Different Patterns of Global and Regional Skeletal Uptake of ^{99m}Tc-Methylene Diphosphonate with Age: Relevance to the Pathogenesis of Bone Loss

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Bone turnover changes with age have been shown by both histomorphometric and scintimetric methods; fewer studies have been performed on the regional differences of bone remodeling in the aging skeleton. To noninvasively investigate this issue, we evaluated the age-related patterns of global and regional bone uptake of ^{99m}Tc-methylene diphosphonate (MDP) in a large sample of healthy women. **Methods:** In a group of 84 healthy women (33 pre- and 51 postmenopausal), the uptake of ^{99m}Tc-MDP was semiquantitatively measured in 5 regions of interest. Total-body digital scans (TBDSs) were acquired at 5 min and at 4 h. Five regions of interest were drawn on the skeleton as a whole, on the lumbar spine, on the iliac wing, on the femoral neck, and on the femoral diaphysis of the 4-h TBDS. Regional skeletal uptake of the lumbar spine (LS-RSU), of the iliac wing (IL-RSU), of the femoral neck (FN-RSU), and of the femoral diaphysis (FD-RSU) was calculated as percentage injected dose retained in these skeletal segments at 4 h. **Results:** As expected, in postmenopausal women the global skeletal uptake (GSU) values were higher than those in premenopausal women (40.7 ± 5.9 percentage injected dose [%ID] versus 35.1 ± 4.2 %ID; $P < 0.0001$). GSU correlated positively with age ($r = 0.70$; $P < 0.001$), but the addition of years since menopause to the regression model did not ameliorate the regression. On the other hand, LS-RSU ($r = -0.55$; $P < 0.0001$), IL-RSU ($r = -0.45$; $P < 0.0001$), and FN-RSU ($r = -0.22$; $P < 0.005$) decreased significantly, whereas FD-RSU increased significantly ($r = 0.39$; $P < 0.001$) with age; the same regressions were not influenced significantly by the addition of menopausal duration to the regression model. The strongest correlation among the different RSUs was that found between LS-RSU and IL-RSU ($r = 0.63$; $P < 0.001$). Moreover, the linear regression coefficients of the various RSUs with age were all significantly different from each other ($P < 0.001$). **Conclusion:** Our data show that the GSU of ^{99m}Tc-MDP increases with age, whereas different skeletal segments display a variable degree of turnover activation at different ages. This could ultimately induce the different rates of bone loss of different skeletal segments at various ages and, consequently, their variable propensity to fracture.

Key Words: trabecular tissue; cortical bone; aging; bone turnover

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Changes of bone mass and structure with aging are main factors leading to the occurrence of skeletal fractures, which is an emerging pattern in elderly people. The progressive age-related decrease in bone mass can be detected by densitometric measurements of various skeletal sites (*1,2*), but the pattern of bone loss is not equivalent in all assessed sites; axial and appendicular skeletal sites, rich in either trabecular or cortical tissue, show unequal trends of bone loss. Because the measured bone mass results from previous metabolic events, even the remodeling of different skeletal segments does not follow a uniform pattern during aging. In this sense, even slight discrepancies of the bone remodeling activity, when associated with a negative imbalance of bone formation and resorption, could lead to a substantial bone loss over time (*3,4*).

Significant age-related changes of skeletal metabolism have been documented by means of bone histomorphometry by Eastell et al. (*5*), who found an increase in the bone remodeling rate in older women. On the other hand, Fogelman and Bessent (*6*) reported higher 24-h skeletal retention of ^{99m}Tc-diphosphonate in older women; the latter data were confirmed by our group (*7*) by a simpler scintimetric method. However, whether the age-related pattern of remodeling rates can be regarded as a generalized phenomenon or whether it may vary both within and among the different bones of the skeleton has not been defined.

Relatively few studies on this topic have been performed because of methodologic constraints. Indeed, the regional differences in skeletal metabolism could be evaluated most reliably by the histomorphometric analysis of tetracycline-labeled bone samples. This approach has been used successfully in animal studies (*8*), but, obviously, it is unacceptable for human studies. Interestingly, Podenphant and Engel (*9*) described the case of an osteoporotic woman who died fortuitously just after labeling for a scheduled bone biopsy; anatomic evaluation of several skeletal sites showed substantial regional variations of histomorphometric parameters in this patient.

To noninvasively investigate the regional variations of bone metabolism related to the aging process, we used

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quantitative measurements of ^{99m}Tc-methylene diphosphonate (MDP) uptake in well-defined small regions of interest (ROIs) of the skeleton in 84 healthy women.

MATERIALS AND METHODS

Eighty-four healthy women, all volunteers (age range, 22–86 y; mean age ± SD, 55.3 ± 15.2 y), were studied. Caucasian subjects alone were selected to provide a homogeneous group for study given the possibility of racial origin influencing bone metabolism. The study population included 33 premenopausal (mean age, 41.4 ± 8.6 y) and 51 postmenopausal (mean age, 64.3 ± 11.2 y) women. The mean number of years since the onset of menopause (YSM) in the postmenopausal group was 17.7 ± 10.7 y.

All women studied were healthy on physical examination, and their body mass indices were between 22 and 27. None of the women had disorders or took medications known to affect bone metabolism; in particular, no subject was taking estrogens. Kidney and liver functions were normal, and the participants had no evidence of compression fractures on lateral spine roentgenography. Witnessed informed consent was obtained from all women.

In all of the women studied, the whole-body retention (WBR) and global skeletal uptake (GSU) of ^{99m}Tc-MDP were calculated from total-body digital scans (TBDSs) acquired at 5 min and at 4 h (*7,10*). Thereafter, regional skeletal uptake (RSU) was assessed by evaluating very small, regular ROIs (Fig. 1); the dimensions of the ROIs were chosen to allow them to be included well within all examined sites. Such ROIs were placed in either axial or appendicular segments of the skeleton characterized by different (either predominantly trabecular or cortical) tissue composition. According to these criteria, ROIs for RSU measurement were placed on a spinal site positioned in the central part of the bodies of 3 lumbar vertebrae (LS-RSU; the corresponding results express the average values of L2–L4); on an iliac site (IL-RSU) put in the middle of a horizontal line that joins the left vertebroiliac junction and the lateral profile of the ileum; on a femoral neck site (FN-RSU) in the middle of the left femoral neck axis; and on a femoral diaphyseal site (FD-RSU) in the middle of the left femoral diaphysis. These ROI positioning sites were selected because they correspond to sites in which either densitometric (LS and FN) or anatomic (IL and FD) evaluations are commonly performed; furthermore, they reflect the behavior of trabecular or cortical tissue in both axial and appendicular skeleton. The positioning of the ROIs for RSU measurements was checked by 3 independent observers.

Technical Details

Subjects were investigated by administering 740 MBq (20 mCi) ^{99m}Tc-MDP (Nycomed Amersham, Sorin, Italy). TBDSs were acquired at 5 min and again at 4 h (7.5 cm/min) after tracer injection; subjects voided immediately before the injection and at the time of the 4-h TBDSs. A short static image of the pelvis was acquired just before the 4-h TBDS to check for the efficacy of micturition; in patients showing a large urinary residue, bladder catheterization was performed to ensure complete voiding. Two rectangular ROIs (1 anterior and 1 posterior) encompassing the whole body were drawn on the 5-min TBDS, and an identical group of ROIs was drawn on the 4-h TBDS; the geometric means were determined from counts of anterior and posterior ROIs of the 5-min and 4-h TBDSs. The geometric means were calculated to correct for depth attenuation in women of different size and weight.

The WBR value is given by the following ratio: (geometric mean of the rectangular ROI counts at 4 h/geometric mean of the rectangular ROI counts at 5 min) × 100. Counts in the rectangular ROIs at 5 min represent the injected dose. GSU was determined by drawing a group of irregular ROIs (anterior and posterior) on the 4-h TBDS, excluding bladder and soft tissues as far as possible; the geometric mean was calculated from counts of this irregular ROI group.

The GSU value is given by the following ratio: (geometric mean of the irregular ROI counts at 4 h/geometric mean of the rectangular ROI count at 5 min) × 100. TBDSs were acquired using the same gamma camera (901 WA; Toshiba, Tokyo, Japan)

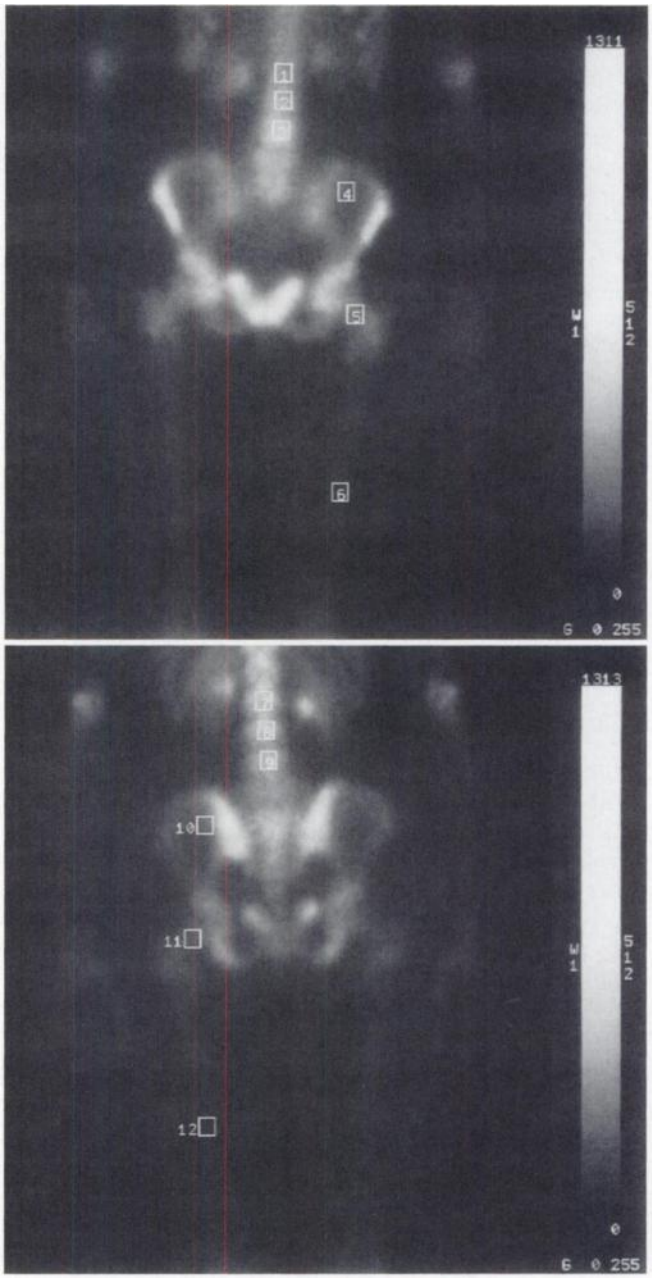

FIGURE 1. ROIs for RSU measurements in anteroposterior (AP) and posteroanterior (PA) views. Twelve ROIs are positioned on same skeletal segments in both AP (ROIs 1–6) (top) and PA (ROIs 7–12) (bottom) views. ROIs 1 and 7 are drawn on L2 spine metamer; ROIs 2 and 8, on L3 metamer; ROIs 3 and 9, on L4 metamer; ROIs 4 and 10, on left iliac wing; ROIs 5 and 11, on left femoral neck; and ROIs 6 and 12, on left femoral dyaphysis.

with a low-energy, multipurpose collimator on all patients. GSU values are expressed as percentage injected dose (%ID) (*7,10*).

Thereafter, RSU is determined by enlarging a 171 × 171 pixel area of the TBDS (Fig. 1). The matrix of the TBDS (anterior and posterior views) is 512 × 512; a rectangular ROI (171 × 171) is positioned from the middle line of the knees upward, and this area is then expanded to a 256 × 256 matrix. In the expanded image, 12 ROIs (7 × 7 pixels each) are drawn, 6 on the anterior view (ROIs 1–6) and 6 positioned on the same skeletal segments of the posterior view (ROIs 7–12). ROIs 1 and 7 are drawn on the L2 spine metamer; ROIs 2 and 8, on the L3 metamer; ROIs 3 and 9, on the L4 metamer; ROIs 4 and 10, on the left iliac wing; ROIs 5 and 11, on the left femoral neck; and ROIs 6 and 12, on the left femoral diaphysis (Fig. 1). To correct for depth attenuation, geometric means are calculated from counts of matched anterior and posterior ROIs and then corrected for ^{99m}Tc decay.

RSU is calculated as (geometric mean of counts of each group of regional ROIs/total counts of GSU ROI) × 1000. The denominator of this ratio is preferred to the counts of the total injected dose to minimize differences related to different skeletal sizes of subjects. Younger women were obviously taller because of the increase in the mean height of the Italian population in recent years.

The in vivo coefficients of variation were 2.4% for GSU, 6.6% for LS-RSU, 2.0% for IL-RSU, 8.5% for FN-RSU, and 7.6% for FD-RSU.

Statistical Analysis

All parameters are expressed as mean ± SD. The relationships between variables were studied by using simple and partial correlation coefficients. To describe these relationships the multiple linear regression model has been used. Furthermore, to evaluate the appropriateness of a model, the explained variance proportion has been considered. Finally, linear regression coefficient comparisons were performed by the *t* test. $P = 0.05$ is considered as the significant limit. All statistical analyses were performed using Statistica 4.1 software (StatSoft, Inc., Tulsa, OK).

RESULTS

Descriptive statistics of the sample studied are reported in Table 1. The mean GSU, LS-RSU, IL-RSU, FN-RSU, and FD-RSU values of postmenopausal women were significantly different from the levels of premenopausal women. The correlations of GSU and all RSUs with age are shown in Figure 2.

TABLE 1
Descriptive Statistics of Parameters Studied

Parameter	Total sample (n = 84)	Premenopausal women (n = 33)	Postmenopausal women (n = 51)
Age (y)	55.30 ± 15.22	41.36 ± 8.62	64.31 ± 11.22
YSM			17.69 ± 10.73
GSU	38.49 ± 5.96	35.06 ± 4.20	40.71 ± 5.91*
LS-RSU	5.58 ± 1.20	6.29 ± 1.24	5.12 ± 0.93*
IL-RSU	2.08 ± 0.44	2.31 ± 0.49	1.93 ± 0.33*
FN-RSU	2.71 ± 0.55	2.86 ± 0.56	2.62 ± 0.53†
FD-RSU	1.52 ± 0.28	1.40 ± 0.29	1.60 ± 0.25*

*$P < 0.001$ vs. premenopausal women.
†$P < 0.05$ vs. premenopausal women.
GSU is expressed as %ID of ^{99m}Tc-MDP; RSUs are expressed as per thousands (‰) of total counts of GSU ROI. Data are expressed as mean ± SD.

Correlations of GSU with Age and YSM

GSU correlated positively with age ($r = 0.70$; $P < 0.0001$), and its age-related increase could be accounted for by a multiplication factor of 0.27. This trend curve explains 48% of the total variance. GSU also correlated positively ($r = 0.57$; $P < 0.0001$) with YSM, with a multiplication factor of 0.31. This curve accounts for 31% of the total variance. However, when multiple regression analysis is performed, the addition of the variable YSM to the regression model of GSU and age do not ameliorate the regression. Furthermore, the partial correlation coefficient between GSU and YSM, after correcting for the influence of age (which is a better predictor for GSU), is only 0.06, indicating that the role of YSM in the regression model, after considering age, is quite marginal.

Correlations of RSUs with Age and YSM

A significant decrease with age was detected for LS-RSU ($r = -0.55$; $P < 0.0001$), IL-RSU ($r = -0.45$; $P < 0.0001$), and FN-RSU ($r = -0.22$; $P < 0.05$), whereas FD-RSU increased significantly with age ($r = 0.39$; $P < 0.001$). However, only for the LS and the IL sites could age be considered a good predictor for RSU values, because of the low r^2 levels found for the other RSUs. In fact, the curves of FN and FD only marginally account for the total variance of the RSUs.

With regard to the relationships between the RSUs and YSM, LS-RSU, IL-RSU, and FN-RSU correlated negatively with YSM, whereas FD-RSU showed a positive correlation with YSM. However, the respective correlation coefficients were not significant. In the multiple regression analysis, though age and YSM are obviously tightly related, the adjunct of YSM to the regression model does not improve our understanding of RSU variability. Partial correlation coefficients between YSM and RSUs, after adjusting for age, are <0.15, so that YSM does not seem to influence the age-related changes in RSU.

Relationships Among Different RSUs

The relationships among different RSUs are shown in Table 2. A positive correlation was found between LS-RSU and both IL-RSU ($r = 0.63$; $P < 0.0001$) and FN-RSU ($r = 0.47$; $P < 0.0001$); on the other hand, LS-RSU and IL-RSU correlated negatively with FD-RSU ($r = -0.29$; $P < 0.001$ and $r = -0.30$; $P < 0.01$, respectively). As shown by the respective coefficients, the strongest correlation among the RSU variables is that between LS-RSU and IL-RSU.

Comparisons of Various RSU Age-Related Trends

When the linear regression coefficients of the various RSUs with age were compared, the respective trend curves were all significantly different from each other ($P < 0.001$). Because the regression coefficients between the RSUs and YSM as an independent variable were not significant, the same tests were not applicable to the latter regressions.

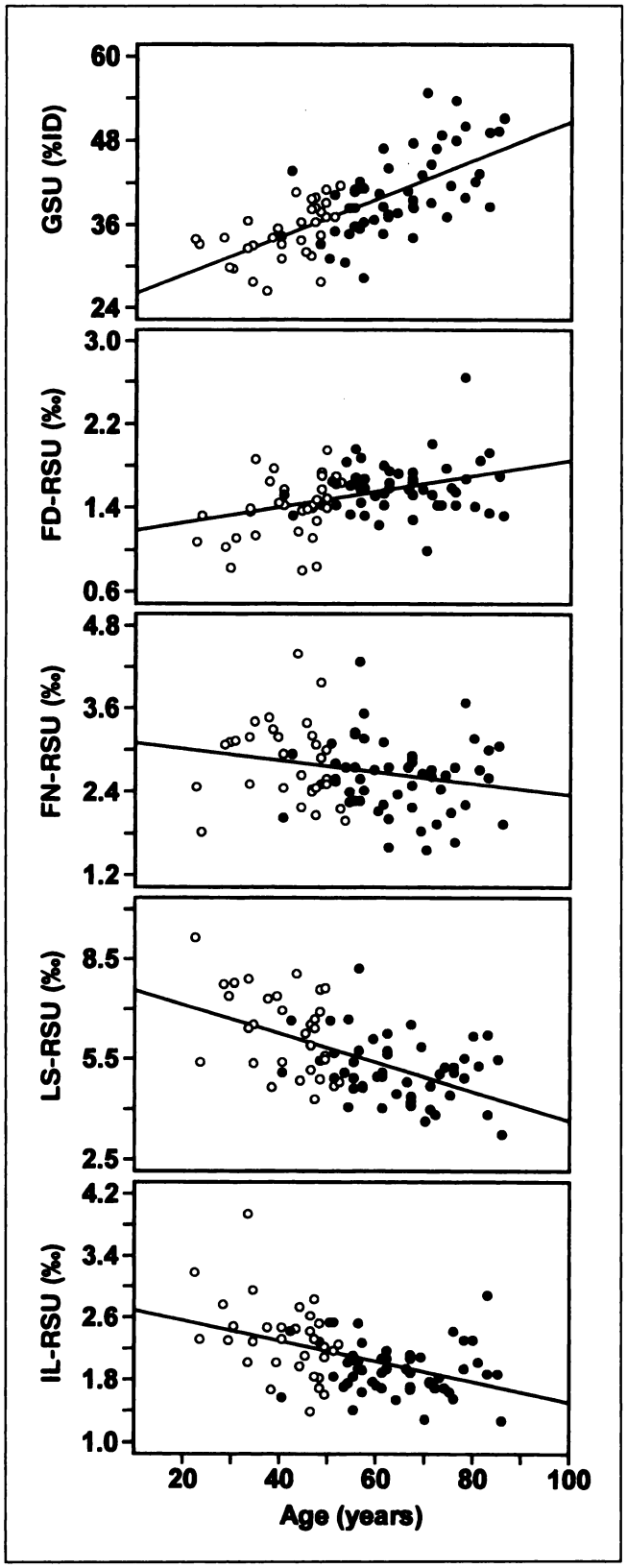

FIGURE 2. Relationships between GSU and RSU of ^{99m}Tc-MDP and age. Results for GSU are expressed as %ID of ^{99m}Tc-MDP. Results for LS-RSU, IL-RSU, FN-RSU, and FD-RSU are expressed as per thousands of total counts of GSU ROI. Premenopausal women (○); postmenopausal women (●).

TABLE 2
Correlation Coefficients Among Different Variables Studied

Parameter	n	Correlation coefficient* IL-RSU	FN-RSU	FD-RSU
LS-RSU	84	0.63 (<0.001)	0.47 (<0.001)	−0.29 (<0.01)
IL-RSU	84		0.36 (<0.01)	−0.30 (<0.01)
FN-RSU	84			0.11 (NS)

*P is given in parentheses.
NS = not significant.

DISCUSSION

Bone mass decreases progressively with age throughout the skeleton (*1*). Because of an increase in the remodeling activation rate with age (*5*), the pattern of bone loss differs in various skeletal sites (*1,2*) and even between sites in the same bone; therefore, different patterns of remodeling should be hypothesized.

Bone turnover is ideally investigated by the histomorphometric study of bone biopsy. However, such invasive practice in living patients is restricted to easily accessible areas, where the procedure does not harm other structures. Therefore, the preferred site is the ileum; however, iliac crest biopsy may not necessarily reflect bone remodeling at other skeletal sites. In the study by Eventov et al. (*11*), histomorphometry indeed revealed significant differences between iliac crest and femoral biopsies. This is in line with the results of Marotti (*8*) on dogs and with a necroscopic study in humans (*9*).

On the other hand, bone scintigraphy can be used as a convenient and simple way to analyze both global and regional skeletal metabolism; in fact, radiotracer uptake by bone surface is largely related to the rate of remodeling activity, though it does not reflect the net (positive or negative) balance of skeletal turnover. We studied the age-related changes of the scintigraphic pattern in adult women by quantifying the RSU and total-body skeletal uptake. We used a new and easy-to-perform method (*10*) that allows measurement of pure bone uptake and does not seem to be influenced significantly by renal function in healthy subjects (*7*). Our data agree with the findings of conventional 24-h whole-body retention measurement (*12*), which is considered the standard method for the scintimetric assessment of bone turnover rate.

The GSU of the tracer shows an age-related increase in healthy women; these findings are in line with histomorphometric studies (*5,13*) and reinforce our previous results (*7*), so that age can be regarded as a good predictor of GSU values. In contrast with a previous report on a large group of perimenopausal women (*14*), these changes (for both GSU and RSUs) appear to be affected only marginally by menopausal duration; we believe that this may be associated with the wide age range of our sample, which may conceal the demonstrated specific effects of menopause on bone turnover.

Particularly noteworthy is the fact that the technique we used is a simple and unique way to evaluate local bone turnover. In fact, we chose to select very narrow ROIs, which could be placed within each skeletal site under study, thus providing a sort of spot evaluation of bone turnover rate. In this way we were also able to investigate different sites of the same bone (i.e., the femur), whose age-related patterns of tracer uptake are dissimilar. Therefore, we believe that our approach appears more appropriate, compared with previous studies (*15–17*), to investigate how differing bone turnover rates of various sites vary throughout life; these changes could justify different bone loss rates of various skeletal sites and may contribute to their unequal bone fragility at different ages (*18,19*). In fact, our data show that the differing rates of turnover and the respective age-related trends are displayed by the various RSUs, so that the pattern of regional remodeling activation of older women is quite different from that of younger subjects.

We found that FD-RSU (which reflects the remodeling activity of a site composed almost exclusively by cortical tissue) increases progressively with age, such as GSU. This is not surprising because the turnover rate is proportional to the surface-to-volume ratio (*20*). An increase in intracortical porosity has been revealed in aging human cortical bones (associated with an increase in the number of haversian systems) by histologic techniques (*21*). Moreover, the whole skeleton contains about 80% cortical bone (*22*); therefore, in terms of the absolute amount of bone metabolism (which is reflected by GSU), cortical bone metabolism may conceivably contribute more than cancellous tissue with advancing age. The latter hypothesis appears especially likely in elderly people, in whom vitamin D deficiency is a common feature (*23,24*). This results in secondary hyperparathyroidism, which in turn increases cortical bone remodeling and loss (*25*). Our findings stress the important role of cortical tissue remodeling in elderly women and support the opinion of Mazess (*26*), who attributes a relevant role to cortical bone.

On the other hand, FN-RSU behavior appears to be intermediate between FD-RSU and the sites composed prominently by trabecular bone, such as both LS-RSU and IL-RSU. This reflects the nearly equivalent contribution of cortical and trabecular tissue in the microanatomic composition of this site.

With regard to other regional ROIs, it should be noted that in sites richer in trabecular tissue (such as LS-RSU, IL-RSU, and, to a lesser degree, FN-RSU), the RSU of ^{99m}Tc-MDP decreases progressively with age, in apparent contradiction with GSU. Indeed, trabecular tissue makes up about 15%–20% of the skeleton (*22*); consequently, we believe that changes in trabecular bone may have a relatively minor effect on the GSU of the tracer with advancing age, when cortical bone turnover is increased. Moreover, both menopause and age induce trabecular thinning and consequent loss of trabecular elements (*27,28*), which result in a local decrease in the surface-to-volume ratio with aging. Such decrease produces a reduction of the surface amenable for tracer exchange. However, a real age-related decrease of trabecular bone turnover rate cannot be excluded. In fact, lower rates of bone turnover are associated with higher degrees of tissue mineralization (*29*), which are also displayed by the aging skeleton; therefore, the older tissue could be less amenable for mineral exchange (*30*). The decreased proportion of cancellous bone surface in contact with red (hematopoietic and basic multicellular unit-producing) bone marrow with aging could decrease the proportion of tissue engaged in trabecular remodeling activity (*31*). Multiple other factors (biochemical, metabolic, mechanical, and anatomic), which are still unclear, may also interact in determining the high intersite variations we observed in the RSU of ^{99m}Tc-MDP. Finally, differing regional sensitivity to the hormones influencing bone metabolism (whose levels vary with age) could partially account for the observed differences.

CONCLUSION

In conclusion, our data show that many segments of the skeleton display a variable degree of skeletal uptake at different ages. If this reflects different regional bone turnover rates, our data strongly indicate different patterns of bone loss, possibly underlying the variable propensity of different skeletal segments to fracture at various ages.

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