
Whole-Body Retention of ^{99m}Tc -imidodiphosphate: A Measurement of Total Body Bone Turnover Rate

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Abstract

The 24-hour retention of ^{99m}Tc -imidodiphosphate has been measured in 39 subjects. The mean retention for five normal premenopausal women was $49 \pm 5\%$. For postmenopausal women the mean retention was $57 \pm 6\%$. The mean retention for eight patients suffering from Paget's disease was $75 \pm 13\%$. Retention was reduced from $57 \pm 8\%$ to $52 \pm 7\%$ following estrogen replacement therapy. These results support the contention that ^{99m}Tc -imidodiphosphate is retained *in vivo* to a greater extent than other ^{99m}Tc -labelled compound phosphates, and that such retention reflects the rate of whole-body bone mineral turnover.

Résumé

Nous avons mesuré la rétention du ^{99m}Tc -imidodiphosphate durant 24 heures dans 39 sujets. La rétention moyenne dans cinq femmes normales n'ayant pas atteint leur ménopause est de $49 \pm 5\%$. Dans les femmes ayant dépassé l'âge de la ménopause la rétention moyenne est de $57 \pm 6\%$. La rétention moyenne dans huit malades souffrant de la maladie de Paget est de $75 \pm 13\%$. La rétention peut être réduite de $57 \pm 8\%$ à $52 \pm 7\%$ après un traitement de remplacement des oestrogènes. Ces résultats supportent la proposition que la rétention *in vivo* du ^{99m}Tc -imidodiphosphate est plus grande que celle d'autres composés de phosphate marqués au ^{99m}Tc et que cette rétention reflète le taux de renouvellement du contenu minéral des os.

Introduction

The uptake of ^{99m}Tc -labelled condensed phosphates by bone is such that images of the skeleton can be obtained which are of sufficiently high quality to allow the detection of various bone disorders [Merrick 1975; Ram and Fordham 1979; Matin 1983]. The fractional retention of such radiopharmaceuticals 24 hours after injection is thought to be an indication of the rate of skeletal turnover. Condensed phosphates that have been used for this measurement include pyrophosphate [Martin *et al.* 1983] and various diphosphonates such as methylene diphosphonate [Hyldstrup *et al.* 1984] and hydroxyethylidene diphosphonate [Fogelman *et al.* 1978].

The fractional uptake of ^{99m}Tc -labelled imidodiphosphate (^{99m}Tc -IDP) into the skeleton is greater than that of either pyrophosphate or the diphosphonates [Brody *et al.* 1976] and has led to the claim that ^{99m}Tc -IDP is the optimum condensed phosphate for bone imaging. The purpose of the work reported here is to present the results of measurements of the 24-hour whole-body retention of ^{99m}Tc -IDP in specific groups of patients in whom bone turnover is expected to be different. To our knowledge, these are the first such measurements using ^{99m}Tc -IDP.

Materials and Methods

Diphosphate retention was measured in a total of 39 subjects divided into three groups: five premenopausal women, 26 postmenopausal women, and eight patients suffering from Paget's disease. The five premenopausal women who served as control subjects were university students with no evidence of bone disease, and were aged from 19 to 30 years.

The effect of age upon retention was assessed cross sectionally from measurements in 26 women attending a menopause clinic. Their ages ranged from 34 to 66 years, and the time since menopause varied from one to 26 years. At the time of the study, three of the 26 women were receiving estrogen replacement therapy.

Keywords: ^{99m}Tc -imidodiphosphate whole body retention, premenopause, postmenopause, Paget's disease, estrogen replacement therapy.

The effect of Paget's disease was assessed from retention measurements in six men and two women. These patients were aged between 55 and 84 and were referred from a metabolic bone disease clinic. The serum alkaline phosphatase in these patients ranged from 131 to 357 U/L (normal < 90).

The effect of estrogen replacement therapy upon retention was assessed using a longitudinal before-after study design. Retention measurements were repeated in eight of the 26 postmenopausal subjects after 6–10 months of estrogen replacement therapy (conjugated estrogen 0.625 mg daily with, in five of the eight women, the addition of 5 mg cyclic progestogen during the last seven days of each estrogen cycle). None of the eight had received supplements prior to the first retention measurement, their ages ranged from 36 to 57 years, and the number of years since menopause ranged from one to 27.

For each retention measurement, approximately 1 MBq of ^{99m}Tc-IDP containing 2 mg of imidodiphosphate is injected at zero time. Whole-body radioactivity is measured at 15 mins and 24 hours using a shadow shield counter containing a single 27.9 × 10.2 cm NaI (TI) detector. For the first measurement the couch speed is 40 cm min⁻¹. At 24 hours the couch speed is 10 cm min⁻¹. Dead time effects are corrected with a pulser. The radiation dose associated with the retention measurement is about 0.03 mSv to the skeleton and about 0.1 mSv to the bladder [Graham *et al.* 1974].

The mean retentions for the three groups of subjects were compared by analysis of variance. Forward stepwise multiple regression was used to investigate the importance of other factors contributing to the variance of retention measurements in the patients with Paget's disease. The influence of estrogen replacement therapy was assessed using a one-way paired t-test.

Results

The means and standard deviations for the measured retentions in the five controls, the 26 postmenopausal women, and the eight patients with Paget's disease are compared in Figure 1. There is a statistically significant difference between these three groups (ANOVA, $F = 17.6$, $p < 0.05$). The means and standard deviations for the diphosphate retentions, body weights, ages, and heights for the three groups are given in Table 1. There was no difference between the mean retentions for the three postmenopausal women who had previously taken estrogen and the 23 women who had not (58 and 57%, respectively).

Diphosphate retention was lower in premenopausal women (49%) than in postmenopausal women (57%). This difference was statistically significant (Scheffé test, $p < 0.05$).

The mean retention for the patients with Paget's disease (75%) was significantly greater than that of the postmenopausal group (Scheffé test, $p < 0.05$). For-

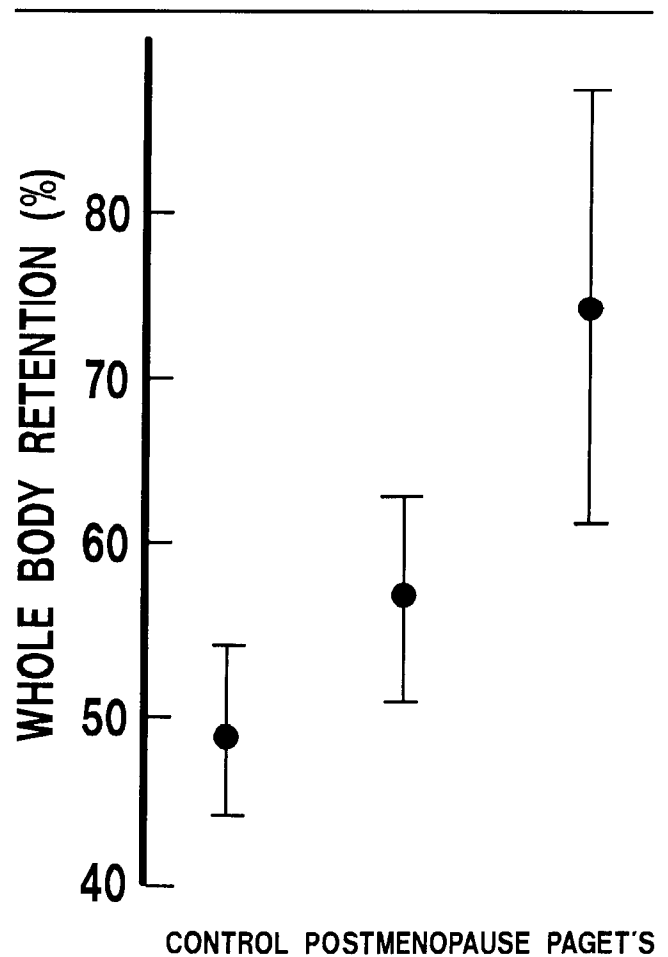


Figure 1: Mean whole body retention in each subject group. The vertical bars equal two standard deviations.

ward stepwise multiple regression analysis indicated that sex and alkaline phosphatase levels were important independent variables that contributed to the variance of diphosphate retention in the patients with Paget's.

For the eight women placed on estrogen therapy there was an inverse correlation ($r = 0.60$) between the initial retention measurement and the number of years since menopause. With estrogen therapy, the mean retention in these eight women fell from $57 \pm 8\%$ to $52 \pm 7\%$. This reduction was statistically significant (paired $t = 2.1$, $p < 0.05$). There was no relation ($r = 0.09$)

Table 1: The Means (Standard Deviations) for the Ages, Heights, Weights and Imidodiphosphate Retentions in Each Subject Group

	Controls	Postmenopause	Paget's
n	5	26	8
Age	23 (4)	56 (10)	67 (10)
Ht (cm)	161 (4)	162 (6)	167 (9)
Wt (Kg)	60 (7)	63 (10)	75 (14)
^{99m} Tc-IDP Retention (%)	49 (5)	57 (6)	75 (13)
Range	41–54	46–68	58–94

between the change in retention and the number of years since menopause. However, the change in retention was correlated with the initial retention value ($r = 0.53$).

Discussion

Our results show that young adults retain about one half of a dose of ^{99m}Tc -IDP, 24 hours after injection. This is about 10% greater than the mean retention of ^{99m}Tc -pyrophosphate measured in 17 women between the ages of 26 and 40 [Martin *et al.* 1983]. However, these same workers found a mean retention of 48% in three women between the ages of 20 and 25. The 24-hour retention of the diphosphonates is considerably smaller than that of both imidodiphosphate and pyrophosphate. For normal adults of various ages, Caniggia and Vattimo (1980) found a mean retention of 33% for ^{99m}Tc -methylenediphosphonate. Hyldstrup *et al.* (1984) measured a mean value of 30% for the same diphosphonate in women aged between 20 and 29 years. Again, in women between 20 and 29 years of age the mean retention of ^{99m}Tc -hydroxyethylidenediphosphonate was only 18% [Fogelman and Bessent 1982]. These observations suggest that the simpler the condensed phosphate the greater will be the retention of the ^{99m}Tc -labelled compound.

The increase in ^{99m}Tc -IDP retention following the menopause is similar to the increases observed with pyrophosphate [Martin *et al.* 1983] and the diphosphonates [Fogelman and Bessent 1982; Caniggia and Vattimo 1980] and probably reflects an increase in bone resorption due to the reduction of endogenous estrogen [Gallagher 1981]. The different retention values between pre- and postmenopausal women are unlikely to be due to age differences, since it has been shown that, at least for pyrophosphate and the diphosphonates, an age-dependent increase in retention is not observed until the eighth decade [Martin *et al.* 1983; Hyldstrup *et al.* 1984]. This age-dependent increase appears to be related to both increased resorption of bone and a reduction in glomerular filtration rate.

As expected, the patients with Paget's disease showed a higher mean retention than both the control and postmenopause groups. Multiple regression revealed that sex and the serum alkaline phosphatase levels were associated with the 24-hour fractional retention of ^{99m}Tc -IDP. The significance of the former correlation is not clear, although it is known that retention is normally greater in males than in females [Fogelman and Bessent 1982] and six of our eight patients were male. The correlation with the serum alkaline phosphatase indicated that both parameters reflect the severity of the disease.

In the small number of women selected for estrogen replacement therapy, an inverse correlation was detected between the initial retention measurement and the number of years since menopause. This suggests

that in these patients there was an increased rate of bone turnover during the early postmenopausal years. After six to 10 months of replacement therapy, there was a significant reduction in ^{99m}Tc -IDP retention. This retention was greatest in those subjects with the highest initial retention values, suggesting that the effectiveness of exogenous estrogen was greatest in those with the highest resorption. Since the change in retention was not related to the number of years since menopause, the effectiveness of exogenous estrogen is not restricted to the early postmenopausal years. These observations are consistent with the concept that exogenous estrogen reduces bone resorption, and the coupling of resorption to formation decreases osteoblastic cellular activity, with a consequent reduction in whole-body diphosphate retention. Although the number of subjects studied is small, and only limited confidence can be placed in these conclusions, our results do support the suggestion of Fogelman *et al.* (1980) that the retention of ^{99m}Tc -labelled condensed phosphates may be used to titrate the effect of a specific dose of estrogen in each subject and to select those who may or may not benefit from replacement therapy.

The data reported here suggest that ^{99m}Tc -IDP is another labelled condensed phosphate, the 24-hour retention of which can be used as an indicator of the rate of whole-body bone turnover. It remains to be shown whether or not ^{99m}Tc -IDP has any advantages in discriminating among various forms of metabolic bone disease.

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