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CORRELATION OF RADIAL BONE MINERAL CONTENT WITH TOTAL-BODY CALCIUM IN VARIOUS METABOLIC DISORDERS*

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Introduction

Loss of the mineral content of bone in osteoporosis and in other metabolic disorders of the skeletal system can be measured directly by total-body neutron activation analysis, TBNAA (Cohn, 71,72). The densitometric technique employing monochromatic photons from ^{125}I when applied to the appendicular skeleton also reflects the loss of bone mineral in osteoporosis (Cameron, 63,68; Johnston, 68; Mazess, 64; Shimmins, 72 and Smith, 72).

The object of the present study is to compare the results of these two techniques in measuring skeletal mass and to observe how they relate in patients with various metabolic disorders. A method has been developed for normalizing data on total-body calcium (Cohn, 73). That is to say, the measured calcium data are compared to a calculated "normal" value for the individual based on sex, age and body size. On this basis, a reasonable assessment can be made as to whether the data fall into a "normal" range of values. An aim of the present study was to formulate a similar method for normalizing the densitometric data, to facilitate intercomparison among individual patients with different diseases.

Method

Eighty patients and nine normal contrast subjects were analyzed for their total-body Ca (by TBNAA). At the same time, the bone mineral content (BMC) of their radius was determined. The groups consisted of forty osteoporotic patients, nineteen renal patients on hemodialysis, five alcoholic individuals, nine patients with Parkinson's disease, seven renal patients, and nine normal contrast subjects (see Table I).

With the TBNAA technique, the patient is uniformly exposed to a beam

of partially moderated fast neutrons which induce the reaction, $^{48}Ca(n,\gamma)^{49}Ca$. The induced ^{49}Ca is then measured absolutely with a whole-body counter. From these data, the absolute level of total-body Ca (TBCa) is calculated (Cohn, 71,72). With this procedure the Ca is measured in a phantom with an accuracy of ±5%.

At the same time, the bone mineral content (BMC) and the width of the radius (W) were measured by the Cameron-Sorenson densitometric technique with the Norland Cameron densitometer (Cameron, 68). The accuracy of this technique is stated to be ±5% (Cameron, 68; Johnston, 68; Maxess, 64). The radius was measured at a point one-third the distance from the distal end of the radius (8 cm site).

A. Normalization of total-body calcium data

In order to calculate the relative deficit in total skeletal Ca in individual patients from an absolute measurement of Ca, it is necessary to normalize the data for each patient with a correction based on sex, age and skeletal size. Thus, in addition to the need for an accurate method of measuring the skeletal mass, a standard reference is needed against which the measurement may be compared. The variation in Ca content of an individual, or a particular component of the skeleton, is so great because of the variation in size of the individual and the degree of mineralization among individuals, that an "average" (even one based on sex of the individual) does not provide a suitable reference value against which an individual measurement can be assessed.

Thus, the following algorithm was used to calculate the "normal" (i.e., expected) skeletal Ca in a subject, on the basis of weight (lean body mass), height, sex and age (Cohn, 73).

$Ca_p = \alpha H \sqrt{K}$ where Ca_p = predicted total body Ca (g) (1)

H = the height (m)

K = the total body potassium (g)

α = 54.5, for males

α = 57.0, for females

The measured total-body Ca (TBCa), expressed in terms of the predicted normal calcium (Ca_p), is referred to as the calcium ratio ($TBCa/Ca_p$). The relative deficit in Ca for an individual patient may then be established as the difference between 1.00 and the measured value of the ratio (or as a percentage, the difference between 100% and the ratio expressed as a percentage).

B. Normalization of bone mineral content of radius

To facilitate intracomparison of the measured BMC in individuals of different sizes, an index of size and age is required, similar to that used to normalize the measure of total-body calcium. For this purpose the width of the radius (measured from the scan) has been employed (Johnston, 68). The width of the radius is a factor of the cross-sectional area (particularly at the 8 cm site). The BMC data, expressed as a ratio of measured value to radius width, are presented in Table I.

Inasmuch as BMC and total-body Ca measurements correlate well, it is clear that the BMC data can also be normalized by the use of the algorithm employed for the normalization of the total-body Ca data:

$BMC = .001188\ TBCa - .0730$ (2)

$TBCa = \alpha H \sqrt{K}$ (see equation 1) (3)

$\therefore BMC_p = 0.647\ H \sqrt{K} - .0730$ for males (4)

$= .0677\ H \sqrt{K} - .0730$ for females (5)

where: BMC_p = predicted normal bone mineral content of radius (g/cm).

Results

The data obtained by TBNAA and by photon absorptiometry are presented in Table I. The mean TBCa, bone mineral content (BMC) and the radius width (W) of each group of patients and of the normal contrast group are tabulated. The coefficients of variation within each group are also presented for each of the above parameters.

The correlation between TBCa and radial BMC in the various metabolic disorders is shown in Table II. The correlation coefficients range from 0.973 and 0.984 (for normal contrast subjects and alcoholics) down to 0.826 and 0.835 (for osteoporotic and renal patients on dialysis). All the slopes and intercepts of the equation relating TBCa and BMC are within 2 SD of normal except for the two renal groups.

The mean Ca ratio (TBCa/Cap) and the BMC ratio (BMC/BMC_p) for each group are also shown in Table I. A Ca ratio of 1.00 indicates that the measured TBCa is equal to the predicted Ca value for a person of that sex, age, height and weight. Similarly, the BMC ratio normalizes the densitometric data for the same parameters.

The lowest mean Ca ratio was noted for the osteoporotic female patients; the mean was 0.818. The corresponding mean BMC and BMC ratio for this group were also the lowest, 0.646 and 0.817, respectively. The mean Ca ratios for the renal patients on dialysis were 0.959 and 0.937 for men and women, respectively. The corresponding BMC ratios for these two groups were 0.953 and 0.969, respectively. The female renal patients (non-dialysis) had a Ca ratio still lower, 0.889 and a BMC ratio of 0.883.

The remaining groups had Ca ratios and BMC ratios intermediate between the osteoporotic and the normal contrast patients.

The variation in these ratios was quite large in the different metabolic disorders studied, particularly the BMC ratio, as can be seen in Figs. 1 and 2. The Ca ratio and BMC ratio are plotted for each individual along with the range of the values ($\pm$ 2 SD) of the normal contrast subjects.

The mean widths of the radius in the normal contrast groups were 1.472 and 1.284 cm for males and females, respectively. These means are also most identical to those of male and female osteoporotic patients. There is no significant difference in the mean width of any of the groups from that of the normal contrast group.

Discussion

It is apparent from the data that there is a very significant correlation between the TBCa and BMC in all the groups studied. The correlation was most significant in the normal contrast group (and the alcoholic group), as would be expected where no disturbance in the calcium metabolism exists, and all parts of the skeleton should be proportional to each other (Trotter, 52). In patients with osteoporosis and in renal patients on dialysis, the different parts of the skeleton are obviously differently affected. It might be expected in osteoporosis, since it is primarily manifest as a loss of density of the trabecular bone in the spine, that the loss of Ca in the appendicular skeleton, and especially in the cortical bone, might be somewhat different. This is obviously true, but the correlation is nevertheless still quite high. Chestnut has reported a correlation of 0.94 ($P < 0.001$) between TBCa

(measured by activation in 14 osteoporotic patients) and the BMC (Chestnut, 73). The same correlation from measurements made at different sites (i.e., mid-radius, ulna and humerus) varied from 0.93 to 0.83 (Chestnut, 73). The correlation was somewhat higher for BMC at the 3 cm trabecular bone sites than at the 8 cm site (cortical bone).

The explanation for the difference in the slope and intercept of the equations relating BMC and TBCa in the two renal groups is not clear. These differences may reflect the presence of metastatic calcification which is measured as TBCa but is not reflected in the BMC measurement. Further, in renal osteodystrophy there is the possibility of a change in the radius bone mineral architecture not reflected in the TBCa.

The variation in TBCa and BMC in each group is large, reflecting skeletal size, age of the individual, body habitus and degree of metabolic disturbance. This variability can be reduced by expressing the calcium data as the calcium ratio (TBCa/Cap). When the calcium data are normalized by means of the algorithm previously discussed, the variability of most groups is reduced considerably (see Table I). For example, for the group of osteoporotic women, the coefficient of variation of the absolute TBCa is $\pm$ 18.1%, compared to 10.4% when data are expressed as the calcium ratio. A good part of this remaining variability, of course, reflects the extent and duration of loss of Ca as a result of the disease process. For example, in the normal contrast population, the decrease in variability between the absolute and normalized TBCa is 75%. That is, the coefficient of variation in men and women in the normal contrast population goes from 16.6% to 4.3%, and from 11.7% to 3.0%, respectively. The 4.3% and 3.0% residual variability thus represents primarily the experimental error of the measurements.

The variability in the BMC values in the various patient groups was generally larger than that for the TBCa values. However, the variability of these two parameters was approximately the same in the normal contrast group.

To date, the only attempt to normalize the BMC data for size, sex, and age has been by use of the radius width. Dividing by the radius width does provide some degree of normalization (Table I). The BMC/W, however, was found to be poorly correlated with the normalized TBCa (TBCa/Ca_p) in the osteoporotic and in the normal contrast group (Cohn, 1973a). This poor correlation (0.45 and 0.41, respectively) reflects the inability of the radius width to normalize effectively the BMC measurement for size and age. This results from the poor correlation of radius width with height, age, or skeletal size. For example, despite cortical thickening, radius width does not change markedly with age (Smith, 72).

The very excellent correlation (0.97) between the measured and predicted BMC in the normal contrast group can be seen in Fig. 3. The BMC of the normal subjects fall within 2 SD ($\pm$ 10.3%) of the predicted normal BMC. All the BMC values of the osteoporotic patients, also plotted in Fig. 3, fall above the normal curve. That is to say, all osteoporotic patients (with two exceptions) had a lower BMC than predicted.

Thus the normalization procedure for BMC data employed in the present study is quite effective in reducing the statistical variability due to size, sex, and age (see Table I). While dividing the BMC by radius width tends to reduce the variability of the data, the use of the BMC ratio results in a lower coefficient of variability.

For the normal contrast group, the corresponding changes in the coefficient of variation of the BMC for men and women are 16.7% to 5.2%

and 9.5% to 5.5%, respectively. This amounts to an average decrease of 55% in the BMC data, compared to the 75% reduction in variability in TBCa ratio by using the algorithm.

The correlation of the Ca ratios with the BMC ratios for both normal and osteoporotic individuals is illustrated in Fig. 1. It can be seen that the calcium ratios are distributed so that only 7.5% of the osteoporotic values fall within 2 SD of normal. On the other hand, the BMC ratios of the same group are distributed so that 35% of the osteoporotic values fall within 2 SD of normal. This same large variability in BMC ratios holds for renal (dialysis and non-dialysis) and parkinson patients as shown in Fig. 2. These patients have Ca ratios and BMC ratios greater and less than 2 SD of the normal values. The variability of the BMC ratio was particularly large in the female renal patients, 31.3% and 25.1%. This may reflect the variable degree of osteodystrophy in the different bones of the skeleton in renal patients. The overall good correlation between the calcium ratio and the BMC ratio, however, is apparent for these four groups of patients.

The normalization procedures for the calcium ratio and the BMC ratio are thus useful for directly comparing individual patients with various metabolic disorders. While the large variability of BMC (even after normalization) precludes its utility as a definitive criterion for distinguishing patients with metabolic bone disorders from normal, it still serves a useful purpose. The BMC can be used as a relative measure of quantitative changes in the same patient. Further, if the BMC ratio is used along with the calcium ratio, it is possible to determine the differential rate of loss of calcium from the appendicular skeleton compared with the total skeletal calcium, particularly in the osteodystrophy associated with renal disease.

ABSTRACT

Loss of bone mineral content of the skeleton in osteoporosis and in other metabolic disorders can be measured directly by total-body neutron activation analysis (TBNAA). The densitometric technique (using monochromatic photons from ^{125}I) applied to the appendicular skeleton (radius) also reflects the loss of bone mineral in osteoporosis.

In the present study the results of these two techniques are compared in 80 patients with various metabolic disorders and in 9 normal contrast subjects. It is apparent that there is good correlation between total body calcium (TBCa) and bone mineral content (BMC) in all groups studied. The correlation was highest in the normal contrast group (0.97) and alcoholics (0.98) and lowest in osteoporotic patients (0.83) and in renal patients on dialysis (0.84).

In order to measure the relative deficit in TBCa in individual patients from the absolute calcium measurement, it is necessary to normalize the data for sex, age, and skeletal size. For this purpose an algorithm was used to predict the normal skeletal Ca in each subject based on weight, height, sex and age. In similar manner, BMC data were normalized using the same algorithm. These normalization procedures allow both the TBCa and BMC measurement of the radius to be used to compare the Ca deficit in individuals with different metabolic disorders.

KEY WORDS: Calcium, Bone, Bone Density, Neutron Activation

LITERATURE CITED

Cameron, J.R., and J. Sorenson, J. 1963. Measurement of bone mineral in vivo: an improved method. Science 142: 230-232.

Cameron, J. R., R. B. Mazess and J. A. Sorenson 1968. Precision and accuracy of bone mineral determination by direct photon absorptiometry. Invest. Radiol. 3: 141-150.

Chestnut,C. H., E. Manske, D. Baylink and W. B. Nelp 1973. Correlation of total body calcium (bone mass) and regional bone mass. J. Nucl. Med. (Abstr.)

Cohn, S. H. and C. Dombrowski 1971. Measurement of total-body calcium, sodium, chlorine, nitrogen and phosphorus in man by in-vivo neutron activation analysis. J. Nucl. Med. 12: 499.

Cohn, S. H., K. K. Shukla and R. G. Fairchild 1972. Design and calibration of a broad-beam ^{238}Pu,Be source for total body neutron activation analysis. J. Nucl. Med. 13: 487.

Cohn, S. H., K. K. Shukla and K. J. Ellis (in press) 1973) A multivariate predictor of total-body calcium. Int. J. Nucl. Med. Biol.

Cohn, S. H., K. J.Ellis, S. Wallach, I. Zanzi, H. L. Atkins and J. Aloia (in press) 1973a Absolute and relative defect in total skeletal calcium and radial bone mineral in osteoporosis. J. Nucl. Med.

Ellis, K. J., K. K. Shukla and S. H. Cohn (in press) 1973 . A predictor for total-body potassium in man: Application in metabolic disorders. J. Lab. Clin. Med.

Johnston, C. C., D. M. Smith, P. L. Yu and W. P. Deiss 1968. In vivo measurement of bone mass in the radius. Metab. 17: 1140.

Mazess, R. B., J. E. Cameron, R. O'Connor, et al.1964. Accuracy of bone mineral measurements. Science 145: 388-389.

Shimmins, J., D. A. Smith, M. Aikens, J. B. Anderson and F. C. Gillespie 1972. The accuracy and reproducibility of bone mineral measurements "in vivo". J. Clin. Radiol. 23: 47-51.

Smith, D. M., C. C. Johnston and P. L. Yu 1972. In vivo measurement of bone mass. J. Amer. Med. Assoc. 219: 325-329.

Trotter, M. and G. Gleser 1952. Estimation of stature from long bones of American Whites and Negroes. Am. J. Phys. Anthro. 10: 463.

Table 1. Total-Body Calcium and Radial Bone Mineral Content of Patients with Various Metabolic Disorders

Patient Category	No.	Sex	TBCA g	$\frac{TBCa}{Ca_p}$	BMC g/cm	Width cm	BMC/W gm/cm^2	$\frac{BMC}{BMC_p}$
Alcoholic	3	M	1159 ±14.8*	1.106 ±8.9	1.279 ±13.6	1.458 ±8.9	.875 ±5.1	1.151 ±1.7
	2	F	820	.968	.899	1.240	.731	1.034
Parkinsonism	5	M	1017 ±9.4	.985 ±9.1	1.015 ±24.1	1.531 ±9.5	.712 ±15.8	.979 ±20.7
	4	F	733 ±27.3	.974 ±8.5	.790 ±30.5	1.365 ±17.7	.572 ±20.6	.929 ±19.9
Renal (non-dialysis)	2	M	942	1.001	1.160	1.505	.775	1.143
	5	F	732 ±16.1	.889 ±12.0	.777 ±27.9	1.272 ±4.8	.614 ±30.1	.883 ±31.3
Renal (dialysis)	13	M	1011 ±12.9	.959 ±12.3	1.106 ±14.2	1.502 ±9.1	.750 ±10.4	.953 ±16.4
	6	F	739 ±23.5	.937 ±26.4	.813 ±22.5	1.247 ±6.3	.654 ±22.8	.969 ±25.1
Osteoporotic	4	M	796 ±13.0	.867 ±8.7	.877 ±17.9	1.406 ±6.4	.625 ±6.4	.858 ±5.7
	36	F	590 ±18.1	.818 ±10.4	.646 ±23.8	1.234 ±12.5	.528 ±22.3	.817 ±16.3
Normal	5	M	1096 ±16.6	1.014 ±4.3	1.248 ±16.7	1.472 ±13.5	.847 ±7.9	1.031 ±5.2
Contrast	4	F	873 ±11.7	1.014 ±3.6	.941 ±9.5	1.284 ±16.9	.741 ±9.7	.993 ±5.5

* - coefficient of variation (percent)
TBCa = total body calcium
CaP = predicted total-body calcium
BMC = bone mineral content of radius
BMC/W = bone mineral content of radius/width of radius
BMCp = predicted bone mineral content of radius

Table 2

The Correlation of Total Body Calcium to Radial Bone Mineral Content in Various Metabolic Disorders.

Classification	No. Subjects Male	Female	Slope M	Intercept B	Correlation Coefficient
Normal	5	4	.001188 ±00011*	-.0730 ±.109	0.973 (p<.001)
Alcoholic	3	2	.001011	.0926	0.984 (p<.002)
Parkinsonism	5	4	.001153	-.0700	0.925 (p<.001)
Renal (Non-dialysis)	2	5	.001710	-.4667	0.912 (p<.003)
Renal (Hemodialysis)	13	6	.000938	.1540	0.835 (p<.001)
Osteoporotic	4	36	.001135	-.0244	0.826 (p<.001)

$BMC = M \cdot TBCa + B$

where TBCa = Total Body Calcium (g)

BMC = Bone mineral content (g/cm)

* = SD

Figure Captions

Fig. 1 Radial bone mineral content ratio plotted against total body calcium ratio in osteoporotic patients and in a normal contrast population. The standard deviation of both of these parameters for the normal contrast population are indicated.

Fig. 2 Radial bone mineral content ratio plotted against total body calcium ratio in renal patients (both prior to and on hemodialysis). Similar values for patients with parkinsonism and alcoholism are also shown.

Fig. 3 Measured bone mineral content is plotted against the predicted bone mineral content in osteoporotic patients and in a normal contrast population.

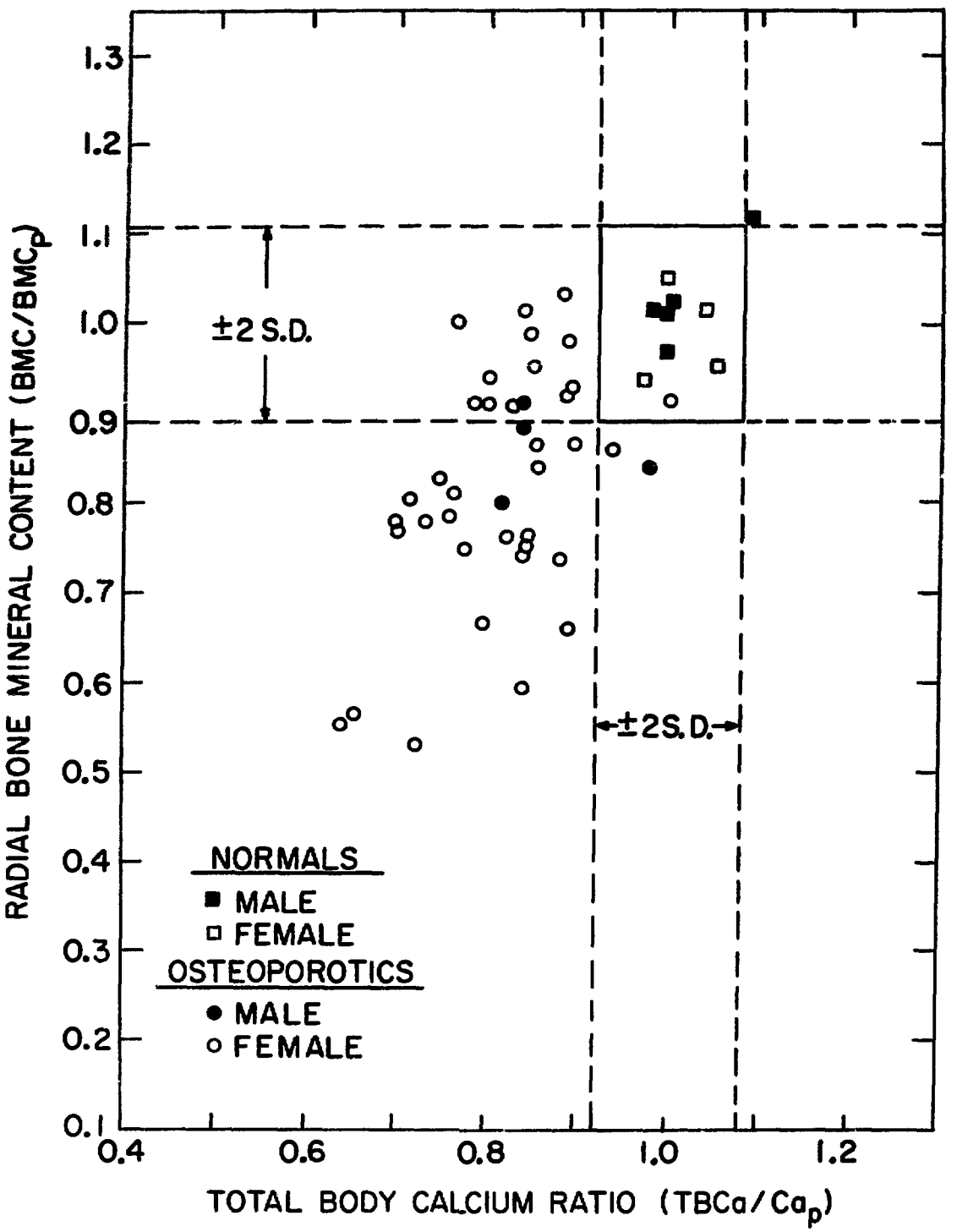
RADIAL BONE MINERAL CONTENT (BMC/BMC$_p$)
TOTAL BODY CALCIUM RATIO (TBCa/Ca$_p$)
±2 S.D.
±2 S.D.
NORMALS
MALE
FEMALE
OSTEOPOROTICS
MALE
FEMALE
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.4
0.6
0.8
1.0
1.2

FIGURE 1

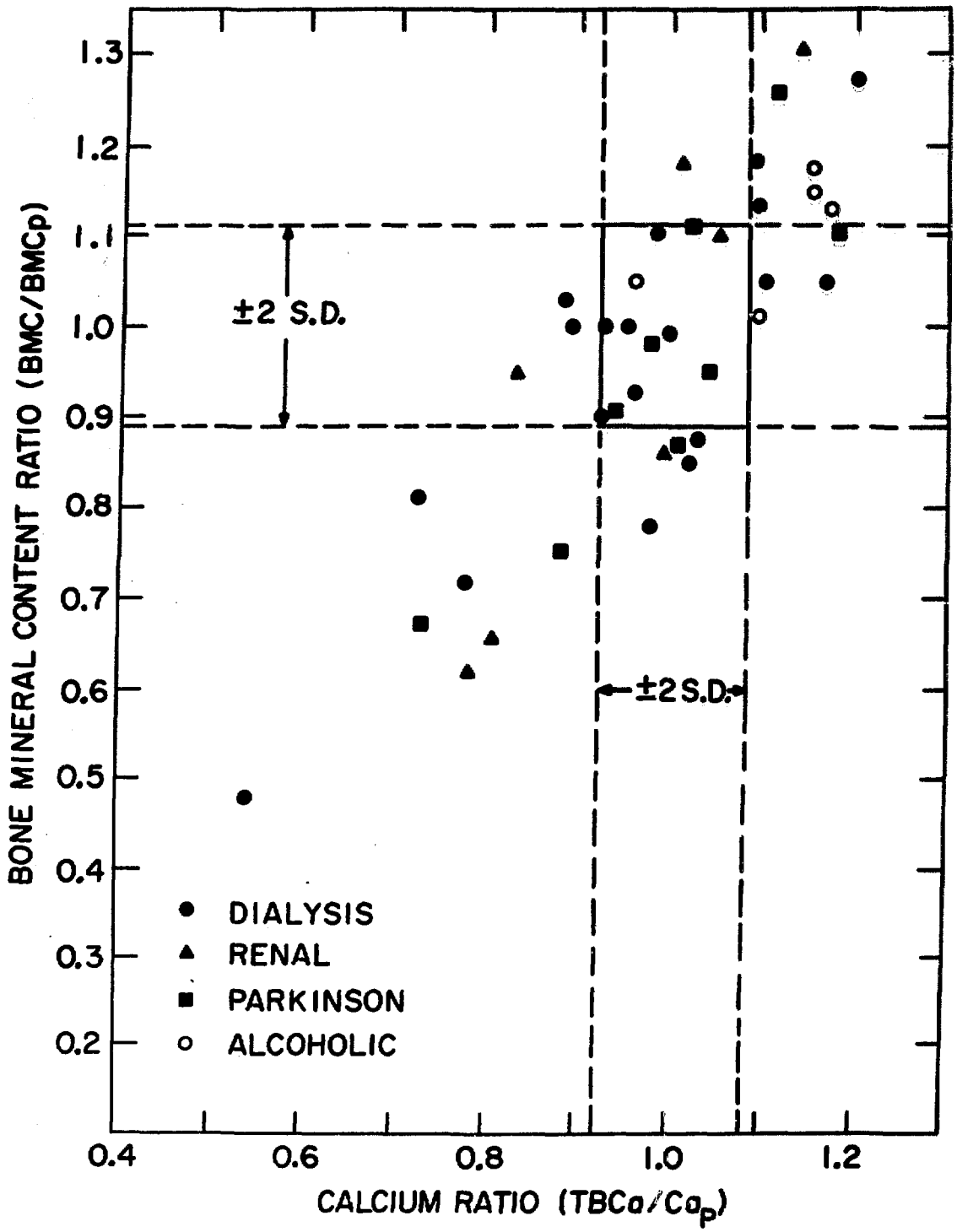
BONE MINERAL CONTENT RATIO (BMC/BMCp)
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
±2 S.D.
±2 S.D.
DIALYSIS
RENAL
PARKINSON
ALCOHOLIC
0.4
0.6
0.8
1.0
1.2
CALCIUM RATIO (TBCa/Cap)

FIGURE 2

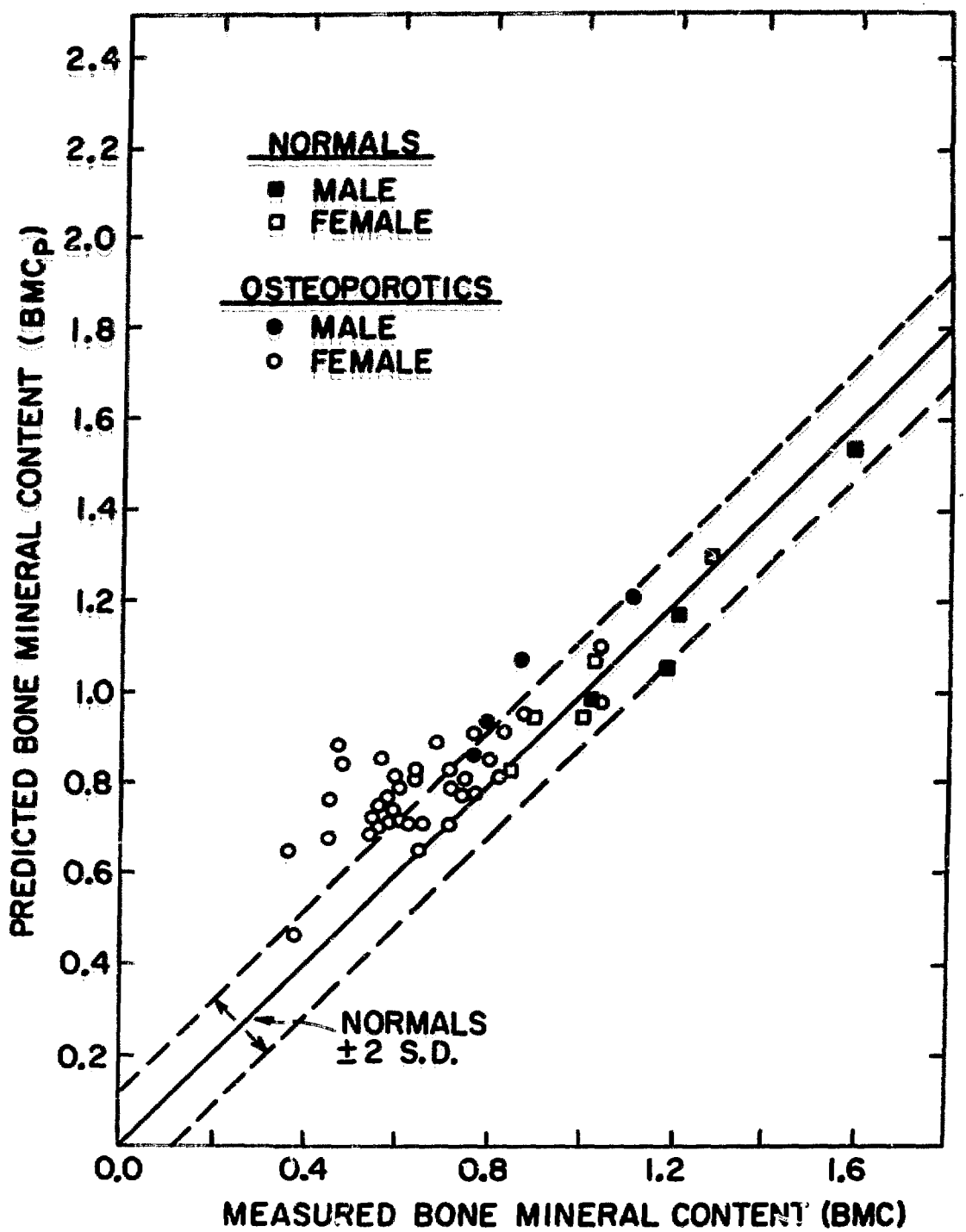
NORMALS
MALE
FEMALE
OSTEOPOROTICS
MALE
FEMALE
NORMALS
±2 S.D.
PREDICTED BONE MINERAL CONTENT (BMCp)
MEASURED BONE MINERAL CONTENT (BMC)
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.4
0.8
1.2
1.6

FIGURE 3