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Relationship between skeletal uptake of ^{99m}Tc-HMDP and bone mineral density in elderly women

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The relationship between bone mineral density in elderly women and the pattern of skeletal uptake of ^{99m}Tc-HMDP, especially in regard to skull uptake, was investigated.

The whole-body skeletal uptake (WBSU) and whole-body skeletal tracer distribution patterns were studied in 86 disease-free women on bone scintigraphy with ^{99m}Tc-hydroxy-methylene-diphosphonate (HMDP). Bone scans were quantified by setting regions of interest (ROI) and bone mineral density (BMD) was assessed by dual-energy X-ray absorptiometry in all patients. WBSU and the skeletal distribution pattern were compared with bone mineral densities of the entire skeleton as well as selected regions.

WBSU was high in the elderly and negatively correlated with regional bone mineral densities ($r = -0.403$ to -0.534). Among the regions, uptake by the skull increased with age more than in other regions in women and had the highest negative correlation with the bone mineral density. The skull uptake correlated negatively with total body BMD ($r = -0.583$) and with lumbar BMD ($r = -0.561$, $p < 0.0001$).

Our results show that increased radionuclide uptake in bone scintigraphy, especially skull uptake was associated with decreased bone mineral density in elderly women, so that, increased skull uptake in elderly women would be a scintigraphic sign of post-menopausal or senile osteopenia.

Key words: bone scintigraphy, skull, bone mineral density, osteoporosis, menopause

INTRODUCTION

DIFFUSELY ENHANCED radionuclide accumulation in the skull on bone scintigraphy, which is sometimes termed "Hot Skull," is often observed in elderly women without any apparent skeletal diseases or symptoms related to bone (Fig. 1). This was originally found in patients with breast cancer, who underwent cytotoxic chemotherapy, and was attributed to the chemotherapy,[1,2] but in routine clinical examination, diffuse increase in radionuclide uptake in the skull is seen in women without chemotherapy. Our previous study which quantified skeletal radionuclide uptake demonstrated a substantial increase in skull uptake after 50 y.o. in women, suggesting a relationship with the menopause.[3] Increased skull uptake in bone scintigraphy is common in some metabolic bone diseases such as hyperparathyroidism, osteomalacia and hyperthyroidism.[4–7] Although details of the mechanism of this increased skull uptake remain unclear, the skull bone, as non-weight bearing bone, might be sensitively affected by systemic metabolic change. In this study we studied apparently normal elderly women who were examined with routine bone scintigraphy, by semi-quantifying the image, applied bone densitometry to correlate it with skeletal uptake in bone scan and discussed the significance of skeletal uptake in bone scintigraphy.

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MATERIALS AND METHODS

Subjects: Patients who underwent bone scintigraphy, but had no focal abnormal uptakes in two consecutive years without any medication, and patients with no skeletal symptoms at their first pretreatment bone survey were

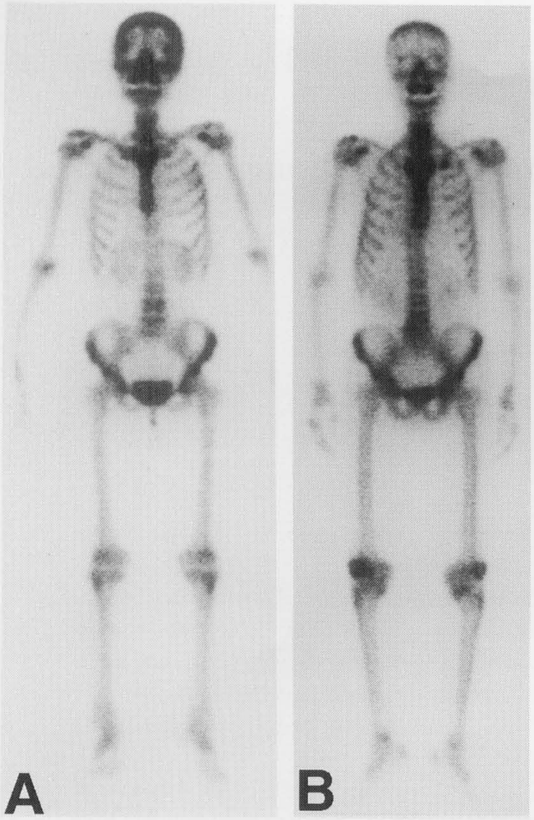

Fig. 1 An example of increased skull uptake in elderly women. A bone scintigram of 56 y.o. woman shows enhanced radionuclide uptake by the skull (A). For comparison, a bone scintigram of 44 y.o. woman is also shown (B).

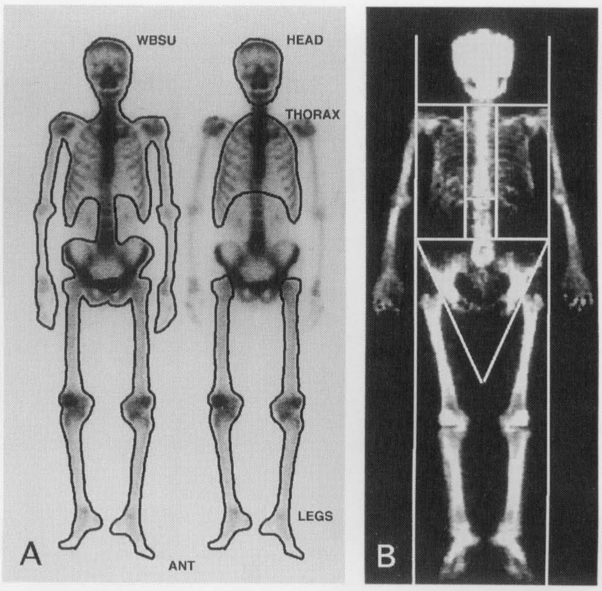

Fig. 2 An example for setting regions of interest (ROIs) on a bone scintigram and for analysis of regional bone mineral measurements. To determine regional bone uptake in bone scintigraphy, ROIs on the bone scan of the head, thorax and lower legs were set in both the anterior and posterior projections as shown in this figure by tracing regions on the computer display (A). The mean of counts from both projections was calculated. For determination of regional bone mineral densities, using the total body scan, the head area was determined as shown in this figure (B). Lumbar (L2–4) BMD and femoral neck BMD were measured separately by regional scan modes.

selected and asked to undergo measurement of bone densitometry. One hundred and thirty-seven patients agreed to enter this study, but after measurement of bone density, twenty-one patients were considered to be inappropriate because of the presence of osteoarthritis, scoliosis, prosthesis or other artifactual causes. Another thirty patients were also excluded due to factors which could possibly influence the results, such as the administration of drugs and the presence of other chronic diseases or the presence of abnormal focal uptakes in their bone scintigram from non-malignant diseases. Finally, eighty-six women (age range 28–75, mean: 51.5 ± 11.6 (mean $\pm$ SD), weight 52.4 ± 8.6 kg (mean $\pm$ SD), height 154.0 ± 5.4 cm (mean $\pm$ SD)) were included in this study and their data were further analyzed. Of these, seventy patients had breast cancer, 14 had other malignant diseases, and 2 had nonmalignant diseases. None received estrogen or other drugs which could possibly influence bone metabolism, such as corticosteroids, progesterone, calcitonin or methotrexate. Approximately two-thirds of the patients were in a disease-free state after therapy and one-third were undergoing initial examination before therapy. Patients who had any metabolic bone diseases such as primary hyperparathyroidism, hyperthyroidism, renal osteodystrophy, osteomalacia, multiple myeloma or other skeletal disorders possibly influencing the results were excluded. All were outpatients, and severely ill patients were also excluded.

Bone scintigraphy: On all subjects bone scintigraphy was performed semi-quantitatively to find regional skeletal uptakes. ^{99m}Tc-hydroxy-methylene-diphosphonate (HMDP; CLEAR BONE, Mediphysics Co. Ltd., Osaka, Japan) was used for bone scintigraphy in all patients. The labeling procedure for the radiopharmaceutical was consistent and the labeling efficiency was checked to assure constant high quality. ^{99m}Tc-HMDP was counted in a Curimeter (Capintec Japan, Tokyo, Japan) and 555 MBq of the radiopharmaceutical was injected intravenously with repeated drawing and injecting to avoid leaving the remnant of the tracer. Four hours later, after complete urination, 10 minute whole body bone scintigrams, with both anterior and posterior projections were obtained by means of a dual whole-body scinticamera with a large field of view (51 × 38 cm; GCA 901A/W2, Toshiba Medical Co., Ltd., Tokyo, Japan) equipped with a high resolution collimator. The protocol for scanning was kept constant, throughout the study: patient positioning, scan speeds (20 cm/min) and other parameters were kept constant. The distance from the nearest body surface to

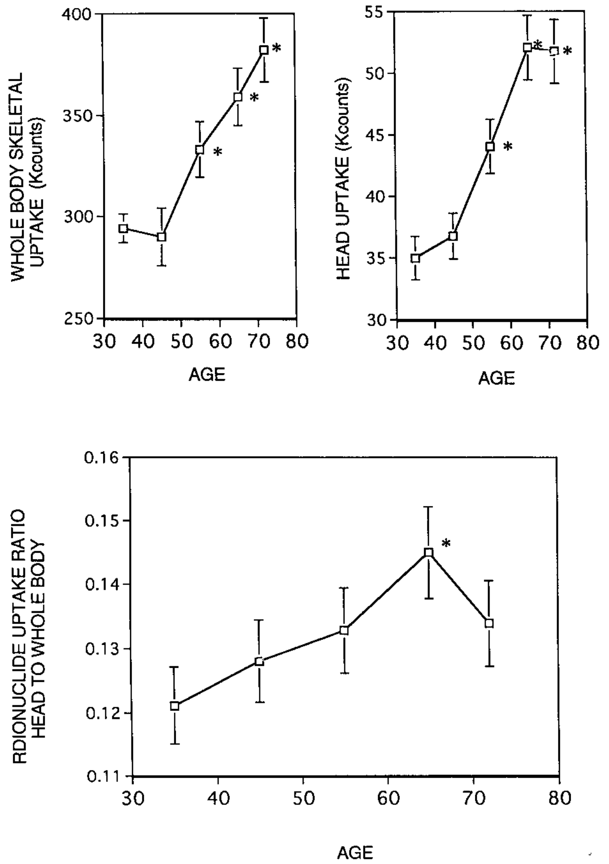

Fig. 3 Age-related changes of ^{99m}Tc-HMDP accumulation in the whole body and in the head. Both the whole body skeletal uptake (Upper Left) and the head uptake (Upper Right) of the radionuclides increased with age, but the head uptake increased more than the whole body uptake. Ratio head uptake to whole body uptake was higher in the elderly women (Bottom).
*: significantly different from values of age 30–49 ($p < 0.001$).

the scinti-cameras was kept at 5 cm. Data were recorded on an optical memory disk (OD-01A, Toshiba Medical Co., Ltd., Tokyo, Japan).

Quantification of bone scintigrams: Skeletal uptakes of ^{99m}Tc-HMDP were analyzed with a data processor (GMS-550U, Toshiba Medical Co., Ltd., Tokyo, Japan) as described previously.[3] In both anterior and posterior views of a whole body scintigram, regions of interest (ROI) were set over selected bone regions as shown in Fig. 2, excluding soft tissue and the urinary tract. Patients with abnormally high uptakes from various skeletal disorders such as arthritis, fracture, sinusitis and/or dental diseases were pre-excluded from the analyses. A simple mean of radioactivities (counts) from both views was calculated after adjusting for the radionuclide half-life decay, and defined as the whole-body skeletal uptake (WBSU). The soft tissue uptake was also monitored by subtracting the activities of the urinary tract (kidney and bladder) and WBSU from the total body uptake. Soft tissue activity was less than one-tenth of WBSU and had a small effect on the WBSU. Bone uptake in the head, thoracic region and lower legs was expressed as the ratio of the uptake in each region to WBSU.

Reproducibility of the procedure for quantitation of bone scan was checked by comparing analyzed results in two distinct examinations which were performed within a year in 10 patients and showed 3.5–10.2% of C.V. in regional skeletal uptakes and 5.5% of that in WBSU.

Bone mineral densitometry: Bone mineral density was assessed by dual-energy X-ray absorptiometry (DXA) with DPX-L (Lunar Co. Ltd., Madison, WI, USA) and was performed within four weeks of bone scintigraphy by a trained technician using constant scanning protocols. Calibration was performed daily prior to measurement for patients. Total body bone mineral density (BMD), anterior-posterior lumbar BMD (integral L2 to L4 BMD; L2–4 BMD) and femoral neck BMD were assessed according to the standard protocols: lumbar BMD was assessed in a position which reduces lumbar lordosis and femoral neck BMD was determined at 30 degree inner rotation of the right leg, placing water-equivalent material at the outside of the lateral thigh. Head BMD was calculated from the total body measurement by setting the region of interest on the head, which was defined as the region over the line between both olecranon processes (Fig. 2), and lumbar BMD and femoral neck BMD were each measured with protocols for regional measurement. Average *in vivo* precision values for these measurements are 1.2% for lumbar BMD, 2.0% for femoral neck BMD, 1.1% for total body BMD and 1.8% for the head BMD (determined by five separate measurements in three healthy volunteers).

Correlation among skeletal radionuclide uptakes and regional BMDs was studied.

Data Analysis: The association between BMDs and radionuclide uptake was examined by simple regression with STAT VIEW SE (Abacus Concepts Inc., Berkeley, CA). Differences between two groups were tested with unpaired t-test (Welch's t-test). A p value less than 0.05 is considered to be significant.

RESULTS

Whole body skeletal uptake (WBSU) and absolute counts of head uptake as a function with age are shown in Fig. 3. Consistent with the previous study,[3] WBSU and head uptake increased from the fifth decade to the seventh decade. Furthermore, relative uptake by the head (a ratio of the head uptake to WBSU) increased with age until the seventh decade (significantly different in the seventh decade from those in the fourth and fifth decades).

WBSU was negatively correlated with regional bone mineral densities ($r = -0.471$ to -0.561, $p < 0.0005$) (Table 1). Lumbar BMD showed the highest negative correlation ($r = -0.561$, $p < 0.0001$), followed by femoral neck BMD ($r = -0.534$, $p < 0.0001$).

Detailed insight of the ROI data revealed that uptake by

Table 1 Correlation among skeletal uptakes in bone scintigraphy and bone mineral densities measured by dual energy x-ray absorptiometry

	Total body BMD	Head BMD	L2–4 BMD	Femoral Neck BMD
WBSU	−0.514	−0.471	−0.561	−0.534
(kcount)	<0.0001	0.0002	0.0001	<0.0001
HEAD	−0.583	−0.471	−0.561	−0.577
(kcount)	<0.0001	<0.0001	<0.0001	<0.0001
THORAX	−0.443	−0.327	−0.282	−0.448
(kcount)	<0.0001	0.0033	0.0119	0.0007
LEGS	−0.479	0.390	−0.488	−0.510
(kcount)	<0.0001	0.0004	<0.0001	<0.0001
HEAD	−0.257	−0.220	−0.361	−0.203
(/WBSU)	0.0222	0.0509	0.0012	0.144
THORAX	0.0223	0.0604	0.256	0.063
(/WBSU)	0.8451	0.597	0.0238	0.6498
LEGS	0.0828	0.0508	−0.117	0.023
(/WBSU)	0.4681	0.6566	0.307	0.8708

The radionuclide uptakes negatively correlated with the bone mineral densities (BMDs), but in comparison with whole body skeletal uptake (WBSU), only head uptake negatively correlated with BMDs.

the head had the highest negative correlation with bone mineral density. The head uptake correlated negatively with total body BMD ($r = -0.583$, $p < 0.0001$) and with lumbar BMD ($r = -0.561$, $p < 0.0001$). The radionuclide uptake by the thorax and legs showed a lower correlation with bone mineral densities ($r = -0.327$ to -0.510). When regional uptakes were expressed as ratios relative to WBSU, only the head uptake showed a significant correlation with BMDs (Table 1, Fig. 4).

To validate the effects of age, the correlation between radionuclide uptake and bone mineral density was examined in each decade group. Although the numbers in each group were relatively small, a tendency to a negative correlation in each age group was observed (Fig. 4).

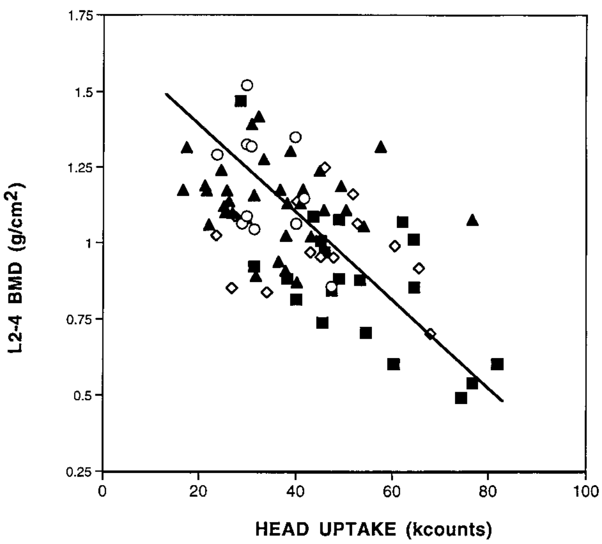

Fig. 4 Correlation between lumbar bone mineral density (BMD) and head uptake. The relationship between lumbar BMD and head uptake (absolute counts) was plotted in terms of age groups (○: under 40, ▲: 41–50, ◇: 51–60, ■: over 61). Although the number of each group is small, there is a tendency of negative correlation between BMD and the uptake in each age group.

DISCUSSION

In this study, we have confirmed the previous results that showed an age-related increase of skeletal uptake in ^{99m}Tc-HMDP scintigraphy in women[3,8,9] and for the first time showed that the regional skeletal uptake correlates negatively with bone mineral density assessed by DXA. Higher radionuclide accumulation showed lower bone mineral density. Among regional bone densities, the correlation with the radionuclide uptake was high in total body BMD, lumbar BMD and femoral neck BMD. Among the regional uptakes in bone scans, uptake by the head showed the highest correlation with BMDs.

Our method estimating WBSU was a modification of a method originally shown by D'Addabbo et al. which makes it possible to calculate WBSU without waiting for 24 hours or harvesting the urine.[10] At 4 hours, radioactivity still remains in the soft-tissue, but by excluding the major source of extra-skeletal activity, namely the activity from the urinary tract, WBSU can be obtained and the influences of remaining activity in the soft tissue is small.[3,10] There can be individual variation in tissue gammma-ray attenuation due to differences in body size, but in our present study differences in body size were relatively small (coefficient variations in body weight and height were 16.4% and 3.5%, respectively) and thus errors should be small. Setting of the ROI was done in as uniform a way as possible and variation in the calculation of regional uptake was also small.

An increase in skeletal uptake with aging in bone scintigraphy was seen in some previous studies; whole-body radionuclide retention measured at 24 hours after the injection was higher in elderly people.[8,9] This was attributed either to a decrease in renal function with aging[9] or to enhanced bone metabolism in the aged.[8] The latter study also demonstrated enhanced bone loss in those who had high whole-body skeletal retention of the radionuclide. Both explanations for the increased skeletal uptake in elderly subjects may be true: radionuclide uptake by bone in bone scintigraphy is influenced by renal function as well as bone metabolic turnover rate.[7] A decrease in renal function might partly contribute to increased WBSU in elderly women in our study, but some part could be explained by increased skeletal turnover in the elderly. Our previous study, which showed a correlation of WBSU with levels of bone metabolic markers,[3] supports this. There is accumulating evidence which shows increased bone turnover in elderly women.[11–14] Increased skeletal turnover causes more bone loss in the elderly,[15,16] in whom bone formation cannot completely compensate for bone resorption, so that lower BMD in those with higher WBSU could be attributed to enhanced skeletal turnover in the elderly.

Increased skull uptake in normal elderly women is a well-known finding in bone scintigraphy.[1,2,17,18] In contrast to WBSU, increased skull uptake is not attributable to decreased renal function, since it is unusual for decreased radionuclide clearance to affect only skull uptake. Increased skull uptake is age-dependent and cannot be attributable to any artifacts in obtaining a bone scan, such as disproportionate tissue attenuation of radioactivity. In addition, increased skull uptake is rarely found in elderly men.[3,17] This was originally discussed in relation to chemotherapy in patients with breast cancer [1,2] and once in connection with hyperostosis cranii in younger women,[18] but in one study,[17] increased skull uptake was related to the post-menopausal bone metabolic change. Recent studies show that postmenopausal bone loss is exaggerated in those with increased bone turnover[11] and bone mass is lower in those with high bone metabolic markers.[19] The present findings combined with the previous results indicate the increased skull uptake would be a sign of bone loss in post-menopausal or elderly women.

Increased skull uptake is a common finding in patients with high-turnover bone diseases such as hyperparathyroidism and osteomalacia.[4,5,6] The reason why skull uptake increases in such diseases is unclear, but the skull, being a non weight-bearing bone, might be early affected by a systemic mineral metabolism change and could show the first and prominent sign of general bone metabolic change as seen in "salt and pepper appearance" in the skull X-ray photograph in hyperparathyroidism.[20] It is therefore probable that the increased skull uptake in elderly women is attributable to enhanced systemic bone metabolism. To ultimately determine the meaning of increased skull uptake in women, a prospective study to assess the rate of bone loss would be necessary.[21]

In summary, we have shown that increased radionuclide uptake in bone scintigraphy is associated with decreased bone mineral density in elderly women, especially increased skull uptake associated with decreased lumbar BMD, so that increased skull uptake in elderly women would be a sign of post-menopausal or senile osteopenia.

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