Validation of Ultrafiltration as a Method of Measuring Free ^{99m}Tc-MDP

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Quantitative studies of the kinetics of ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) in metastatic and metabolic bone disease require the measurement of free tracer in plasma to derive the input function. Several methods of measuring free ^{99m}Tc-MDP have been described including ultrafiltration, precipitation using trichloroacetic acid, and a direct in vivo measurement based on the assumption that free MDP is cleared through the kidneys by glomerular filtration. The aim of this study was to validate ultrafiltration as a convenient and accurate method of measuring the free fraction of ^{99m}Tc-MDP by comparing it with the glomerular filtration rate (GFR) method. A second aim was to measure the percentage of free ^{99m}Tc-MDP in a cross-section of patients using ultrafiltration to determine the interpatient variability and, therefore, whether individual measurements are required for bone kinetic studies. **Methods:** In study 1, 10 volunteers (7 women, 3 men; mean age, 37 y; range, 26–55 y) were injected with 3 MBq ^{99m}Tc-MDP and 3 MBq ^{51}Cr-ethylenediaminetetraacetic acid, and multiple blood and urine samples were taken between 0 and 4 h. Plasma samples were spun in 5-, 10-, and 30-kDa filters and counted in a γ-counter. In study 2, 51 randomly selected patients (26 women, 25 men; mean age, 66 y; range, 31–87 y) attending our department for a routine bone scan were injected with 600 MBq ^{99m}Tc-MDP, and 4 blood samples were taken between 0 and 4 h and spun in 10-kDa filters. **Results:** In study 1, the mean percentages ($\pm$SD) of free ^{99m}Tc-MDP at 5 min and 4 h after injection measured using the 10-kDa filters were 83.1% $\pm$ 3.4% and 44.0% $\pm$ 10.0%. The mean ratios ($\pm$SEM) of the free ^{99m}Tc-MDP in ultrafiltrate compared with the GFR method for the 5-, 10-, and 30-kDa filters were 0.894 $\pm$ 0.010, 0.943 $\pm$ 0.009, and 0.987 $\pm$ 0.010. In study 2, the mean percentages ($\pm$SD) of free ^{99m}Tc-MDP at 15 min and 4 h were 75.3% $\pm$ 8.0% and 48.8% $\pm$ 9.5%, with a precision error of 2.3%. The percentages of free MDP at 150 min and 4 h were significantly correlated with GFR but not with serum albumin. **Conclusion:** Ultrafiltration provides an accurate method of evaluating free ^{99m}Tc-MDP in plasma for bone kinetic studies. The results from both the healthy volunteers in study 1 and the patients in study 2 show that protein binding varied with time and showed significant differences between individuals that were partly dependent on GFR. It is thus necessary to measure individual protein binding values for bone kinetic studies.

Radionuclide studies using the short-lived tracer ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) [1] or ^{18}F-fluoride [2] allow quantitative measurements in bone that reflect blood flow and osteoblastic activity [3]. Several different techniques have been described for evaluating whole-skeleton or regional bone tracer kinetics, including 24-h whole-body retention of ^{99m}Tc-MDP [4–6], compartmental modeling to evaluate whole-skeleton plasma clearance of ^{18}F-fluoride or ^{99m}Tc-MDP [7–9], gamma-camera studies of ^{99m}Tc-MDP [10–13], or PET studies of ^{18}F-fluoride [14–17]. Imaging techniques based on gamma-camera or dynamic PET studies are of particular interest because they allow studies of regional tracer kinetics in diffuse bone diseases such as osteoporosis or hyperparathyroidism or at sites of focal abnormalities in Paget's disease and metastatic bone disease, including studies of the effect of treatment of these diseases.

^{18}F-Fluoride dynamic PET and quantitative gamma-camera studies with ^{99m}Tc-MDP are alternative methods for performing bone tracer kinetic studies that have several comparative advantages and disadvantages [3]. PET systems using bismuth germanium oxide detectors have higher spatial resolution and allow for more accurate attenuation correction methods than with SPECT using the gamma camera [18]. However, PET remains a relatively expensive technology and supplies of ^{18}F are not presently widely available. In contrast, gamma-camera imaging using ^{99m}Tc-MDP is widely available and, after the recent introduction of SPECT gamma cameras with transmission line sources and improved scatter correction algorithms for image reconstruction, there is considerable scope for improvement in the accuracy of quantitative bone kinetic studies with gamma-camera systems.

One advantage of ^{18}F-fluoride for quantitative studies in bone is the absence of plasma protein binding [19–21]. In contrast, protein binding of ^{99m}Tc-MDP is substantial, varying from around 25%–30% immediately after tracer administration and increasing to 45%–55% at 4 h and 60%–70%

at 24 h (*22,23*). Not only does protein binding of ^{99m}Tc-MDP vary with time, but also there is evidence of significant differences between different individuals (*24*). It follows that quantitative gamma-camera studies of ^{99m}Tc-MDP plasma clearance in bone are likely to require individual measurements of the time variation of protein binding to allow the accurate measurement of the free ^{99m}Tc-MDP plasma input curve.

Of the different methods reported in the literature for measuring protein binding of radiopharmaceuticals (*25*), ultrafiltration is a standard method for removing protein-bound substances from plasma. For bone kinetic studies using ^{99m}Tc-MDP, measurements of protein binding are necessary so that tracer pharmacokinetic calculations can be performed for free MDP. However, ultrafiltration has never been used in conjunction with γ-counting of whole plasma to derive the free ^{99m}Tc-MDP input curve. This study had 2 aims: (a) To compare results of the percentage of free ^{99m}Tc-MDP measured using ultrafiltration with those obtained using a direct in vivo method developed by Park-Holohan et al. (*23*) and Blake et al. (*24*) based on the assumption that free ^{99m}Tc-MDP is cleared through the kidneys by glomerular filtration (*22*). This method of measuring MDP protein binding is referred to as the glomerular filtration rate (GFR) method. (b) To compare results of the percentage of free ^{99m}Tc-MDP measured using ultrafiltration in a cross-section of patients referred for radionuclide bone scans to determine the range of individual differences and whether individual measurements of the fraction of free tracer are a prerequisite for accurate bone kinetic studies.

MATERIALS AND METHODS

This study was conducted in 2 parts: (a) In 10 healthy volunteers (7 women, 3 men; mean age, 37 y; range, 26–55 y) the percentage of free ^{99m}Tc-MDP measured by ultrafiltration was compared with the values determined using the GFR method (*23,24*). (b) Values of the percentage of free ^{99m}Tc-MDP measured using ultrafiltration were determined in 51 randomly selected patients (26 women, 25 men; mean age, 66 y; range, 31–87 y) referred to our department for a routine radionuclide bone scan. The aim was to determine the range of values and time variation of the percentage of free ^{99m}Tc-MDP between 0 and 4 h after injection. The study was approved by the Local Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee, and all subjects gave written informed consent.

Study 1

The 10 volunteers were each injected intravenously with 3 MBq ^{99m}Tc-MDP and 3 MBq ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA) into a forearm vein, and multiple blood samples were taken at 5, 15, 30, 60, 120, 180, and 240 min after injection through an indwelling venous cannula. Subjects were asked to drink at least 300 mL of fluids per hour (water, fruit juice, or tea) and four 1-h urine collections were made between 0 and 4 h after injection. Syringes were weighed before and after administration to determine the relative activities used for the patient dose and for making the standard. Blood samples were centrifuged, and 2 mL of plasma were placed in 5-, 10-, and 30-kDa filters (Ultrafree-4

centrifugal filter units with Biomax membrane; Millipore Corp.) and spun for 30 min at 2,000*g*. In 2 subjects, additional measurements were made with 50- and 100-kDa filters. One-milliliter aliquots of whole plasma and ultrafiltrate were counted in an automatic γ-counter together with standards and a ^{51}Cr source for cross-channel correction. Urine collections were weighed to determine the volume, and 2-mL aliquots were counted with the plasma samples. After counting, all samples and standards were weighed and counts were corrected to an exact weight of 1 g. Urine measurements of recovered ^{99m}Tc-MDP and ^{51}Cr-EDTA were compared with the corresponding concentrations in whole plasma to determine the percentage of free MDP in plasma using the GFR method (*23,24*). The percentage of free ^{99m}Tc-MDP measured by ultrafiltration was determined from the ratio of concentrations in the ultrafiltrate and the whole plasma. Each subject's GFR was determined from the area under the ^{51}Cr-EDTA plasma clearance curve. A blood sample was taken for the measurement of serum albumin.

Study 2

Fifty-one randomly selected patients attending our department for a radionuclide bone scan were enrolled. Each patient was injected with 600 MBq ^{99m}Tc-MDP for a bone scan examination, and blood samples were taken at 15, 60, 150, and 240 min after injection. Blood samples were centrifuged, 2 mL of plasma were placed in a 10-kDa filter and spun for 30 min at 2,000*g*, and 1-mL aliquots of whole plasma and ultrafiltrate were counted in an automatic γ-counter. For 9 patients, a reproducibility study was performed by dividing the plasma between two 10-kDa filters and centrifuging for 60 min at 2,000*g*. One-milliliter aliquots of whole plasma and two 0.8-mL aliquots of ultrafiltrate were counted. Serum albumin was measured, and measurements of serum creatinine were used to estimate each patient's GFR using the formula of Wright et al. (*26*).

RESULTS

Study 1

Demographic data for the 10 subjects who completed study 1 including results for GFR and serum albumin are shown in Table 1. The percentage of free ^{99m}Tc-MDP measured using the 10-kDa ultrafilters was plotted against time for each of the individual volunteers (Fig. 1). The mean percentage ($\pm$SD) of free ^{99m}Tc-MDP at 5 min and 4 h after injection were 83.1% $\pm$ 3.4% and 44.0% $\pm$ 10.0%. At 5 min after injection, the percentages of free ^{99m}Tc-MDP

TABLE 1
Demographic Data for Study 1 Population

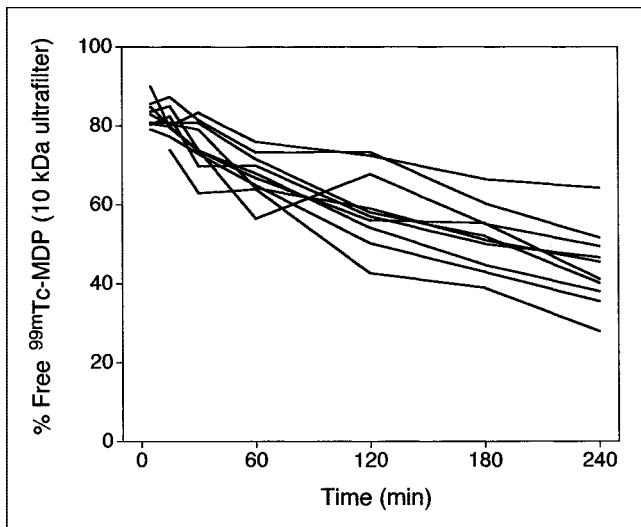| Parameter	Male (*n* = 3)		Female (*n* = 7)	
	Mean	Range	Mean	Range
Age (y)	39.7	32–54	35.3	26–55
Height (cm)	178.9	172–183	164.7	158–176
Weight (kg)	81.03	75–84	63.4	50–85
Body surface area (m^2)	2.0	1.9–2.1	1.7	1.5–2.0
GFR (mL/min)	111.5	103–118	94.2	74–128
Corrected GFR (mL/min)	96.9	86–109	91.3	76–117
Albumin (g/L)	42	41–43	43	41–48

FIGURE 1. Percentage of free ^{99m}Tc-MDP measured using 10-kDa ultrafilter plotted against time after injection for each of 10 volunteers in study 1.

varied between 79% and 90%. By 4 h, the spread of values was between 28% and 64%. When expressed as a percentage of injected activity, the mean ($\pm$SD) absolute concentration of free tracer in plasma was 9.90%/L $\pm$ 1.94%/L at 5 min after injection decreasing to 0.58%/L $\pm$ 0.17%/L at 4 h. The mean concentration of bound tracer in plasma was 2.32%/L $\pm$ 0.86%/L at 5 min decreasing to 0.77%/L $\pm$ 0.20%/L at 4 h.

The percentage of free ^{99m}Tc-MDP measured by ultrafiltration for each of the different sized filters was plotted against the corresponding measurement derived using the GFR method (Figs. 2A–2C). Each of the 3 figures includes 40 points corresponding to four 1-h urine collections in each of the 10 volunteers. When weighted by the free ^{99m}Tc-MDP plasma concentration, the mean time of the 0- to 1-h urine excretion was estimated to be 17 min (23); these data were therefore compared with the 15-min ultrafiltrate data. The 1-

to 2-h, 2- to 3-h, and 3- to 4-h urine data were compared with the mean of the ultrafiltrate data at 1 and 2, 2 and 3, and 3 and 4 h, respectively. For each of the 3 scatter plots, the percentages of free ^{99m}Tc-MDP measured by ultrafiltration were slightly lower than the values determined by the GFR method with the closest agreement for the 30-kDa filter (Fig. 2C). When each scatter plot in Figure 2 was fitted by a linear regression line passing through the origin, the slopes ($\pm$SE) were 0.894 $\pm$ 0.010, 0.943 $\pm$ 0.009, and 0.987 $\pm$ 0.010 for the 5-, 10-, and 30-kDa filters, respectively. For the 2 subjects who had measurements with 50- and 100-kDa filters, the slopes of the regression lines were 1.018 $\pm$ 0.025 and 1.039 $\pm$ 0.025, respectively. Figure 3 shows the slope data plotted for all 5 filters. From the scatter about the regression lines, the root-mean-square (RMS) error for a single measurement was inferred to be 4.1%.

The percentages of free ^{99m}Tc-MDP inferred from the 5 different filters were compared with each other by plotting data for the 5-, 30-, 50-, and 100-kDa filters against the data for the 10-kDa filter. When the data were fitted with a regression line passing through the origin, the slopes ($\pm$SE) were 0.948 $\pm$ 0.007, 1.051 $\pm$ 0.006, 1.072 $\pm$ 0.012, and 1.091 $\pm$ 0.013, respectively. The RMS error was 3.4%. The mean ratio ($\pm$SEM) of the renal clearance of ^{99m}Tc-MDP to ^{51}Cr-EDTA calculated from the data for the 5-, 10-, 30-, 50-, and 100-kDa filters were 1.123 $\pm$ 0.017, 1.051 $\pm$ 0.019, 0.980 $\pm$ 0.019, 0.983 $\pm$ 0.044, and 0.961 $\pm$ 0.038, respectively.

Study 2

Demographic data for the 51 subjects who completed study 2, including results for serum albumin and GFR calculated from the Wright formula, are shown in Table 2. Reasons for referral for a ^{99m}Tc-MDP bone scan were investigation of metastatic bone disease ($n = 19$ patients), loosening or infection of a hip or knee prosthesis ($n = 8$ patients), unexplained bone pain ($n = 9$ patients), Paget's disease ($n = 8$ patients), osteoporotic fracture ($n = 5$
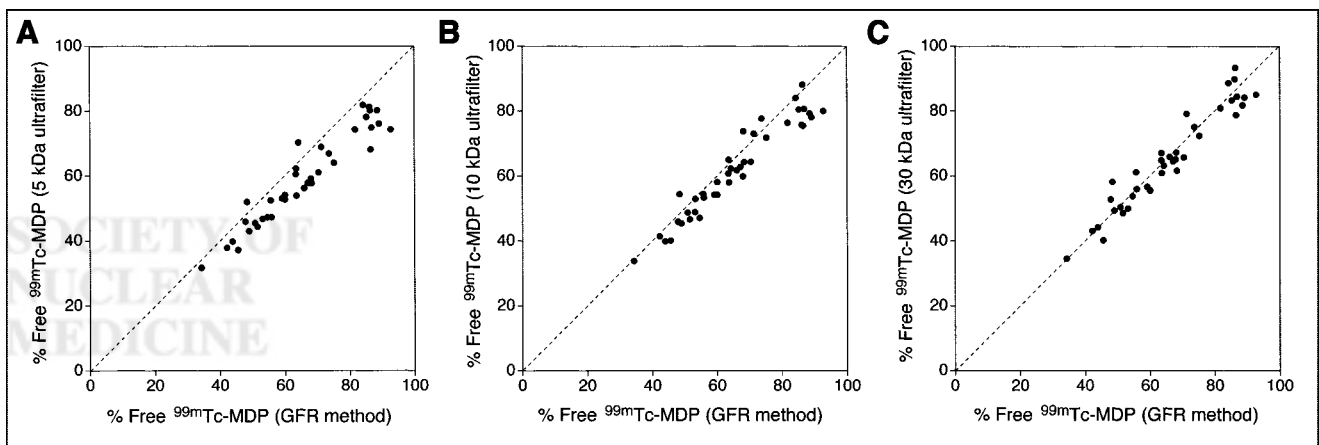

FIGURE 2. Percentage of free ^{99m}Tc-MDP measured by ultrafiltration plotted against corresponding measurement derived using GFR method (23,24) for 5-kDa (A), 10-kDa (B), and 30-kDa (C) molecular weight filters. Dashed line shows line of identity.
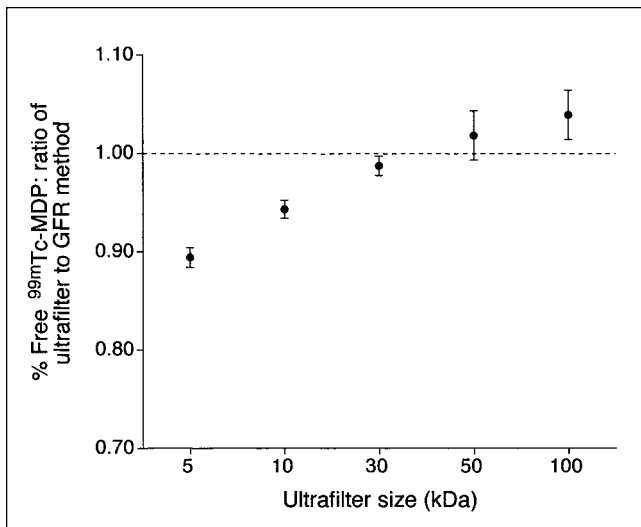
FIGURE 3. Slope of regression line of ultrafiltration vs. GFR method determined from ultrafiltrate data plotted for 5-, 10-, 30-, 50-, and 100-kDa filters in study 1. Dashed line shows ratio of unity.

patients), osteopetrosis ($n = 1$ patient), and facet-joint disease ($n = 1$ patient). Of the 19 patients in study 2 investigated for metastatic bone disease, 5 had breast cancer, 6 had prostate cancer, 4 patients had high erythrocyte sedimentation rate or prostate-specific antigen values, and 4 had bone pain. Clinical reports of scans gave the following interpretations: metastatic bone disease ($n = 9$ patients), infection of a prosthesis ($n = 2$ patients), Paget's disease ($n = 9$ patients [3 nonactive]), compression fractures ($n = 2$ patients), osteopetrosis ($n = 1$ patient), facet-joint disease ($n = 4$ patients), degenerative changes ($n = 16$ patients), benign lesion ($n = 1$ patient), metabolically active lesion ($n = 3$ patients), and normal scan ($n = 4$ patients). Forty-six of 51 patients showed only modest changes on the bone scan that would be expected to have minimal effect on whole-body MDP kinetics. The remaining 5 patients (3 with metastatic bone disease, 1 with Paget's disease, and 1 with osteopetrosis) had very extensive disease with increased tracer uptake throughout most of the skeleton, including the skull, spine, pelvis, and femur. Two of these patients showed scan findings of extremely extensive metastatic involvement of the skeleton and the appearance of a "superscan" of malignancy.

The percentage of free ^{99m}Tc-MDP measured by the 10-kDa filters at each time point was plotted for each patient

TABLE 2
Demographic Data for Study 2 Population

Parameter	Mean ± SD	Range
Age (y)	66 ± 13.4	31–87
Albumin (g/L)	39 ± 2.7	35–44
Creatinine (μmol/L)	90 ± 22.5	56–138
GFR (mL/min)	75 ± 19.9	42–127

(Fig. 4). The mean percentages (±SD) of free ^{99m}Tc-MDP at 15 min and 4 h after injection were 75.3% ± 8.0% and 48.8% ± 9.5%, respectively. At 15 min after injection, the percentages of free ^{99m}Tc-MDP varied between 54% and 91% and by 4 h were between 27% and 72%. When the relationship between the percentage of free ^{99m}Tc-MDP and the patients' age, sex, serum albumin, and GFR were investigated, no effect of sex or serum albumin was found. However, both age and GFR were significantly correlated with the 150-min and 4-h ultrafiltration measurements. Age and GFR were themselves highly correlated ($r = 0.80$), with the result that older patients had lower GFR and higher values of the percentage of free ^{99m}Tc-MDP at 150 min and 4 h, whereas the reverse trends were found in younger patients. The same trends were found for the 10 volunteers in study 1; therefore, data from the 2 studies were pooled. When the pooled data were analyzed, highly significant correlations were found between the percentage of free ^{99m}Tc-MDP and age and GFR at 150 min ($P = 0.004$) and 4 h ($P < 0.001$), but no correlations were found for the 15-min or 1-h data. In the reproducibility study in 9 subjects with 36 repeated measurements, the RMS precision error for a single measurement was 2.3%.

In Figure 5 the data for the mean percentage of free ^{99m}Tc-MDP obtained in study 1 and study 2 using the 10-kDa ultrafilters are compared with the data obtained in 49 patients by Park-Holohan et al. (23) using the GFR method.

DISCUSSION

For bone kinetic studies using ^{99m}Tc-MDP, measurements of protein binding are required if tracer kinetic calculations are to be made for free MDP (22). It is important to measure free ^{99m}Tc-MDP because the bound fraction is not available for clearance to the skeleton. When combined with accurate
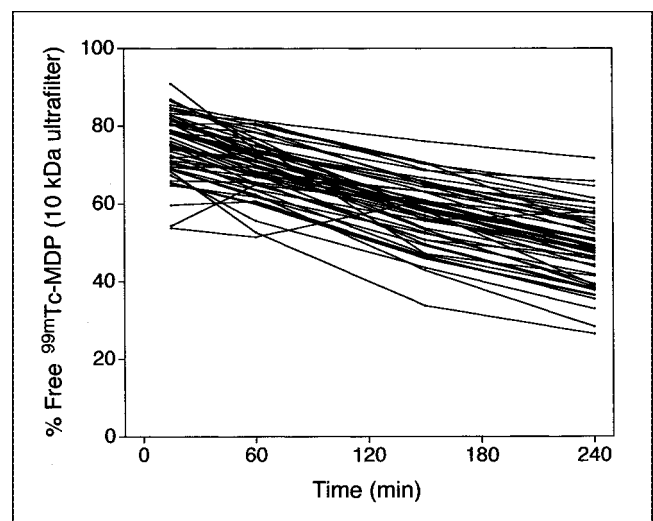

FIGURE 4. Percentage of free ^{99m}Tc-MDP measured using 10-kDa ultrafilter plotted against time after injection for each of 51 patients in study 2.
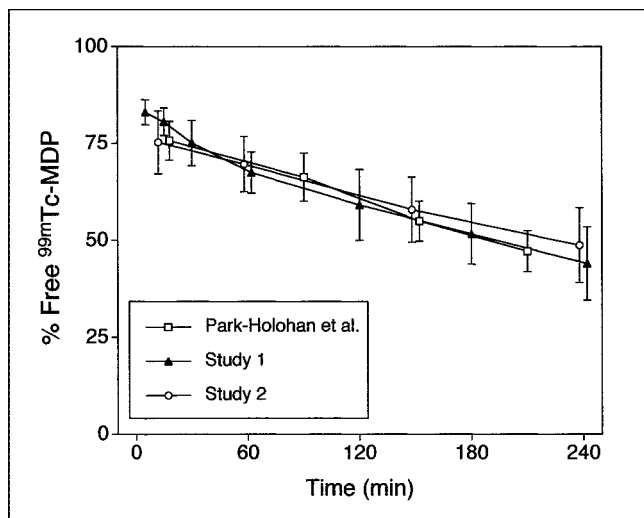
FIGURE 5. Data for mean percentage of free ^{99m}Tc-MDP obtained in study 1 and study 2 using 10-kDa ultrafilters are compared with measurements obtained from 49 postmenopausal women by Park-Holohan et al. (*23*) and Blake et al. (*24*) using GFR method.

dynamic SPECT measurements of skeletal uptake of ^{99m}Tc-MDP, the measurement of the free MDP plasma input curve would allow accurate measurements of regional ^{99m}Tc-MDP skeletal plasma clearance (*27*).

In the ultrafiltration method, protein binding is measured by separation of unbound substance from protein-bound substance. The first aim of our study (study 1) was to validate ultrafiltration as an accurate and convenient method of measuring the free fraction of ^{99m}Tc-MDP by comparing it with the GFR method (*23,24*). The latter allows a direct in vivo measurement of free ^{99m}Tc-MDP based on the assumption that free MDP is cleared through the kidneys by glomerular filtration. The second aim (study 2) was to study the differences in the fraction of free ^{99m}Tc-MDP between individual patients and determine whether individual measurements are required for bone kinetic studies or whether the population mean figure is adequate.

The ultrafiltration data for the 10 healthy volunteers who participated in study 1 showed that the fraction of free ^{99m}Tc-MDP decreased progressively with time after injection (Fig. 1). Similar results were found for the 51 patients who participated in study 2 (Fig. 4). The 5-min to 4-h curves for the mean percentage of free ^{99m}Tc-MDP against time measured by ultrafiltration were in close agreement with the mean percentage of free ^{99m}Tc-MDP curve measured by Park-Holohan et al. (*23*) in 49 healthy postmenopausal women using the GFR method (Fig. 5). There was also good agreement with the mean curve in 5 patients reported by Hyldstrup et al. (*22*) based on precipitation of protein using trichloroacetic acid.

In study 1, when the fraction of free ^{99m}Tc-MDP measured by ultrafiltration was compared with the GFR method there was relatively little difference in the data for the

different molecular weight filters (Fig. 2). The results varied slightly with filter size, with progressively increasing removal of protein-bound activity with decreasing filter size. The closest agreement between the ultrafiltration and GFR method was found for the 30-kDa filter. However, the 5-, 10-, or 30-kDa filters could be used in future studies provided allowance is made for the appropriate correction factor (Fig. 3). The mean ratios of the renal clearances of ^{99m}Tc-MDP and ^{51}Cr-EDTA calculated from the ultrafiltrate data for the 5-, 10-, 30-, 50-, and 100-kDa filters were all close to unity with a small dependence on filter size. These data were therefore consistent with the assumption that free ^{99m}Tc-MDP is cleared through the kidneys by glomerular filtration. This hypothesis was suggested by the study of Hyldstrup et al. (*22*), who showed by direct arterial-venous sampling that the filtration fraction of free ^{99m}Tc-MDP in the kidneys approximates that of ^{51}Cr-EDTA.

When repeated measurements of the percentage of free ^{99m}Tc-MDP measured by ultrafiltration were compared the precision error was 2.3%. This figure was based on 36 duplicate measurements in 9 patients. The number of degrees of freedom (df) for measuring the precision error (df = 36) is larger than the minimum number (df = 27) recommended for adequate statistical accuracy in bone densitometry studies (*28*).

The principal kinetic pathways for tracers used in quantitative bone radionuclide studies are plasma clearance to the kidneys and skeleton (*29*). The results from the volunteers in study 1 showed that there was a rapid fall in plasma concentration of free ^{99m}Tc-MDP from an average of 9.9%/L at 5 min after injection to 0.58%/L at 4 h as free MDP equilibrates with the extravascular extracellular fluid compartment and is cleared to the kidneys and skeleton. In contrast, the concentration of bound ^{99m}Tc-MDP fell more slowly, from 2.3%/L at 5 min to 0.77%/L at 4 h. The different behavior of the free and bound MDP plasma concentration curves emphasizes the importance of the time variation of the fractional protein binding and suggests that reequilibration between the bound and free fractions occurs on a relatively long time scale (*24*).

The ultrafiltration data from subjects in both study 1 and study 2 confirmed that the fraction of free ^{99m}Tc-MDP did vary with time and, compared with the precision error of 2.3%, showed large differences between individuals. The wide range of values in Figure 4 suggests that it is important to make individual measurements of the fraction of free ^{99m}Tc-MDP during bone kinetic studies. This result is consistent with the findings of Blake et al. (*24*), who reported that the fraction of free ^{99m}Tc-MDP varied with time and showed significant differences between individuals.

When the percentage of free ^{99m}Tc-MDP in the patients in study 2 was analyzed for the effect of age, sex, serum albumin, and GFR, there was no effect of either sex or albumin. Serum albumin was measured because it is the principal protein in blood that binds ^{99m}Tc-MDP and might affect the protein binding results (*30*). Although no relation-

ship between the fraction of free MDP and albumin levels was found, this may be because the range of albumin values was relatively small (all but 1 subject had results within the reference range). As expected, age and GFR were highly correlated ($r = 0.80$), and both variables showed significant correlations with the 150-min and 4-h free MDP data. Older patients had lower GFR and a higher percentage of free ^{99m}Tc-MDP. The observed relationship between age, GFR, and free MDP is explained if older patients with lower GFR had a slower clearance of free ^{99m}Tc-MDP through the kidneys. Given the evidence for the slow reequilibration between the bound and free fractions noted above, this would lead to an apparently larger fraction of free MDP at later time points in patients with low GFR. A limitation of this study was that no attempt was made to measure the absolute plasma concentration of bound and free tracer in patients in study 2, because the above explanation could be confirmed by demonstrating a strong correlation between free ^{99m}Tc-MDP plasma concentration and GFR but a relatively weaker correlation between GFR and the concentration of bound tracer (24).

Because the total plasma clearance of ^{99m}Tc-MDP is the sum of the clearances to the kidneys and the skeleton, the type and extent of skeletal disease should also affect the percentage of free MDP measured by ultrafiltration in a similar way to GFR. Patients with particularly active or extensive disease will have an elevated total skeleton plasma clearance and, hence, lower plasma concentrations of free ^{99m}Tc-MDP and lower fractional free MDP. However, there was evidence for such an effect in only 1 subject in this study, an elderly male patient with extremely extensive metastatic bone disease throughout most of the skeleton and the appearances of a superscan of malignancy. Despite a low GFR (57 mL/min), which should otherwise give rise to a higher-than-average figure for the percentage of free ^{99m}Tc-MDP, this patient had the lowest 4-h result plotted in Figure 4 (27%). That there was little evidence of an effect due to disease extent in study 2 is partly explained by the fact that the majority of patients had only minimal changes from normal on their bone scan images, such as a small focus of increased uptake in 1 region. However, apart from the case noted above, a further 4 patients with very extensive skeletal disease involving increased tracer uptake in the skull, spine, pelvis, ribs, and femur (2 with metastatic bone disease, 1 with Paget's disease, 1 with osteopetrosis) had the percentage of free ^{99m}Tc-MDP values within the average range of the other patients. The relationship between the percentage of free ^{99m}Tc-MDP and the extent of skeletal involvement needs further investigation in a larger number of patients, including skeletal kinetic measurements to quantify bone uptake.

CONCLUSION

This study set out to validate a simple method of measuring free ^{99m}Tc-MDP using ultrafiltration by comparing the results obtained with ultrafiltration with those obtained using the GFR method (23,24). The results show that ultrafiltration provides an accurate and convenient method of evaluating free ^{99m}Tc-MDP in plasma for bone kinetic studies. In the second part of the study, the results in both the healthy volunteers in study 1 and the patients in study 2 showed that MDP protein binding varied with time and showed significant differences between individuals that were dependent on GFR among other factors.

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