INVESTIGATIVE NUCLEAR MEDICINE

Total-Body Sodium and Sodium Excess

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Total-body levels of sodium (TBNa), chlorine (TBCl), calcium (TBCa), and potassium (TBK) were measured by neutron activation and analysis of results by whole body counting in 66 postmenopausal women. The relationship between TBNa, and TBCl, TBK, and TBCa on the one hand, and height and weight on the other, were found to compare with those previously reported. The hypothesis that TBNa and TBCl are distributed normally could not be rejected.

The sodium excess (Na_{es}) is defined as the sodium that is present in excess of that associated with the extracellular fluid (chlorine) space; the Na_{es} approximates nonexchangeable bone sodium. In these 66 postmenopausal women, and in patients with different endocrinopathies previously described, the values of Na_{es} did not differ from the normal values except in the thyrotoxicosis patients, where they were decreased. A close relationship between Na_{es} and TBCa was maintained in the endocrinopathies studied. This relationship was found in conditions accompanied by either an increment or a loss of skeletal mass. It appears that the Na_{es} value is primarily dependent upon the calcium content of bone.

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Body composition has been studied in the past by indirect measurement of exchangeable pools, using radioisotopes of Ca, K, Na, and Cl (*1–4*). Recently the technique of total-body neutron activation analysis (TBNAA) has been applied to the determination of absolute levels of total-body calcium (TBCa), sodium (TBNa), and chlorine (TBCl) (*5–7*). Total-body levels of potassium (TBK) may be measured by whole-body counting (*8*).

In order to interpret these absolute measurements in an individual, the values must be normalized for body size and sex. This normalization may be achieved by comparing the observed value with a predicted value based on sex, weight, and height. Empirical equations have been reported for the normalization of TBCa, TBK, and TBNa, which may be expressed as the Ca ratio, K ratio, and the Na ratio (*9–11*).

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Total extracellular sodium constitutes about 98% of the TBNa. A considerable portion of the extracellular sodium resides in bone and is considered to be nonexchangeable (*12*). Edelman presented evidence that sodium is present in bone in three phases: (a) free sodium in extracellular fluid, (b) exchangeable sodium adsorbed to the surface of the bone crystals, and (c) nonexchangeable sodium in crystalline bone (*13*). His studies suggest that bone is the only source of the nonexchangeable sodium pool. Recently attempts have been made to estimate the nonexchangeable sodium on the basis of neutron-activation data alone (*11–14*). Since the chlorine space approximates extracellular fluid volume, and the approximate ratio of Na to Cl in extracellular fluid is known, the quantity of TBNa in excess of that associated with the chlorine space may be estimated as follows:

$$Na_{es} = 0.023\ TBNa\ (mEq) - 1.2\ TBCl\ (mEq)$$

where Na_{es} (g) represents the sodium excess value (*11*).

Nonexchangeable skeletal sodium correlates closely with the sodium excess value. Nelp et al. (*14,15*) determined TBNa and TBCa by total-body neutron activation analysis (TBNAA) in five normal males, and simultaneously measured exchangeable sodium by isotope dilution. The ratio of nonexchangeable sodium to TBCa was 20.3 g Na/kg of TBCa. This may be compared with 20.2 g Na/kg TBCa, where the value of 20.2 is the sodium excess value, derived solely from TBNAA data (*11*).

Since it has been estimated that 27% of the TBNa and 8% of body water reside in bone, it has been suggested that bone might act as a reservoir of sodium to mitigate electrolyte and acid-base disorders. Thus the concept has arisen that "nonexchangeable sodium" may, under pathologic conditions, become exchangeable. While a variety of animal studies have provided support for this concept of bone as a sodium reservoir, direct measurement of bone mineral composition has failed to demonstrate alterations of bone sodium in uremia, congestive heart failure, or disorders of serum sodium in man (*16-21*).

TBNa and TBCl have been determined previously by TBNAA in 42 women and men with an age span of 30 to 90 yr (*11*). In the current study, these observations were extended by the measurement of TBNa and TBCl in 66 normal postmenopausal women who fell within a narrow age range (45-55 yr). In addition, TBNa and TBCl were examined in patients with various endocrine disorders that are known to affect skeletal mass and total-body sodium. The objective was to determine whether changes in skeletal mass or total-body sodium result in changes in the Na_{es} value.

METHODS

Subjects. Sixty-six postmenopausal, white women who were in general good health were recruited by an announcement in the press. Subjects who had evidence of cardiac, renal, hepatic, endocrine, or gastrointestinal disease, or any chronic disorder, were excluded from the study. The women were 1-5 yr postmenopausal. All these subjects had normal screening tests that included CBC, urinalysis, SMA 12/60 (including Ca, P, and alkaline phosphatase), serum electrolytes, serum thyroxine, EKG, Papanicolaou smear, and radiographs of the chest and spine.

Total-body levels of Na and Cl were also measured in patients with acromegaly, Cushing's syndrome, thyrotoxicosis, and hyperparathyroidism. Some of these values were reported before the development of the normative data (*22-25*). The TBNa and TBCl values were not previously reported in the hyperparathyroid patients (*25*). All patients had active disease—i.e., growth hormone, serum thyroxine, serum calcium, and urinary steroids were elevated in the acromegalic, thyrotoxic, hyperparathyroid, and Cushing's patients, respectively. One previously described acromegalic patient, who had baseline growth-hormone levels in the normal range, was omitted from the analysis. One adolescent boy with Cushing's syndrome was also omitted from analysis because of the unavailability of normative values for TBNa in his age group.

Total-body neutron activation and whole-body counting. The details of in vivo neutron activation analysis, and the characteristics of the Brookhaven 54-detector whole-body counter, have been described previously (*7,8,26*). The patients were uniformly exposed to a beam of partially moderated fast neutrons. The radiation dose for each activation is 0.28 rem. The subjects were transferred to the Brookhaven whole-body counter, where the activity induced by the following reactions was measured: $^{23}Na(n,\gamma)^{24}Na$ and $^{37}Cl\ (n,\gamma)^{38}Cl$.

The absolute values of TBNa and TBCl were calculated from these data. The precision and accuracy of this method, as determined with an anthropomorphic phantom, are 1.9% for TBNa and 2% for TBCl (*20*). Total-body potassium (TBK) and total-body calcium

TABLE 1. TOTAL-BODY SODIUM AND CHLORINE AND SODIUM EXCESS (Na_{es}) IN POSTMENOPAUSAL WOMEN* (MEAN ± s.d.)

Subjects	N	Na/BSA† (g/M²)	Cl/BSA (g/M²)	Na/Ca (g/g)	Na/Cl (g/g)	Na/K (g/g)	Na_{es} (g)	Na_{es}/Ca (g/g)
Postmenopausal women	66	37.3 ±3.1	37.4 ±3.1	0.077 ±0.008	1.000 ±0.086	0.75 ±0.07	13.34 ±4.95	0.016 ±0.005
Reported values (age 50-59)‡	12	36.7 ±2.5	37.7 ±3.0	0.077 ±0.006	0.97 ±0.08	0.76 ±0.07	11.40 ±3.50	0.014 ±0.004

* No significant differences, determined by t-test of independent data, in any of the values tabulated.

† BSA is body surface area (m^2) calculated as: $BSA = 0.202\ W^{0.425}H^{0.725}$, where weight (W) is in kilograms and height (H) in meters.

‡ Data from Ellis et al. (*11*).

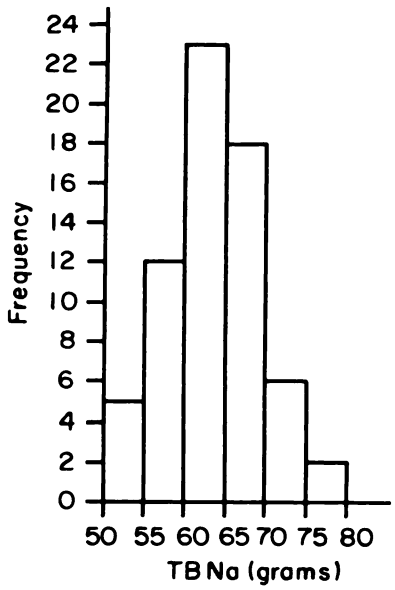

FIG 1. Distribution of TBNa in postmenopausal women; hypothesis that TBNa is normally distributed cannot be rejected.

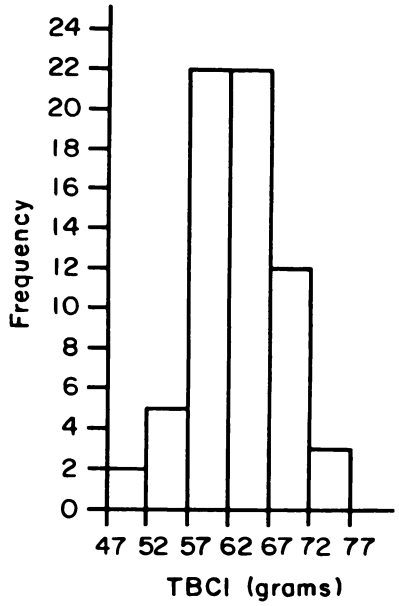

FIG 2. Distribution of TBCl in postmenopausal women; hypothesis that TBCl is normally distributed cannot be rejected.

were also measured in these women (*27*).

RESULTS

Postmenopausal women. The mean age of the postmenopausal women (Table 1) was 52 yr ± 4 (s.d.). The mean values for TBNa and TBCl were 63.4 g ± 5.5 and 63.4 g ± 5.3, respectively. The ratio of Na/Cl was 1.00 ± 0.9 (s.d.), which is comparable to the value of 0.97 ± 0.08 that was previously reported for this age group (*11*). Indeed, the relationship between TBNa and TBCl, TBK, and TBCa are all in good agreement with the previous findings in 42 normal women. The value for Na_{es} was not statistically different from the previously reported value. By chi-square test of goodness of fit, the hypothesis that the distributions of TBNa and TBCl were distributed as in other normal women could not be rejected (Figs. 1 and 2). The previously derived equations based on weight and height (*11*) predicted the TBNa in these subjects with reasonable reliability (Fig. 3).

Endocrine patients. The values for TBNa and Na_{es} for the endocrine patients are given in Table 2. Adjustments must be made for age and sex differences to allow intercomparisons among the various groups and with a normal population (*11*). For example, the high value for Na_{es} in acromegaly in Table 2 resulted from a preponderance of males in the acromegalic group (Na_{es} is normally higher in men than in women). Therefore, the observed values were compared for statistically significant differences from normals matched for age and sex, using the t-test of independent data (*11*). In Fig. 4, the data are expressed as the percentage above or below the values predicted for the endocrine patients (based on age and sex) (*11*). Only those parameters where the observed and predicted values were significantly different are presented in this figure.

The TBNa/BSA (TBNa divided by body surface area) was significantly increased in all patients except those with Cushing's syndrome. The TBNa was increased by 37, 6, 14, and 13% in the acromegalic, Cushing's, thyrotoxic, and hyperparathyroid subjects, respectively, but the increase apparently present in the patients with Cushing's syndrome was not statistically significant.

The sodium-excess value was decreased significantly in the patients with thyrotoxicosis but was not altered in patients with the other conditions. The Na_{es}/Ca ratios

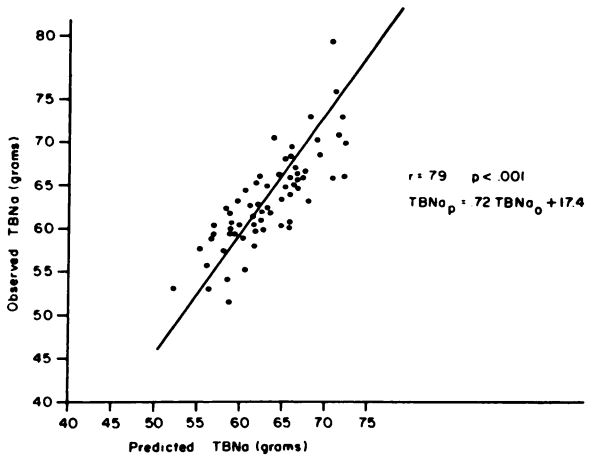

FIG. 3. Relationship between the TBNa observed ($TBNa_o$) in postmenopausal women to that predicted ($TBNa_p$) based on weight and height ($TBNa_p = W^{0.296}H^{1.1458}$, where $TBNa_p$ is in grams, W is weight in kilograms, and H is height in meters).

TABLE 2. TOTAL-BODY ELECTROLYTES AND SODIUM EXCESS (Na_{es}) IN PATIENTS WITH ENDOCRINE DISORDERS (MEAN ± s.d.)

Subjects	(N)	Na/BSA* (g/M^2)	Na/Ca (g/g)	Na/Cl (g/g)	Na/K (g/g)	Na_{es} (g)	Na_{es}/Ca (g/g)	Na_o/Na_p†	Ca/Ca_p†
Acromegaly	(9)	59.5‖	0.099‖	1.11	0.86‖	30.9	0.025	1.37*	1.080§
		±3.9	±0.008	±0.08	±0.14	±9.3	±0.006	±0.08	±0.130
Cushing's syndrome	(7)	37.5	0.083	0.99	0.82	16.3	0.021	1.06	0.859‖
		±6.8	±0.014	±0.18	±0.11	±6.5	±0.007	±0.16	±0.121
Thyrotoxicosis	(10)	43.6‖	0.090‖	1.00	0.84	15.3¶	0.019	1.14‖	0.800‖
		±3.6	±0.010	±0.09	±0.17	±3.7	±0.007	±0.10	±0.253
Hyperparathyroidism	(9)	41.6§	0.090‖	0.96	0.82	13.6	0.016	1.13‖	0.775‖
		±5.4	±0.006	±0.08	±0.14	±6.4	±0.006	±0.09	±0.258

* BSA as in Table 1.

† NA_o/Na_p and Ca_o/Ca_p represent ratio of values of sodium and calcium actually observed to those predicted by empirically derived equations.

‖ Statistically different from age- and sex-matched normals (t-test for independent data), $P < 0.001$.

§ $P < 0.01$.

¶ $P < 0.02$.

did not differ from the normal values in any group (including thyrotoxicosis). There was a close relationship between the Na_{es} and TBCa in Cushing's syndrome ($r = 0.75$, $P < 0.01$), hyperparathyroidism ($r = 0.69$, $P < 0.01$), and acromegaly ($r = 0.72$, $P < 0.01$), but a significant correlation was not observed in the patients with thyrotoxicosis. A close correlation ($r = 0.66$, $P < 0.001$) was also noted between the Na_{es} value and the TBCa ratio (the ratio of the observed to predicted TBCa, an estimate of increased or decreased bone mass).

DISCUSSION

The foregoing correlation observed in the endocrine disorders associated with increased or decreased skeletal mass (TBCa), suggests that the nonexchangeable sodium in bone is primarily determined by the amount of bone that is lost or gained as a result of the particular disorder. Furthermore, the Na_{es}/Ca value remained unchanged in a variety of endocrine disorders associated with an increase in the ratio for total-body sodium

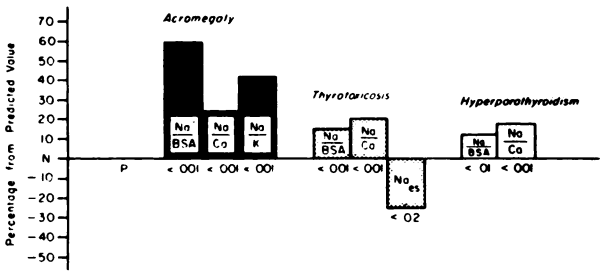

FIG. 4. Ratios in endocrine patients that differed significantly from those of age- and sex-matched normals. Data are expressed as percentages above or below predicted normal values.

(Na_o/Na_p). Thus, no evidence was found to support the contention that bone acts as a reservoir for sodium when there is an increase in the total-body sodium burden.

We have previously noted that the changes in body composition in acromegaly are consistent with the effects that would be predicted, based on the metabolic actions of growth hormone (*22*). Besides increasing the fat-free protoplasm, which requires increments in total-body levels of K, Cl, P, and Na, growth hormone is antinatriuretic, resulting in a still greater increment in TBNa. This is associated with an increase in total-body water and in the chlorine space.

An increase in body sodium was expected in thyrotoxicosis and Cushing's syndrome, since these conditions are associated with an increase in exchangeable sodium. The failure to demonstrate a marked increase in TBNa in Cushing's syndrome may have resulted from the normalization of TBNa by body surface area, which also increases in Cushing's syndrome. The increase in body sodium in the hyperparathyroid patients may have been the result of secondary hyperaldosteronism caused by hypercalcemic nephropathy.

The current study confirms previous observations concerning the relationship of TBNa to body size, lean body mass (TBK), and skeletal mass (TBCa) (*11*). Total-body sodium can be predicted with reasonable reliability ($r = 0.79$) from previously derived relationships between body weight and height (see Fig. 3). The hypothesis that TBNa and TBCl were distributed as in other normal women could not be rejected, which suggests that the postmenopausal population is homogeneous for these elements. The constancy of the total-body Na/Cl ratio in the patients with endocrine disorders is noteworthy. Despite marked changes in body

composition of calcium, potassium, or sodium, the ratio of TB Na/Cl remained unchanged.

ACKNOWLEDGMENT

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ERRATUM

This figure was originally printed with the wrong orientation in "Thyroid Carcinoma in an Autonomously Functioning Nodule," by Muhammad Abdel-Razzak and James H. Christie (*J Nucl Med* 20: 1001-1002, 1979).