

Age-Related Change of Technetium-99m-HMDP Distribution in the Skeleton

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To understand age-related changes of whole-body and regional skeletal metabolism, it is important to investigate the mechanisms of age-related bone loss and to develop suitable treatments for it. Bone biopsies show metabolism of the particular site examined while biochemical markers for bone metabolism reflect total skeletal metabolism. Bone scintigraphy is a convenient and simple way to analyze whole-body and regional skeletal metabolism. We attempted to study and understand age-related changes in bone metabolism by quantifying the bone scan and correlating it with biochemical bone metabolic markers. **Methods:** The whole-body skeletal uptake (WBSU) and whole-body skeletal tracer distribution pattern were studied in men and women by bone scintigraphy using ^{99m}Tc -hydroxy-methane-diphosphonate (HMDP). Bone scans were performed using a standard protocol and quantified by setting regions of interest (ROIs) on selected regions. WBSU and the skeletal distribution pattern were compared with simultaneously obtained serum biochemical markers. **Results:** WBSU showed an increase with age in both sexes, but in women, uptake in the head and legs increased more relatively than in the thoracic region, while in men no such tendency was observed. Increase of WBSU and relative increase of uptakes in the head demonstrated a weak correlation with the serum levels of alkaline phosphatase and type 1 collagen metabolites. **Conclusion:** These results show an age-related increase of skeletal turnover and sex-dependent regional skeletal metabolism. The age-related changes seen in bone scintigrams might be a sign of progressive bone loss, reflecting changes in local bone metabolism.

Key Words: whole-body skeletal uptake; regional skeletal metabolism; technetium-99m-HMDP

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Bone scintigraphy with ^{99m}Tc -labeled phosphonates is one of the most common procedures in nuclear medicine and its role in the diagnosis of various skeletal disorders is firmly established. A major advantage of radionuclide bone scan is its sensitivity in detecting bone metastases and other skeletal disorders. Bone scintigraphy can be used to survey the total body, which cannot be easily done by other radiological procedures. Although the mechanism of the accumulation of ^{99m}Tc -labeled phosphonates in bone still remains to be clarified, the uptake of the radiopharmaceuticals is thought to reflect local bone turnover (1). Other methods utilized in the evaluation of bone metabolism include ^{18}F -fluoride scintigraphy (2), calcium kinetic studies (3) and bone biopsies, all of which require special devices or a more invasive procedure. Some biochemical markers report bone metabolism accurately (4), but they represent the cumulative total body metabolic activity. Bone scintigraphy with ^{99m}Tc -labeled phosphonates is a simple and unique way to evaluate local bone turnover.

Age-related changes shown by whole-body bone scintigraphy

with ^{99m}Tc -labeled phosphonates are well known; in growing children, bone uptakes are high in general, and especially at the growth plates, and in postmenopausal women skull uptake often increases diffusely (5-10). An increased uptake in the calvarium (a "hot skull") was first attributed to extensive cytotoxic treatment in patients with breast cancer (6), but more recent studies have shown this to be neither specific to breast cancer nor cytotoxic treatment (7-9), and in men extensive chemotherapy or malignant diseases do not cause the hot skull. Since such increased skull uptake is predominantly observed in women over the age of 50, it has been discussed in relation to menopause without evidence of a connection between the two (7,8).

In this study, we investigated the changes of the bone scintigraphic pattern associated with age in adults by quantifying regional and total-body skeletal uptake and correlating them with metabolic bone markers.

MATERIALS AND METHODS

Subjects

A total of 144 women and 130 men suffering from a variety of disorders, in whom no focal abnormalities of skeletal uptake were seen on their bone scan (age range 20-84, mean 55.3 ± 13.6 (mean \pm s.d.), weight 55.8 ± 9.9 kg (mean \pm s.d.), height 159.6 ± 8.4 cm (mean \pm s.d.). Of the women patients; 91 had breast cancer, 41 had other malignancies and 12 had nonmalignant diseases. Of the men; 45 had lung cancer, 20 prostate cancer, 54 other malignancies and 11 nonmalignant diseases. Patients who had metabolic bone disease such as primary hyperparathyroidism, hyperthyroidism, renal osteodystrophy and osteomalacia were excluded from the study. Additionally, severely ill patients and patients with chronic renal failure or liver cirrhosis were also excluded.

Bone Scintigraphy

Technetium-99m-hydroxy-methane-diphosphonate (HMDP) was used for bone scintigraphy in all patients. The labeling procedure of the radiopharmaceutical was consistent and the labeling efficiency was checked to assure constant high quality. Technetium-99m-HMDP was counted by a Curimeter was adjusted at 555 mBq (at noon), and packed in a disposable glass syringe and shipped to our department. The radiopharmaceutical was injected intravenously into a different patient every 20 min, with repeated drawing and injecting to avoid the remnant of the tracer. Four hours later, 10-min bone scintigrams, with both anterior and posterior projections were obtained by a dual whole-body scinticamera with a large field of view equipped with a high-resolution collimator. Patient positioning was constant, throughout the study, scan speeds (20 cm/min) and other parameters were kept constant. The distance from the nearest body surface to the scinticameras was kept at 5 cm. Data were recorded on an optical memory disk.

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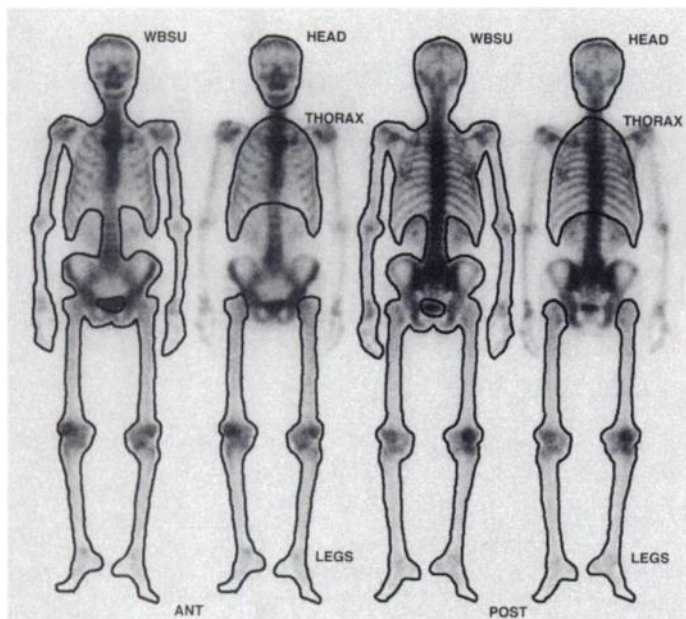


FIGURE 1. During counting of whole-body skeletal uptake, activities from the urinary bladder and kidneys were carefully excluded. For counting regional bone uptake, ROIs on the head, thorax and lower legs were set in both the anterior and posterior projections. The mean of both projections was calculated.

Quantification of Bone Scintigrams

Skeletal uptakes of ^{99m}Tc -HMDP were analyzed on a data processing system using the method reported by D'Addabbo et al. (11), with slight modifications. In both anterior and posterior views of a whole-body scintigram, ROIs were set over selected bone regions (Fig. 1), excluding the soft tissue and the urinary tract. Patients having abnormally high uptakes from various skeletal disorders such as arthritis, fracture, sinusitis and/or dental diseases were excluded from the analyses. A 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). Just after administration, 555 mBq of ^{99m}Tc -HMDP gives approximately 880 k counts and thus it is possible to obtain the absolute whole-body skeletal uptake ratio. In this study, however, we represent the WBSU as a simple mathematical mean of anterior and posterior projections. The soft tissue uptake was also assessed by subtracting the activities of the urinary tract (kidney and bladder) and WBSU from the total body uptake. 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 ten patients.

Measurement of Metabolic Bone Markers

At the time of the bone scan, blood samples were obtained and stored as serum at -30°C . C-terminal propeptide of type 1 procollagen (P1CP) and C-terminal telopeptide of type 1 collagen (1CTP) were measured using radioimmunoassay kits (12,13). These two radioimmunoassay kits have shown low intra- and inter-assay variations (C.V.: 8–15%) (14,15). Alkaline phosphatase (ALP) was measured by a conventional colorimetric method also using a kit. Of these biochemical markers, P1CP and ALP are for bone formation and 1CTP is for bone resorption (4,12–15). Statistical analysis was done using an unpaired Welch's t-test.

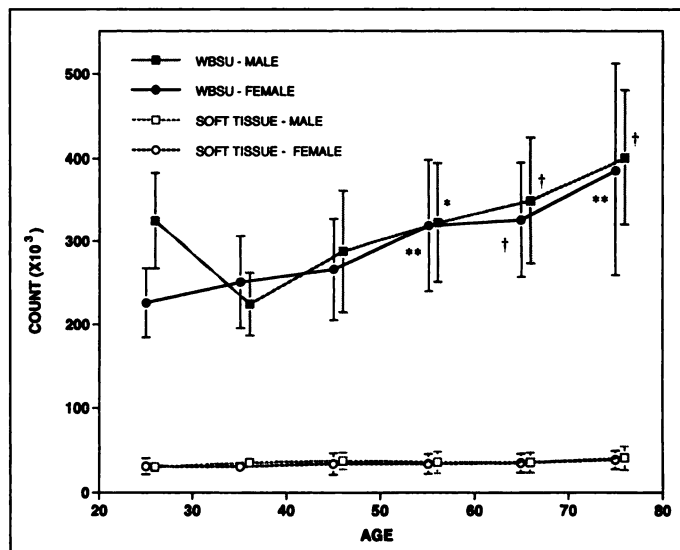


FIGURE 2. In men and women, WBSUs increased with age. No statistical differences between the genders were observed. Each point represents mean \pm 1 s.d. of WBSU in each decade. * $p < 0.05$ compared to WBSUs at age 20–50 yr. ** $p < 0.01$ compared to WBSUs at age 20–50 yr. † $p < 0.001$ compared to WBSUs at age 20–50 yr. n.s. = not significant.

RESULTS

Reproducibility of Quantitation of Bone Scans

Variations of quantitated results in repeated bone scans were as follows; $6.57 \pm 5.36\%$ for WBSU, $10.15 \pm 7.91\%$ for the head, $3.73 \pm 2.92\%$ for the thorax and $8.83 \pm 6.37\%$ for the legs (data represent mean \pm s.d. in ten patients).

Whole-body Skeletal Uptake and Distribution Pattern

WBSUs in both men and women increase with aging (Fig. 2). The soft tissue uptakes were very low compared to WBSU and showed a slight increase with age, but the absolute variations were too small to affect WBSUs (Fig. 2). When WBSUs under age 50 were compared with those over age 50, the latter were approximately 12% higher, showing statistically significant differences (Fig. 2).

Changes of distribution pattern with aging, however, were significantly different in men and women. Uptakes by the head and the lower legs increased with age in women, while that in the thoracic region decreased. In men no such tendency was clearly observed (Fig. 3). In women over 50 yr of age, significantly higher uptakes were observed at the head and/or legs and significantly lower uptake in the thorax compared with those in women of under 50. Male patients demonstrated no such significant differences. In absolute counts, however, the uptake by the thoracic region still showed a small increase with age in women. Relative skull uptakes at all ages were significantly higher in women than in men. Thus, skeletal uptakes in men increased proportionately, but the head and legs were disproportionately large in women.

Correlation of Skeletal Uptakes or Distribution Pattern with Biochemical Markers

Table 1 summarizes the correlations between WBSU or local region uptakes and the biochemical markers. There were significant associations of biochemical markers with WBSU in both males and females; in males with P1CP ($r = 0.387$, $p = 0.0038$) and 1CTP ($r = 0.359$, $p = 0.0077$), in females with P1CP ($r = 0.333$, $p = 0.0055$) and ALP ($r = 0.248$, $p = 0.0360$).

There are significant associations of ALP with skeletal uptakes in women; WBSU: $r = 0.248$, $p = 0.0360$, head: $r =$

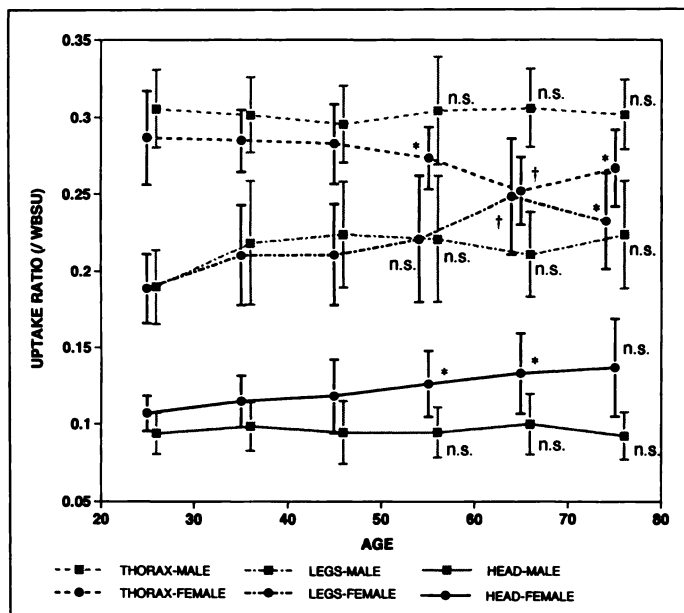


FIGURE 3. Relative head and leg uptake increases with age in women, while thoracic uptake decreased. In men, no significant changes of regional skeletal uptakes are seen. Data represents mean \pm 1 s.d. of uptake ratios of each region to the total body. * $p < 0.05$ compared to uptakes at age 20-50. † $p < 0.001$ compared to uptakes at age 20-50 yr. n.s. = not significant.

0.295, $p = 0.0118$, thorax: $r = -0.382$, $p = 0.0009$, legs: $r = 0.247$, $p = 0.0365$. In men, ALP was not associated with skeletal uptake.

In the head uptake, there was a positive correlation of all serum biochemical markers in females and a negative correlation in males; in females, $r = 0.295$, 0.336 and 0.007 , and in males, $r = -0.031$, -0.146 and -0.486 with ALP, P1CP and 1CTP, respectively.

DISCUSSION

We have shown changes of WBSU and the regional distribution pattern by quantifying routine bone scans. The radiopharmaceutical employed was commercially available pre-labeled ^{99m}Tc -HMDP, which can be obtained in relatively constant quality and quantity. Careful attention to the scan protocol was used when taking scintigrams. Use of a dual whole-body scintiscamera with a large field of view made it easier to maintain a constant scanning condition. We set ROIs

TABLE 1
Correlation of Serum Biochemical Markers with Skeletal Uptake

	WBSU		Head		Thorax		Legs	
	Male	Female	Male	Female	Male	Female	Male	Female
ALP								
r	0.168	0.248	-0.031	0.295	-0.004	-0.382	-0.097	0.247
p	0.2200	0.0360	0.8232	0.0118	0.9781	0.0009	0.4815	0.0365
P1CP								
r	0.387	0.333	-0.146	0.336	0.073	-0.061	-0.123	-0.109
p	0.0038	0.0055	0.2925	0.0052	0.6001	0.6239	0.3751	0.3748
1CTP								
r	0.359	0.131	-0.486	0.007	0.040	0.095	-0.068	-0.092
p	0.0077	0.2768	0.0002	0.9536	0.7758	0.4319	0.6244	0.4438

Each correlation was calculated and regression results were analyzed. Data show a regression coefficients (r) and p values (p). WBSU = whole-body skeletal uptake.

on the bone and excluded major soft tissue radioactivities. This method, reported by D'Addabbo et al. (11), allowed us to assess whole-body skeletal uptake in routinely performed bone scintigraphy without waiting 24 hr, which is necessary with the conventional method to exclude soft tissue activity.

Renal function decreases with aging and the increase of WBSU on aging may be attributable to this. We cannot completely exclude this possibility because our setting of ROI on the skeleton includes overlaying soft tissue, but as shown in Figure 2, changes of soft tissue activities with aging are too small to affect the WBSU. Furthermore, our finding that the increase of WBSU on aging is weakly correlated with serum metabolic bone markers such as P1CP and ALP shows that WBSU represents bone metabolism, since levels of P1CP and ALP are not affected by renal function alone. The increase of WBSU implies increasing bone turnover with aging, which was consistent with previous findings (7,16-18). Recent studies employing measurement of bone metabolic markers have also shown enhanced bone turnover in the aged (14,15,19,20). Our data show no statistical differences of WBSU between males and females and thus, increase of bone turnover with aging is universal.

To study the regional distribution pattern of radionuclide uptake, we set ROIs on the head, thoracic region and the lower legs. We chose the thoracic region as a representative of the axial bone, because other axial regions, such as the lumbar or pelvic region, have the potential of being affected by urinary tract radioactivity. The upper and lower extremities showed similar results in a preliminary study, varying less in the lower extremities, and both are representative of the cortical bone. The regional radionuclide distribution pattern differed in men and women. Increases of skull uptake in postmenopausal women are often observed in routine bone scintigrams (5-10) and we proved this clinical impression by quantifying bone scintigraphy.

The fact that the head uptake has a positive correlation to, and was associated with, bone metabolic markers may be a reflection of increased bone turnover in aged women. The skull is the bone in which increased bone turnover is reflected markedly in several metabolic bone diseases, such as hyperparathyroidism and osteomalacia. An unexpected result revealed in this study was the increase of uptake by the lower legs and uptake by the axial bones decreased relatively in aged women. The difference in body size between men and women may affect the absolute counts in each region, leading to different distribution patterns. More uptake by the head in women than in men might be attributable to this, but it does not explain why the differences are related to aging. Thus, increased uptake by the head may be caused by increased turnover in the skull in older women, possibly due to increased parathyroid hormone levels (21). Further studies to explain these findings are necessary. There may be a correlation with post-menopausal osteoporosis (22). There is substantial evidence that elevation of bone metabolic markers after menopause is correlated with the speed of bone loss in women (16,20,23). It is possible that increased radionuclide accumulation in the skull or in the lower legs is a sign of osteoporosis.

In men, by contrast, the distribution pattern changed proportionately, with an increased WBSU. The negative correlation of the head uptake with serum biochemical markers, clearly different from that in women, requires more extensive investigation.

CONCLUSION

We have shown by a quantitative method that sex-specific changes are observed by bone scintigraphy which also reveals the association of serum biochemical markers with skeletal uptake.

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Opioid and Opioid-Like Drug Effects on Whole-Gut Transit Measured by Scintigraphy

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We studied the effects of several drugs on gastrointestinal transit (tramadol HCl, acetaminophen with codeine and placebo) in a randomized, double-blind, crossover study. **Methods:** Combined gastric emptying, small bowel and colonic transit scintigraphy was performed in 12 normal subjects. Each subject received a standardized diet and study drug on Days 1-5. On Day three, subjects received a radiolabeled solid and liquid phase meal. **Results:** No significant difference in the gastric $T_{1/2}$ (mean \pm s.e.m.) of solids for placebo (69 ± 7 min), APAP/C (74 ± 15 min) or tramadol (686 ± 8 min) ($p = 0.86$) were seen. Similarly there was no significant difference in the $T_{1/2}$ of liquids for placebo (31 ± 4 min), APAP/C (41 ± 6 min) or tramadol (41 ± 7 min) ($p = 0.29$). Orocecal transit times were not significantly different for placebo (237 ± 20 min), APAP/C (311 ± 26 min) or tramadol (311 ± 10 min) ($p = 0.12$). Colon geometric centers (GC) for placebo at 24, 48 and 72 hr were 4.6 ± 0.35 , 6.0 ± 0.28 and 6.8 ± 0.08 . The GC for tramadol and APAP/C were all significantly lower at 72 hr, 6.4 ± 0.17 and 6.2 ± 0.17 , respectively compared to the placebo. The GC of tramadol at 24 and 48 hr (3.8 ± 0.4 , 5.4 ± 0.26) were not significantly different from placebo. In contrast, the GC for APAP/C at 24 and 48 hr (3.3 ± 0.31 , 5.0 ± 0.26) were significantly delayed. All subjects recorded a significant increase in constipation on drugs compared to placebo ($p = 0.04$). **Conclusion:** Tramadol and APAP/C had no effect on gastric emptying or small bowel transit. At equianalgesic doses, tramadol caused less delay in colonic transit than APAP/C for 48 hr

and delay in the GC agreed with the subjective complaints of constipation on both drugs.

Key Words: gastric emptying; small bowel transit; colon transit; opioid drugs

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Analgesics are widely prescribed for acute and chronic pain. Codeine, a commonly used opioid analgesic, frequently causes constipation (1). Tramadol hydrochloride, a new, opioid-like centrally acting analgesic may result in less constipation (2), but this effect has never been quantified.

We have previously shown that scintigraphy can be used to quantify changes in gastrointestinal transit in response to medications including opioid analgesics (3,4). The purpose of this study was to compare the effects of tramadol, acetaminophen with codeine (APAP/codeine) and placebo on gastrointestinal transit times in healthy male subjects. Additionally, we sought to refine our technique for performing combined gastric emptying, small bowel and colon (whole-gut transit) scintigraphy and to correlate the findings of quantitative scintigraphy with the clinical symptoms of constipation.

MATERIALS AND METHODS

We performed a randomized, double-blind, placebo controlled crossover study comparing the effect of 100 mg tramadol HCl to acetaminophen 600 mg with codeine 60 mg (APAP/codeine) on gastric emptying, small bowel and colon transit.

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