone mineral density, BMD, in the peripheral, central or whole skeleton, as well as in the trabecular or cortical bone envelopes; e.g., MD, CXD, and DIP for the metacarpal bone, SXA for the calcaneus and radius, DXA for the radius, lumbar spine, femoral neck, calcaneus, as well as the whole skeleton, QCT for the lumbar spine, pQCT for the radius and tibia, and QUS for the calcaneus and tibia (Table 1).

The ratios of trabecular to cortical bone differ in various sites. In general, peripheral bone is mainly composed of cortical bone, whereas axial bone is mainly composed of trabecular bone. Bone loss progresses at variable rates in different anatomic regions. Furthermore, there exist differences in weight-bearing bone and non-weight bearing bone, and differences in proximal and distal sites even in the same bone.

Each bone densitometric method has a peculiar feature. Precision is most important in bone densitometry. Excellent precision is essential in estimating the therapeutical response of BMD and the bone loss rate. Precision errors are in the range of one to five percent for all bone densitometry methods (Table 2). In general, the precisions of peripheral DXA, pQCT and QUS are better than those of other methods. As for data acquisition time, it is shorter for bone densitometries of peripheral bone than those of axial bone (Table 3).

Techniques such as MD, SXA, DXA, QCT and pQCT depend on the absorption of X-rays, and all work on the same principle. But the principle of QUS is transmission of ultrasound, and QUS has no radiation dose. The effective radiation dose in bone densitometric techniques, reported by Genant et al.,[11] has been relatively low in absorptiometric bone measurements, less than 4 μSv, except for QCT of the lumbar spine, 50 μSv.

The correlations between *in vivo* measurements made at one site and those made at another are shown in Table 4. The coefficients of correlation between mainly cortical and mainly trabecular bone are between 0.6 and 0.8 so that measurement at one site, for example the forearm, can be used to predict BMD in the lumbar spine.

Table 1 Non-invasive measurements of bone mineral in Japan

Method	Site	Instrument
MD/CXD/DIP	Metacarpal Bone	Bonalyzer, DIP-1000
SXA	Calcaneus/Radius	SXA-2000, DTX-100
DXA	Radius	DCS-600, -600E, DTX-200, pDXA
	Calcaneus	Heel Scan
	Lumbar Spine/ Femoral Neck or/and Whole Skeleton	QDR-1000, -1500, -2000, -4500/DPX, -α, -L, -EXPERT/XR-26, -30/ DCS-3000/BMD1X
QCT	Lumbar Spine	—
pQCT	Radius or/ and Tibia	XCT-960, Densiscan-1000
QUS	Calcaneus	A-1000, AOS-100, Benus, CUBA, UXA-300
	Tibia	Sound Scan-2000

Table 2 Precision errors in bone densitometric methods

Site	Method	CV (%)
Metacarpal Bone	CXD	1.7
	DIP	1.1
Radius	DXA	1.2
	pQCT	0 5
Calcaneus	QUS	0.8
	SXA	1.5
L_{2-4} (Anterior)	DXA	1.8
(Lateral)	DXA	3.1
L_3	QCT	5.0
Femoral Neck	DXA	2.0
Whole Skeleton	DXA	2.0

Improvement of DXA System for Axial Bone Mineral Measurement

At present, several kinds of axial DXA instruments are commercially available in Japan. Since DXA was introduced in Japan in 1988, both its hardware and software

Table 3 Data acquisition time in bone densitometric methods

Method	Site	Data Acquisition Time (min.)
CXD/DIP	Metacarpal Bone	2–4
SXA	Calcaneus/Radius	3–5
DXA	Peripheral Bone	–5
	Axial Bone	–15
QCT	L_3	10–20
pQCT	Radius/Tibia	10–15
QUS	Calcaneus	–7

Table 4 Correlations of BMDs between *in vivo* measurements at one site and those made at another site

Metacarpal Bone (DIP) vs.	
L_{2-4} (DXA)	r = 0.655
Femoral Neck (DXA)	r = 0.734
Radius (DXA)	r = 0.890
Radius (DXA) vs.	
L_{2-4} (DXA)	r = 0.724–0.788
L_{2-4} (DXA)	
Femoral Neck (DXA)	r = 0.640
Whole Skeleton (DXA)	r = 0.622

Table 5 Comparisons of femoral axis length (FAL) and femoral neck area (FNA) in elderly females with or without hip fracture

	Hip Fracture	
	(+)	(−)
N	23	23
Age (yrs.)	76.9 ± 9.9	75.8 ± 6.3
Height (cm)	147 ± 7	147 ± 3
Weight (kg)	44.2 ± 7.5	44.0 ± 8.3
F-BMD (g/cm^2)	0.472 ± 0.097	0.470 ± 0.076
FAL (cm)	9.489 ± 0.388	9.302 ± 0.532
FNA (cm^2)	*4.86 ± 0.35	*4.51 ± 0.32

*$p < 0.001$

Table 6 Bone densitometric methods of radius in Japan

System	Method	Index
DTX-100	SXA	BMD (g/cm^2)
DCS-600, -600E	DXA	BMD (g/cm^2)
DTX-200	DXA	BMD (g/cm^2)
pDXA	DXA	BMD (g/cm^2)
XCT-960	pQCT	BMD (mg/cm^3) (Total, Trabecular and Cortical + Subcortical)
Densiscan-1000	pQCT	BMD (mg/cm^3) (D50, D100 and P100)

have been improved.[12] First, with the initial DXA instruments the examination procedure took six to fifteen minutes, but newly developed instruments with enhanced generators and fan beam multi-detectors instead of a pencil beam X-ray source and a single detector have shortened the examination time to two minutes or less.[13] Second, the percent weight of fat and lean mass could be calculated by a whole body scan mode. Third, the adverse effect on reproducibility of measurements of the lumbar spine on the lateral decubitus position has been addressed with newer densitometers which have a tube-detector system that can be rotated. Fourth, to reduce the effect of bone size, a volumetric BMD can be calculated from both posteroanterior and lateral DXA. In addition, as a result of the high resolution of DXA scanners, anatomic details of the examined region are depicted clearly; e.g., there is better definition of vertebral dimensions for morphometric analysis and a better assessment of geometric properties in the proximal femur.

Previous studies have shown that Japanese females have lower femoral neck BMD than American whites.[14] Although low bone mass in the proximal femur is associated with higher hip fracture incidence, the incidence of hip fractures among Japanese is about half that of American whites. The geometric characteristics of the femoral neck, hip axis length or neck width, may possibly account for reduced fracture incidence among Japanese. On DXA analysis software, we defined the length of the femoral neck axis, instead of the hip axis length, as the distance from below the lateral aspect of the greater trochanter through the femoral neck to the femoral head.[15] Neck width is defined as the shortest distance within the femoral neck region of interest, corresponding to the neck area. The femoral axis length and femoral neck area were significantly influenced by height in 140 females; $r = 0.416$, for femoral neck axis length, $p < 0.0001$ and $r = 0.335$, for femoral neck area, $p < 0.001$. After age, height, weight and femoral BMD were adjusted, we found that the femoral neck area, reflecting neck width, was significantly associated with hip fractures, independently of age and BMD (Table 5).

Bone Mineral Measurement in Radius

Various techniques, such as SXA, DXA and pQCT, are being applied to bone densitometry of the radius in Japan (Table 6). Among these techniques, much attention has been paid to pQCT.[7] QCT can determine in three dimensions the volumetric BMD of trabecular or cortical bone separately. But the *in vivo* precision error, the accuracy error affected by fat content in the bone marrow, and the radiation dose in lumbar QCT are generally higher than those observed for lumbar DXA. On the other hand, pQCT has the advantage of high precision and accuracy, and a low radiation dose.

The Densiscan-1000, a pQCT instrument with which a thin- and multi-slice technique is employed, is a low dose X-ray method for performing precise bone mineral measurement of the trabecular and cortical bone separately or integratedly. Because it has a high spatial resolution of 200 μm, pQCT also permits analysis of bone microarchitecture. The measuring site for routine examinations is the distal radius. *In vivo* reproducibility is excellent, and CV is 0.5%.[16] In quantitative examinations, three parameters are routinely calculated: D50, trabecular BMD, and D100, integrated cortical and trabecular BMD in the epiphyseal region, and P100, cortical BMD in the meta- and diaphyseal region. Two series of tomograms, 1 mm in thickness with a slice interval of 1.5 mm, are measured. Ten slices in the epiphysis and six slices in the diaphysis are obtained. The proximal site permits the assessment of cortical bone and the distal site permits that of trabecular bone.

Figure 1 shows the correlations between lumbar BMDs measured by DXA, and radial BMDs at three different sites measured by pQCT. Compared with D100 or P100, the trabecular BMD, D50, proved to be more closely related to the lumbar BMD than those at other sites.

Bone Mineral Measurements in Calcaneus

Various techniques, such as SXA, DXA and QUS, are also being applied to bone densitometry in the calcaneus in Japan (Table 7).

In QUS, several indices such as the speed of sound,

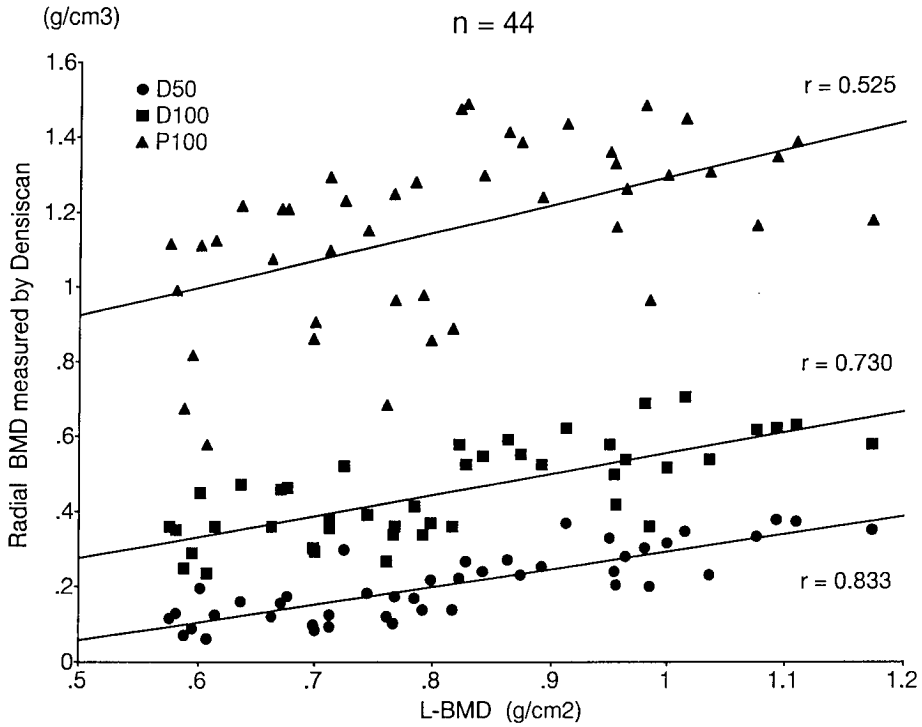

Fig. 1 Correlations between lumbar BMDs (L-BMD) measured by DXA and radial BMDs (D50, D100 and P100) measured by pQCT.

Table 7 Bone densitometric methods of calcaneus in Japan

System	Method		Index
SXA-2000	SXA	Wet	BMD
Heel Scan	DXA	Dry	BMD
A-1000	QUS	Wet	SOS, BUA, Stiffness
AOS-100	QUS	Dry	SOS, TI, OSI
Benus	QUS	Water Bag	SOS, % Trabecular Area
CUBA	QUS	Dry	SOS
UXA-300	QUS + SXA	Wet	SOS, V-BMD, E-I

SOS: speed of sound, BUA: broadband ultrasound attenuation TI: transmission index, OSI: osteosono-assessment index, V-BMD: volumetric BMD, E-I: elastic index

SOS, attenuation of sound, BUA, AOS, TI and Stiffness are calculated. Recently, a new bone densitometric instrument, the UXA-300, a hybrid of QUS and SXA for the calcaneus, has been developed.[17] With the UXA-300, speed of sound and attenuation of sound through the calcaneus are measured by QUS. In addition, volumetric BMD is measured from cross-sectional BMD by SXA and bone width by QUS. The speed of an ultrasonic wave through a certain material is dependent on the modules of elasticity of the material and its mass density. On this basis, the elastic index, EI, is calculated by SOS and volumetric BMD. We expected EI to reflect the elasticity of bone. In 100 females, we studied, EI measured by UXA-300 moderately correlated with lumbar BMD (r = 0.731) by DXA or SOS (r = 0.845), BUA (r = 0.637) and

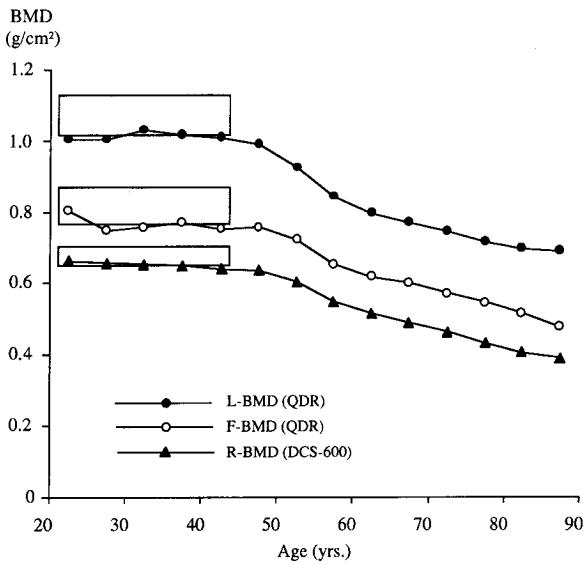

Fig. 2 Age-related changes of BMDs in lumbar spine (L), femoral neck (F), and radius (R) in Japanese females.

Stiffness (r = 0.827) measured with another QUS instrument, the A-1000.

Application of Bone Mineral Measurements to Diagnostic Criteria for Primary Osteoporosis

The Study Group of the Japanese Society for Bone and

Mineral Research proposed diagnostic criteria for primary osteoporosis in Japanese females in 1995, and revised them in 1996.[18] Among these criteria, bone loss was assessed by grading of radiographic osteopenia on lateral lumbar radiograms or BMD in the lumbar vertebrae, radius, femoral neck, calcaneus, and second metacarpal bone by DXA, pQCT and MD. After data for more than 5,000 females were collected from several centers, the standard values for BMD in Japanese females were determined as a function of aging. BMD values are constant from age 20 to 44 years, and decrease rapidly in post-menopause, age 50 to 60 years (Fig. 2). The BMD value from age 20 to 44 years was therefore defined as young adult normal, YAM. Grading of radiographic osteopenia is also used in the assessment of bone loss.[19] Radiographic osteopenia is classified, according to trabecular spacing, into four grades on lateral radiograms: Grade 0, both transverse and vertical trabeculae are dense, Grade I, vertical trabeculae are prominent, Grade II, vertical trabeculae are sparse, and Grade III, vertical trabeculae are indistinct. After the differential diagnosis is completed, diagnostic criteria are introduced. The diagnostic criteria for primary osteoporosis have been employed as follows: In a case with non-traumatic spinal fracture, osteoporosis is diagnosed when bone loss of more than Grade I or a BMD value of more than 20% below the YAM is observed. On the other hand, in a case without spinal fracture, normal is defined when radiographic osteopenia is Grade 0 or the BMD value is within 20% below the YAM. Osteopenia is defined when radiographic osteopenia is Grade I or the BMD value is more than 20% below the YAM, but less than 30%. Osteoporosis is defined when radiographic osteopenia is more than Grade II or the BMD value is 30% or more below the YAM. These criteria can be applied only to females.

Annual Rates of Bone Loss in Lumbar Vertebrae in Japanese Females

In postmenopausal osteoporosis, BMD values at any time after menopause will depend in part on the peak bone mass and the amount of bone loss thereafter. The rate of bone loss after menopause varies. Individuals who lose BMD at faster rates are more likely to reach a threshold of fracture risk. Multi-center studies advocated by the Longevity Science Osteoporosis Research Group, which is sponsored by the Japanese Ministry of Public Health and Welfare, were performed to document annual rates of bone mass change in the lumbar spine with DXA throughout pre- and postmenopausal life in 740 Japanese women. The findings were as follows; + 0.51% at age 30 and + 0.15% at age 35 for premenopausal women, and −2.26% at age 45, −1.68% at age 50, −0.90% at age 60, −0.65% at age 70, and −0.92% at age 80 for postmenopausal women.[20]

Future Prospects

Bone quality is another determinant of bone strength. Bone quality or trabecular architecture can be assessed by quantitative and qualitative examinations such as CT, ultrasound and MRI.[21] In the future, the combination of bone mineral measurement and structural analysis should improve the detection of individuals at risk for osteoporotic fracture and of bone strength.

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