Modification and Validation of a Single-Isotope Radiocalcium Absorption Test

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This study was done to establish and allow for the influence of body weight on plasma radioactivity after administering radiocalcium to measure calcium absorption. **Methods:** We administered 5 μCi ^{45}Ca in 20 mg of calcium carrier in 250 ml distilled water to 103 premenopausal volunteers over the age of 40 yr, after an overnight fast. Venous blood was withdrawn when the dose was given (to serve as a blank) and exactly 60 min later, and the counts were determined in a liquid scintillation counter. After the exclusion of three outliers, the fraction of the administered dose per liter of plasma at 60 min was a curvilinear inverse function of body weight and a positive linear function of the reciprocal of body weight, with an r value of 0.45 ($p < 0.001$). This latter relationship then was used to correct the plasma radioactivity to a standard body weight of 65 kg, in which the volume of distribution of the dose was assumed to be 10 liters. This yielded the estimated fraction of the dose circulating at 1 hr, which then was converted into a fractional absorption rate from our previously published equation. **Results:** In the 100 volunteers, the mean value of the radiocalcium absorption rate (termed α_2, to distinguish it from our original calculation) was 0.75/hr, with 98 of the 100 values falling between 0.30 and 1.20. The value α_2 was significantly related to serum calcitriol in these 100 volunteers ($r = 0.29$; $p = 0.003$) and in 89 normal postmenopausal women ($r = 0.46$; $p < 0.001$). It also was significantly related to the 24-hr urine calcium in the same 89 women ($r = 0.48$; $p < 0.001$) and to net calcium absorption corrected for intake in balance studies on another 103 postmenopausal women ($r = 0.44$; $p < 0.001$). In most respects, α_2 was marginally superior to α_1 but, unlike α_1, was independent of body weight. **Conclusion:** The modified low-carrier radiocalcium absorption test is a valid indicator of calcium absorption status over a wide range of calcium intakes and is independent of body weight.

Key Words: calcium absorption; radiocalcium; serum calcitriol; body weight; osteoporosis

J Nucl Med 1998; 39:108–113

Calcium absorption is central to the body's calcium homeostasis (*1*). In metabolic balance studies on human subjects, it accounts for more than half the variance on calcium balance (*2*). Therefore, the investigation of calcium disorders, whether for research or clinical management purposes, requires some measurement of calcium absorption, for which three methods are available: a full calcium balance, which, strictly speaking, requires a stay of at least 2 wk in a metabolic unit (*3*) and is impractical for routine use; a double-isotope procedure, with two stable or radioactive calcium isotopes (*4,5*), which is fraught with technical difficulties and may involve a delay of several weeks before yielding a result; and a single-isotope procedure, which is the simplest, cheapest and quickest method.

Received Nov. 19, 1996; revision accepted Mar. 25, 1997.

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The single-isotope radioactive absorption test was introduced by Bhandarkar et al. (*6*) in 1961, who gave 5 μCi ^{45}Ca in 250 mg of calcium carrier and measured the plasma radioactivity 2 hr later. The first low-carrier test was reported in 1965 by Avioli et al. (*7*), who used 20 mg of calcium as the chloride, measured the plasma activity at hourly intervals but relied on the 60-min value for diagnostic purposes. The first kinetic analysis of plasma activity–time curves after oral calcium isotope administration was made by Marshall and Nordin (*8*) in 1969, who gave a 5-μCi dose of radiocalcium in 20 mg of calcium carrier to fasting subjects and collected six blood samples over the next 2 hr. From the radioactive counts in these samples and by means of differential equations, they were able to calculate the rates of radiocalcium entering (α) and leaving (β) the extracellular compartment. They made three assumptions: the rate of radiocalcium entry was a function of the residual concentration in the small intestine, the rate of radiocalcium removal was a function of its concentration in the plasma, and the volume of distribution of the calcium isotope in the plasma and extravascular fluid was equivalent to 15% of body weight.

In subsequent clinical studies, the Marshall and Nordin test yielded results that were highly correlated with calcium absorption, measured by the balance and double-isotope techniques (*9,10*). The normal absorption rate was found to be 0.30–1.30 of the dose in the first hour, with a mean value of 0.65 and a logarithmic-normal distribution (*3*). The rate of radiocalcium absorption was high in hyperparathyroidism and renal stone disease and low in osteomalacia and renal failure (*3*) and in women with hip fractures (*11*); it also fell with age (*12*), as Avioli et al. (*7*) previously had reported with his procedure. It was subsequently shown to rise in response to treatment with 1-α-hydroxyvitamin D3 in osteoporosis (*13*) and in renal failure (*14*) and to be significantly related to the serum level of calcitriol in normal and osteoporotic women (*15,16*). However, further experience showed that the radioactivity in the plasma 60 min after administration of the test dose correlated so highly with the absorption rate calculated from the six blood samples (r values around 0.9) (*17,18*) that this single blood sample provided a satisfactory measure of calcium absorption. This simplified test has been shown to behave in the same way as does the full procedure and to have an imprecision of about 11% (*19,20*).

Although the clinical and research value of this single-isotope radiocalcium absorption test has been confirmed amply (*21,22*), it has become apparent that the assumption of a dilution pool equivalent to 15% of body weight over the whole weight range introduces a dependence of estimated calcium absorption on body weight that is inconsistent with current physiological knowledge and tends, for instance, to exaggerate the calcium absorption deficit in osteoporotic women because of their low body weight (*20*). We have, therefore, sought to remedy this

artifact by reformulating the calculation from data derived from premenopausal volunteers and to validate it against other independent variables.

MATERIALS AND METHODS

The primary data are derived from 103 female volunteers whose premenopausal status was confirmed by a serum level of follicle-stimulating hormone below 20 units/liter, but we have excluded three subjects who were outliers because their 60-min plasma radioactivities fell more than 3 s.d. outside the mean of the whole set. The mean age of the remaining 100 women was 47.4 yr (range = 43–53 yr); mean weight was 69 kg (range = 49 –109 kg); mean height was 1.63 m (range = 1.53–1.75 m); and mean body mass index was 26.0 (19.2–40.8). The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

Two further clinical series were included for validation of the test. The first comprised 89 untreated postmenopausal women from our osteoporosis and menopause clinics, in whom lateral spine radiographs were normal and who had our standard protocols and provided 24-hr urine collections as part of their home diets. Their mean age was 64 yr (range = 46–82 yr), and their mean weight was 62 kg (43–109 kg). The second comprised 103 mainly osteoporotic postmenopausal women for whom calcium balance data were available. Their mean age was 62 yr (45–88 yr), and their mean weight was 57 kg (41–86 kg).

The subjects arrived at 9:00 a.m. after an overnight fast. A basal venous blood sample was withdrawn to serve as a blank and (in the Adelaide subjects) for measurement of serum 1,25-$(OH)_2$ vitamin D_3 by immunoassay after separation by high-pressure liquid chromatography (*23*). They then were given an oral dose of 5 μCi ^{45}Ca in 20 mg calcium (in chloride form) in 250 ml distilled water and a further blood sample taken exactly 60 min later. The samples were centrifuged, the activity in plasma aliquots was measured in a liquid scintillation counter and the results were expressed as fractions of the dose per liter of plasma (Fx/liter). We then multiplied Fx/liter by 15% of body weight to yield the notional fraction of the dose circulating at 1 hr in the plasma and extracellular compartments (FC). [This body weight correction was derived from the generally accepted volumes of plasma and extravascular extracellular fluid, i.e., 5% and 15% of body weight, respectively (*24*).] Because the calcium concentration in the extracellular extravascular fluid is about 65% of that in the plasma (1.6 compared with 2.4 mmol/liter or 6.4 compared with 9.6 mg/dl), the total circulating calcium is made up of 5% body weight times plasma calcium concentration, plus 15% of body weight times two-thirds of plasma calcium concentration, which amounts to total plasma calcium times 15% of body weight. In a 65-kg individual, this amounts to about 25 mmol (or 1 g) of calcium, which is approximately the calcium pool size 1 hr after intravenous radiocalcium injection (*9,25*). The fraction of the dose absorbed per hour (called α_1 to distinguish it from the modified calculation, α_2) was then calculated from the empirical formula:

$$\alpha_1 = 1.17\ FC + 2.54\ FC^2, \qquad \text{Eq. 1}$$

derived from the relationship between the absorption rate determined from the six blood samples and the circulating radioactivity in the 1-hr sample (*8,17*). It is the modification of the calculation of FC, which is the main theme of this paper.

The calcium balances were performed in 103 postmenopausal women, with varying degrees of osteoporosis, who were kept on a constant diet over a 2-wk period, using polyethylene glycol as the nonabsorbable fecal marker (*3*). In these unpublished balances, performed in the metabolic unit of the general infirmary in Leeds (United Kingdom) in the 1970s, net calcium absorbed (calculated as dietary calcium minus fecal calcium) is expressed both in mmol/day and as deviations from the predicted normal net absorbed calcium at each intake. The latter was calculated from 212 calcium balances in the literature on 84 normal subjects (*26*) and is described by the Michaelis–Menten-type equation (*27*):

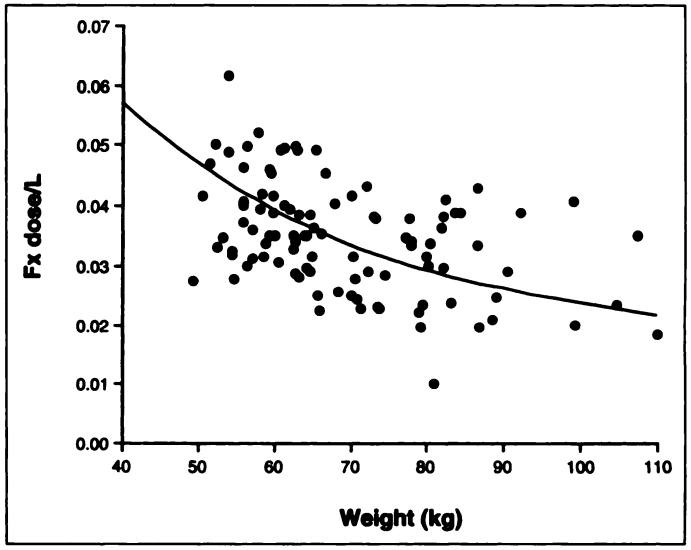

FIGURE 1. Fraction of the dose per liter of plasma at 60 min as a function of body weight in 100 normal premenopausal women. The line represents a constant xy product of 2.35.

Net Ca absorbed

$$= \frac{12.28 \times i}{7.18 + i} + 0.06i - 5.15 \pm 1.9\ \text{mmol/day}, \qquad \text{Eq. 2}$$

where i represents calcium ingested, 12.28 mmol is the maximum transport capacity, 7.18 is a notional K_m and 0.06 is the diffusion slope (*9*).

When radiocalcium absorption was compared with the absorption calculated from calcium balances, we used the geometric mean slope (*28*) because neither is the determinant of the other.

RESULTS

Modification of Test

In 100 premenopausal women, the Fx/liter of plasma at 60 min was 0.035 (s.d. = 0.0090), which is close to that reported by Avioli et al. (*7*). There was an inverse correlation ($r = -0.43$; $p < 0.001$) between Fx/liter and body weight (Fig. 1), but inspection of the data suggested that the relationship was not linear and could represent a rectangular hyperbola, as would be expected from simple dilution of radioactivity, i.e., if weight × Fx/liter were constant. The mean value of weight × Fx/liter was 2.35 (s.d. = 0.59), and the curve representing this mean value is shown in Figure 1 and fits the data very well. However, in a relationship in which xy = K, y is a linear function of 1/x, so that the plasma radioactivities were plotted against the reciprocal of body weight and yielded a linear relationship, as shown in Figure 2. The coefficient of correlation was 0.45 ($p < 0.001$), and the equation became:

$$\text{Fx/liter} = 0.0117 + 1.54 \times 1/\text{weight}. \qquad \text{Eq. 3}$$

This equation permits a relative correction of plasma activity for dilution space but does not provide an absolute value of pool size, as is required for the calculation of actual absorption rates. We, therefore, assumed a dilution space equivalent to 15% of body weight (for the reasons given above) at a standard weight of 65 kg, i.e., 10 liters, and adjusted this pool size upwards for

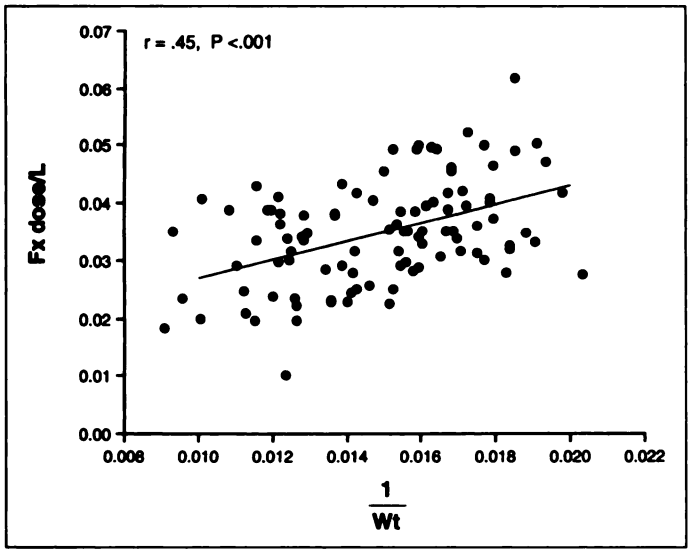

FIGURE 2. Fraction of the dose per liter of plasma at 60 min as a function of the reciprocal of body weight in the same subjects as in Figure 1. The regression line is shown.

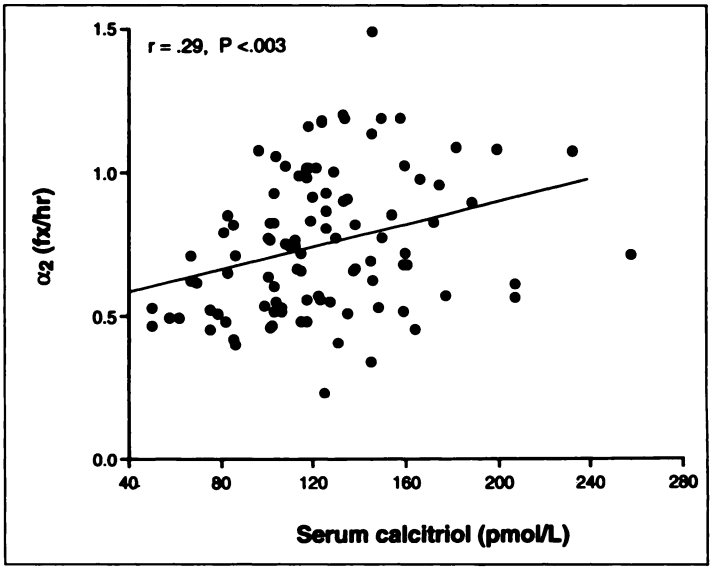

FIGURE 3. The value α_2 as function of serum calcitriol in the same subjects as in Figures 1 and 2. The regression line is shown.

body weights over 65 kg and downwards for body weights below 65 kg, in accordance with the body weight coefficient in the above equation. The fraction of the dose in 10 liters of plasma was then converted to the fraction of the dose circulating at 60 min (FC) as follows:

$$FC = Fx \text{ in } 10 \text{ liters} - \left[15.4 \times \left(\frac{1}{\text{weight}} - 0.0154\right)\right], \quad \text{Eq. 4}$$

where 0.0154 is the reciprocal of 65.

This means that, at a body weight of 65 kg, the Fx in 10 liters of plasma at 60 min is the FC. If the body weight is above or below 65 kg, the plasma activity is corrected accordingly. Fraction circulating then is converted to the fractional hourly rate of calcium absorption from the empirical Equation 1.

We have called the absorption rate calculated in this way α_2 to distinguish it from the original calculation, which we now call α_1. The mean value of α_2 in the 100 premenopausal women was 0.750 (s.d. = 0.24), with 98 of the values falling between 0.30 and 1.20. The mean value of α_1 was 0.798, with a s.d. of 0.27 and 98 of the values falling between 0.30 and 1.50. α_2 was not related to body weight in this set (r = 0.002), whereas α_1 was (r = 0.302; $p < 0.001$).

Validation

Relationship to Serum Calcitriol. In 100 premenopausal women, the mean serum calcitriol was 124 pmol/liter (s.d. = 37.7), and the coefficient of correlation between α_2 and serum calcitriol was 0.29 (p = 0.003) (Fig. 3), compared with 0.24 (p = 0.016) between α_1 and serum calcitriol. In the 89 postmenopausal clinic patients with normal spine radiographs, the mean α_1 was 0.69 (s.d. = 0.27), and the mean α_2 was 0.66 (s.d. = 0.28); the mean serum calcitriol was 109 pmol/liter (s.d. = 44). The coefficients of correlation between both α_1 and α_2 and serum calcitriol were 0.46 ($p < 0.001$) (Fig. 4).

Correlation with Urine Calcium. In the 89 normal postmenopausal women, the mean 24-hr calcium on a free diet was 3.78 mmol (s.d. = 2.10). The coefficient of correlation with α_1 was 0.52 ($p < 0.001$) (Fig. 5), and with α_2, it was 0.48 (p for both < 0.001).

Comparison with Calcium Balance. The mean calcium intake in the 103 balance studies was 22.3 mmol (6.4 mmol–38.5 mmol), mean net absorbed calcium was 2.29 mmol (−4.8 mmol–8.2 mmol) and mean urine calcium was 3.72 mmol (0.8 mmol–8.3 mmol). The mean value of α_1 was 0.52 (s.d. = 0.23), and that of α_2 was 0.56 (s.d. = 0.28). The coefficients of correlation between net calcium absorbed and both α_1 and α_2 were 0.37 ($p < 0.001$). However, because the balances were performed on a wide range of calcium intakes, the absorbed calcium needs to be corrected for intake before it can be regarded as a measure of absorption performance. Net absorbed calcium, therefore, is shown as a function of calcium intake and compared with the normal slope (Eq. 2) in Figure 6. It is clear that calcium absorption was low in most of these cases, the mean deviation from the line being −2.91 mmol/day (s.d. = 2.46). The mean net calcium absorbed as a fraction of the predicted value was 0.45 (s.d. = 0.47). The relationship between this fraction and α_2 is illustrated in Figure 7. The coefficient of correlation between α_2 and absorbed calcium expressed in this way was 0.44, and it was 0.41 between α_1 and

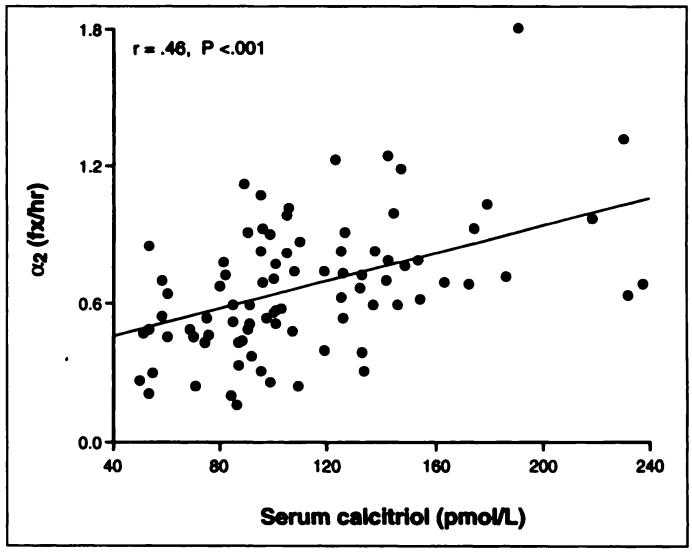

FIGURE 4. The value α_2 as a function of serum calcitriol in 89 postmenopausal women with normal spine radiographs. The regression line is shown.

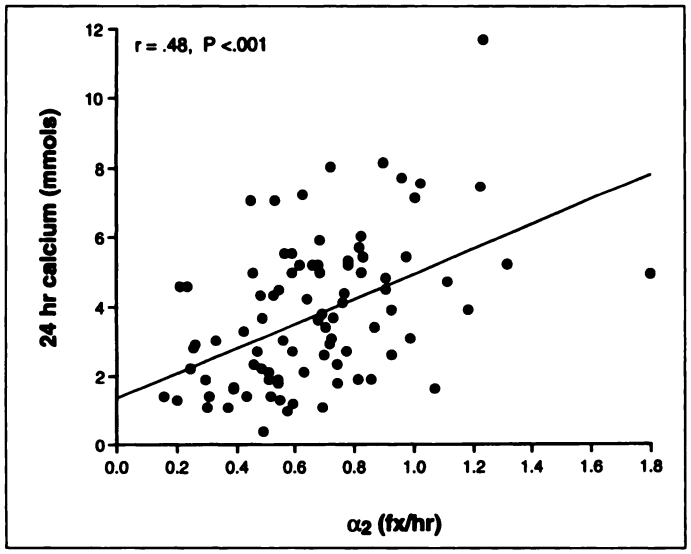

FIGURE 5. Twenty-four-hour urine calcium on free diets as a function of α_2 in the same subjects as in Figure 4.

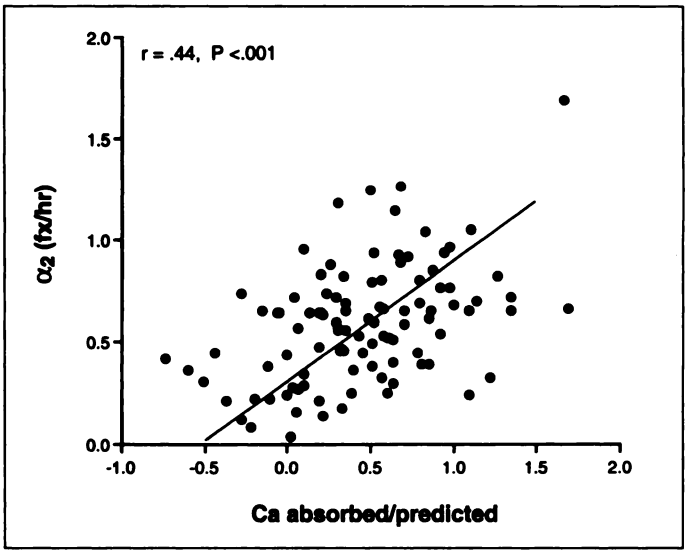

FIGURE 7. The value α_2 as a function of the ratio of calcium absorbed to predicted in the same subjects as in Figure 6. The line represents the geometric mean regression.

absorbed calcium (p for both < 0.001). The geometric mean regression of α_2 on calcium absorbed/predicted was:

$$\begin{aligned} & & t & \quad p \\ \alpha_2 &= 0.595 \text{ absorbed/predicted} & 4.9 & < 0.001 \\ &+ 0.294 \text{ Fx/hr} & 13.0 & < 0.001 \\ R^2 &= 19.1\%. \end{aligned} \qquad \text{Eq. 5}$$

From this equation, the α_2 value is 0.89 when the ratio of observed to predicted calcium absorption is unity.

DISCUSSION

A knowledge of calcium absorption performance is central to the understanding of calcium and bone status in any individual or group of individuals. Calcium balances have tended to fall into abeyance, mainly for reasons of cost but also perhaps because badly performed studies have tended to bring the procedure into disrepute. As a consequence, calcium absorption is being neglected by most workers in the field, with some notable exceptions (*29,30*). This is unfortunate on both theoretical grounds because the elucidation of critical aspects of calcium metabolism is being delayed unduly, and on practical grounds because the management of individual cases of osteoporosis, for instance, tends to be indiscriminate and applied without reference to the metabolic abnormalities in a particular patient. Thus, vitamin D metabolites are administered without reference to calcium absorption status (*31*), although their main and probably only effect is to raise calcium absorption (*32*). A similar situation is likely to develop with bisphosphonates (*33*).

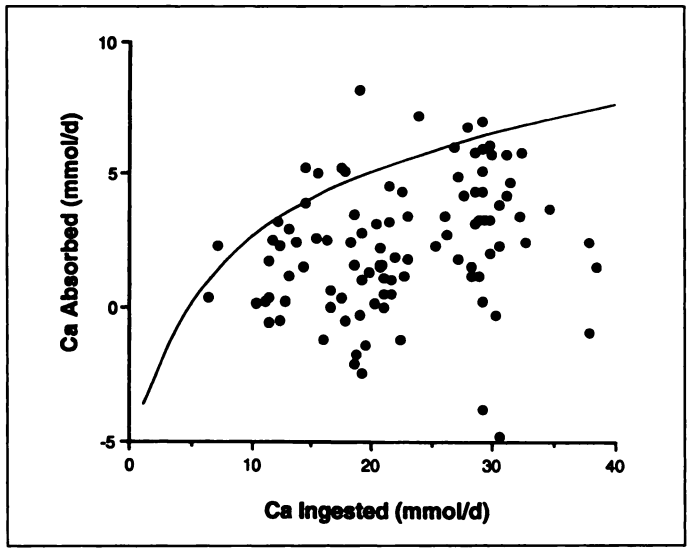

FIGURE 6. Net calcium absorbed as a function of calcium ingested in 103 calcium balances on normal and osteoporotic postmenopausal women. The line represents the normal relationship.

There can be no doubt about the overwhelming importance of calcium absorption in regulating the body's calcium homeostasis, but there is uncertainty as to which methodology should be used to measure it. Cost-benefit considerations point unequivocally to the use of a single radioactive isotope of calcium, namely ^{45}Ca, which is inexpensive, easy to measure and has a convenient half-life of 63 days. The estimated radiation dose to the individual from the oral administration of 5 μCi is 220 μS (22 mrem) (*34*), compared with the Australian recommended upper limit of 5 mS (500 mrem) in volunteers (*35*). This radiation dose is only about 10% of the annual background radiation exposure. Needless to say, however, it should not be administered to children and should only be administered to nonpregnant premenopausal women.

A single-isotope test should only be used with a tracer quantity of calcium carrier. Its validity, whether it is based on a six-blood sample analysis or an empirical one-blood sample analysis, depends on the absorption of the test dose being completed over a short period of time from a limited segment of the small intestine, thus producing a relatively sharp peak of radioactivity about 60 min later (*9*). The rate of calcium absorption is inversely related to the calcium load, and the addition of more carrier to the test dose not only reduces the proportion of the dose that is absorbed but spreads the absorption process over a larger surface of small intestine, extending the time during which absorption takes place and flattening the radioactivity-time curve. It also reduces sensitivity because, as examination of balance data shows (*36*), the difference between low absorbers and high absorbers is proportionally greater at low calcium intakes than it is at high calcium intakes. This is probably because regulation of calcium absorption by vitamin D and its metabolites, the principal regulators, operates through

the active transport rather than the diffusion component of calcium absorption (*37,38*). The use of a standard meal of 100 mg of calcium (*39,40*) has the effect of flattening the activity-time curve and, thus, reducing sensitivity. This is compounded if the radioactivity is measured 5 hr later, when residual activity is very low. Such a procedure is unlikely to be sufficiently sensitive to be of practical diagnostic value, which may explain why some of its advocates are now turning to the use of strontium instead of calcium (*41*). Nor has the higher-carrier, single-isotope test been shown to correlate with the serum calcitriol (*42*), as do the double-isotope, high-carrier (*43*) and single-istotope, low-carrier (*15,20*) tests. It must be remembered that, at calcium intakes around 20 mmol (800 mg), about 80% of calcium is absorbed by active transport (*9*), as is clear from Equation 2. For most purposes, therefore, the intention must be to measure active transport capacity, which is what the low carrier-test measures. Calcium absorption can, in theory, be measured at any intake and, after correction for intake, almost certainly indicates absorptive status at all other intakes. However, the larger the carrier dose, the more interference there will be from the diffusion process and the less valid the single-isotope procedure for technical reasons will be.

There is another, purely empirical reason for using as small a quantity of calcium carrier as possible, namely, to restrict the radiation dose to the lowest practicable level. Because of the high fractional absorption rate from the low-carrier dose, the activity in the 60-min plasma sample after 5 μCi ^{45}Ca yields sufficient counts for acceptable accuracy in 20 min, even in patients with low absorption. As the carrier load is increased, the fractional absorption rate falls steeply (*9*) and either the dose of radioactivity or the counting time has to be increased to yield the same precision.

Any test of calcium absorption needs to be validated by comparison with other procedures and/or with variables known to be related to calcium absorption. We previously validated the single-isotope test against balance data and a double-isotope procedure (*10*) and showed that radiocalcium absorption is strongly related, in the expected manner, to the underlying clinical condition of the subject (*3*). The modification to our formula proposed in this study again has been validated by comparison with serum calcitriol levels and rigorous calcium balances and has the great merit of being independent of body weight. It is equally suitable for research purposes and routine clinical management, costs very little, yields an answer within a few hours and is technically easy to perform. We are at a loss to understand the reference to "measurement difficulties" related to ^{45}Ca, discussed in a recent publication (*43*).

Whether the calculation of absorption rate should be derived from a six-blood sample analysis of the plasma radioactivity-time curve or from the empirical 60-min value (as we have done here) depends on the circumstances. The full analysis is theoretically sounder, but in our experience, the gain from multiple blood sampling is generally marginal and hardly justifies the additional cost and discomfort, at least in a clinical setting. Even in states of high bone turnover, such as Paget's disease, we have failed to find any systematic discrepancy between radiocalcium absorption calculated from six blood samples and from one blood sample.

The explanation is almost certainly that, in the early phase of radiocalcium absorption from a low carrier dose, interindividual differences in the rates of isotope removal from plasma are much smaller than interindividual differences in rates of entry from the gut. The robustness of the procedure and the importance of calcium absorption are indicated clearly by the significant correlation between radiocalcium absorption and 24-hr calcium excretion on a free diet shown in this paper. That the low-carrier procedure also predicts absorptive status at higher intakes also is borne out by the correlation between our radiocalcium absorption test and the rise in ionized calcium and the fall in serum parathyroid hormone that follows the acute administration of a 1-g calcium load (*44*).

CONCLUSION

The low-carrier, single-isotope radiocalcium absorption test is a measure of calcium absorptive status that is probably valid at all calcium intakes. The modification introduced here has effectively removed the dependence on body weight that was a source of error in our earlier calculation.

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Hypoplastic Dysplastic Kidney with a Vaginal Ectopic Ureter Identified by Technetium-99m-DMSA Scintigraphy

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Ectopic insertion of a ureter draining a hypoplastic dysplastic kidney is a significant cause of urinary incontinence in girls. In this case, such a kidney was detected with ^{99m}Tc-DMSA scintigraphy but not by intravenous pyelography. Scintigraphy facilitated further delineation of the anatomy with CT prior to nephrectomy. Based on this case and a literature review, we suggest that ^{99m}Tc-DMSA scintigraphy be performed early when evaluating girls with urinary incontinence.

Key Words: technetium-99m-dimercaptosuccinic acid; kidney; urinary incontinence; ectopic ureter

J Nucl Med 1998; 39:113–115

CASE REPORT

An 8-yr-old girl with urinary incontinence was referred for renal cortical scintigraphy due to a suspected ectopic hypoplastic right kidney with an ectopic ureteral orifice. The patient's urologic history was otherwise remarkable only for urosepsis at age 3 wk. Diagnostic evaluation at that time revealed left vesicoureteric reflux (VUR) and a left megaureter. Ultrasonography and intravenous pyelography (IVP) showed a solitary left kidney with pelvicalyceal dilatation. At cystoscopy, a right ureteral orifice was not identified. Left ureteral reimplantation was performed, and a follow-up voiding cystourethrogram indicated that VUR was no longer present. Subsequent to this, and after toilet training at a normal age, she regularly had damp underwear every day and night. Before referral to our institution, work-up had included four additional IVP studies, which demonstrated only a normal appearing left kidney, and urodynamic evaluation, which showed normal uroflow, normal urethral pressure profile and adequate bladder compliance. Bladder training exercises, biofeedback and oxybuty-

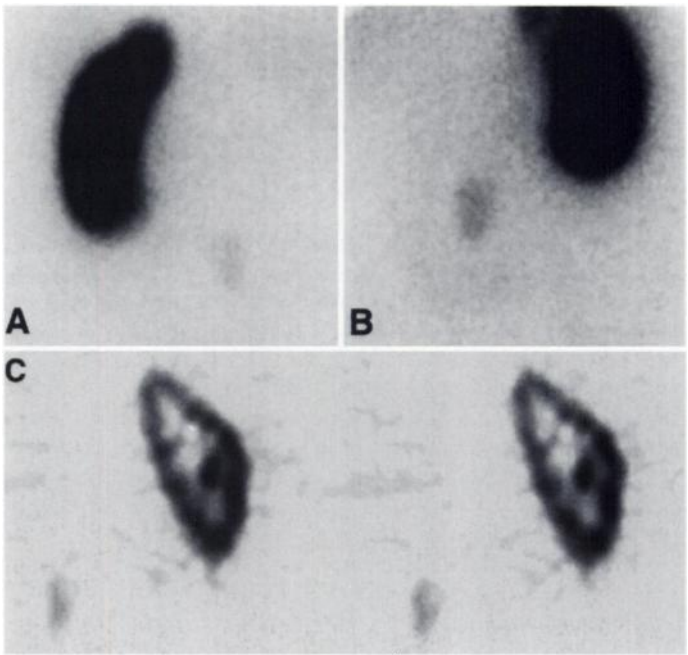

FIGURE 1. Planar images: (A) posterior; (B) anterior; (C) coronal SPECT reveal tracer localization in a small ectopic right kidney.

Received Feb. 1, 1997; accepted Mar. 27, 1997.

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