Development and Regulation of Calcium Metabolism in Healthy Girls\textsuperscript{1,2,3}

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ABSTRACT The major components of calcium metabolism, as evaluated by a dual-tracer stable isotope method, were determined in 100 studies of 68 healthy girls, aged 5–18 y and analyzed from a developmental and regulatory viewpoint. Bone calcium deposition and removal rates were closely correlated with the size of the exchangeable bone calcium compartment. All three quantities, as well as intestinal calcium absorption, peaked at or near menarche. Both bone calcium deposition and removal rates were positively and linearly correlated with calcium absorption. However, in this correlation, because bone calcium deposition increased 70\% faster than calcium absorption, most of the increase in the bone calcium compartment and its turnover must have occurred in response to something other than intestinal calcium input; presumably this occurred in response to developmental signals. Nevertheless, the constancy of the serum calcium in the face of a large intestinal calcium input and the modest way in which excretion overcame the calcium load in this population point to the importance of the exchangeable bone calcium compartment, in dynamic equilibrium with the bone mineral, as the site at which most of the load is taken up. In this population of girls, as in older women, this increase in the skeletal calcium balance resulted from a decrease in the bone calcium removal rate that was greater than the corresponding increase in the bone calcium deposition rate. \textit{J. Nutr.} 128: 1474–1480, 1998.

KEY WORDS: • calcium absorption rate in healthy girls • bone calcium deposition rate • bone calcium removal rate • exchangeable bone calcium • age-dependent changes

Calcium is a principal element of bone mineral. To understand skeletal development demands not only knowledge of the time course of calcium accumulation by the skeleton, but also of the time course of the rates of calcium deposition and removal in the skeleton and of calcium absorption and excretion by the body, i.e., the components of the body's calcium metabolism. Definition and quantitation of the components of calcium metabolism became possible with the availability of calcium isotopes, initially as radioisotopes (Aubert and Milhaud 1960, Bronner 1982, Bronner et al. 1956, Heaney et al. 1964, Neer et al. 1967) and, more recently, as stable isotopes (Abrams et al. 1992, 1994 and 1996, Moore et al. 1995, Yergey et al. 1990). Because the latter present no risk to human subjects, they can be used in studies of children and adolescents (Abrams et al. 1991a and 1991b, Mauras et al. 1994, Wastney et al. 1996). Evaluation of the major components of calcium metabolism also makes it possible to infer how these components might function in regulation. The body calcium pool is made up of the plasma calcium in rapid exchange with three other calcium compartments, the largest of which represents calcium in rapid exchange with the calcium in bone mineral (Aubert and Milhaud 1960, Bronner 1982, Neer et al. 1967). In adults, the constancy of the body calcium pool in response to an increase in calcium input, as via increased absorption, is largely brought about by a decrease in the bone calcium removal rate, \(v_{o--}\); excretion under these circumstances increases only a little, and the bone calcium deposition rate, \(v_{o++}\), is raised just barely (Bronner 1982).

We now report an analysis of how the major components

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\textsuperscript{*}Abbreviations used: BCaC, exchangeable calcium compartment in bone; [Ca], plasma calcium concentration; \(v_a\), true calcium absorption rate; \(v_o--\), excretion rate of endogenous fecal calcium; \(v_o++\), bone calcium deposition rate; \(v_u\), bone calcium removal rate; \(v_u/v_{BCaC}\), bone calcium deposition rate divided by the size of the bone compartment of exchangeable calcium. The units of mass used in this article are mg Ca; 1 mg Ca = 0.025 mmol. Plasma concentrations are mg Ca/dL = 2.5 mmol/L.

of calcium metabolism vary with age in a group of 68 healthy girls, black, white and Hispanic, aged 5–18 y, 32 of whom were studied twice at a 2-y interval, thus yielding a total of 100 kinetic and metabolic studies. This permits us also to examine whether and how regulation of calcium metabolism, i.e., the relationship between components, is altered in the course of this crucial 13-y period.

SUBJECTS AND METHODS

Sixty-eight girls, aged 5–18 y, recruited for the study by public advertising, served as subjects. The girls had no chronic illnesses that required regular use of medication. Children with asthma that required regular medication were specifically excluded. Thirty-two of these healthy girls were studied twice, at 2-y intervals. All subjects denied substance abuse and, together with parents, completed a medical history questionnaire. Written informed consent was obtained from a parent or legal guardian for each study; written assent was obtained from girls ≥ 7 y. The Institutional Review Board of Baylor College of Medicine approved this protocol.

The protocol, the use of stable isotopes, 46Ca given orally and 42Ca injected intravenously, sample analysis, calculations and statistical evaluation have been previously described (Abrams et al. 1991a and 1994, Mauras et al. 1994, Yergey et al. 1990). In brief, the oral tracer, allowed to equilibrate overnight in 120 mL of milk, was drunk at the end of breakfast of the study day. The breakfasts consisted of eggs, toast and either bacon or sausage for those girls who habitually consumed either. The diets were individualized so as to represent the usual meals eaten by each subject, with the calcium intake at breakfast constituting one third of a person’s daily intake.

At the end of the breakfast, 42Ca was infused intravenously over a 3- to 5-min period. All quantities of isotope were weighed before and after administration. Milk was drunk under staff supervision and glasses were rinsed with water to ensure that all isotope was ingested. Records of the diets eaten during the first 24 h spent by the subjects in the metabolic unit and of the subsequent 48 h spent at home were analyzed.

Blood samples were obtained just before breakfast and at 6, 12, 30, 45, 60, 120, 240 and 480 min after isotope infusion. Blood plasma and urine were analyzed for total Ca concentration, as well as for their content of the two stable isotopes.

Samples were prepared for mass spectrometric analysis by oxalate precipitation and analyzed for isotopic enrichment with a magnetic sector TIMS (Finnigan 261, Bremen, Germany). Accuracy, compared with standard data, was 0.15% and precision, including sequential measurements, was 0.2%.

Fractional dietary absorption of calcium was calculated by dividing the first 24-h total in the urine of the isotope given by mouth by the equivalent total in the urine of the isotope given by vein. This fractional absorption, multiplied by the mean 3-d calcium intake based on the dietary records, yielded the value for true calcium absorption, v0 (Yergey et al. 1994).

The kinetic components were evaluated from a three-compartment model with the aid of the SAAM (simulation, analysis and modeling) program to yield numerical values for compartments 1 (equivalent to compartments 1 plus 2 of Neer et al. 1967), 2 (equivalent to compartment 3 of Neer et al. 1967) and 3 (equivalent to compartment 4 of Neer et al. 1967), as well as for the rates of calcium deposition in bone, vBCaC, and removal from bone, v0. Compartment 3 is the exchangeable calcium compartment of bone, BCaC.6

Statistical analysis was with the aid of Statview 4.5 (Abacus Concepts, Berkeley, CA) and utilized least-squares relationships and ANOVA. The mean values of slopes and intercepts are shown with SEM in parentheses. Degrees of freedom, F-values and probability values are indicated for all least-squares relationships of independent variables.

FIGURE 1 Correlation between the exchangeable bone calcium compartment (BCaC) and the rates of bone calcium deposition (vBCaC) (panel A) and bone calcium removal, (v0) (panel B) in 68 girls (100 studies), 5–18 y.

(A) vBCaC = 507 (133) + 0.39 (0.05) BCaC units: mg Ca/d

(B) v0 = 429 (127) + 0.37 (0.04) BCaC units: mg Ca/d

Numbers in parentheses are standard errors of their respective means.

RESULTS

The exchangeable calcium compartment in bone (BCaC) is in rapid, near-instant equilibrium with surface bone calcium in the solid state. (For a more detailed analysis of this point, see Abrams et al. 1994, Bronner and Stein 1995 and Heaney 1976.) The rates at which bone calcium is deposited or removed were a positive linear function of the size of this compartment at all ages studied here (Fig. 1). It is therefore not surprising that age dependencies of the bone calcium compartment, its turnover rate and of the rates of bone calcium deposition and removal were comparable (Fig. 2), all rising to a peak at 11–12 y of age in the population of girls studied here.

The nature of that peak can be examined by asking questions about compartmental regulation. In a given individual, compartment size is considered constant at any one time. When disturbed, as by calcium entry from the gut, the body attempts to maintain compartment size by increasing excretion, diminishing bone calcium resorption and increasing bone calcium deposition. Inasmuch as the difference between re-

6 In a two-compartment model (Bronner and Lemaire 1969, Heaney 1976), the second compartment is approximately equal to BCaC (Bronner 1964).
Calcium is stored in the skeleton, as is well known. In the balance. In other words, as calcium absorption increases, more the former and increase in the latter will increase the calcium regulate the plasma calcium (see below). As shown in Figure 1, BCaC, treating mineralization as the leading function. He explained this relationship as “an expression of the important role played by surface bone calcium in the rapidly exchanging compartment of the pool,” at least in the normal situation.

The findings reported here can be analyzed in terms of age, i.e., how development affects the intensity of each component. They can also be analyzed from the systems viewpoint, e.g., whether the correlation between components such as BCaC and $v_{o+}$ changes with developmental age.

Figure 1 shows that throughout the age range studied here, a direct linear relationship existed between the size of the bone calcium compartment, on the one hand, and the rates of bone calcium deposition and removal, on the other. The bone calcium compartment represents the soluble calcium that is in equilibrium with surface bone calcium in the solid state. Therefore it is not surprising that a linear relationship existed between the size of the compartment and the rates of calcium entry or removal. From these relationships it is not clear, however, which is the leading function, the rate of deposition or removal on the one hand, or compartment size, on the other.

Heaney (1976) showed some years ago that there was a positive linear relationship in women between mineralization, presumably related to $v_{o+}$, and the bone calcium pool, BCaC, treating mineralization as the leading function. Rodan (1997) has suggested that the body attempts to maintain its bone mass constant by modulating deposition or removal rates, with mechanical stimulation acting as a “coupling factor” between formation and resorption. Bone mass is a resultant of a variety of genetically programmed processes, involving endocrine, enzymatic and growth factors, all of which directly and indirectly must modulate bone calcium deposition and removal. We therefore think it is logical to treat $v_{o+}$ and $v_{o-}$ as feedback responses to changes in BCaC (Fig. 1). BCaC changes in response to $v_{o+}$ (Fig. 4), acting to regulate the plasma calcium (see below). As shown in Figure 2, the exchangeable bone calcium compartment (BCaC) and the rates of bone calcium deposition ($v_{o+}$) and removal ($v_{o-}$) as a function of age in 68 girls (100 studies), 5–18 y. The box plots were done for subjects 5–6 y ($n = 7$), 7–8 y ($n = 12$), 9–10 y ($n = 19$), 11–12 y ($n = 22$), 13–14 y ($n = 23$) and 15–17 y ($n = 17$). The square dot represents the mean value, the horizontal line in the box the median value, the upper and lower lines of the box include individual values in the 25–75% range; the uppermost and lowermost lines include individual values in the 10–90% range. Analysis of the relationship between $v_{o+}$ and $v_{o-}$ reveals that these rates varied linearly with one another, but that an increase in $v_{o+}$ was accompanied by a 70% increase in $v_{o-}$ (Fig. 3B). The rate of bone calcium removal also increased linearly with $v_{o+}$ (Fig. 3B). However, the value of the slope of the relationship between $v_{o+}$ and $v_{o-}$ was only half the corresponding value in the relationship between $v_{o+}$ and $v_{o-}$ (Fig. 3B). Thus, in these girls, the disturbance to pool size due to entry of calcium from the gut via $v_{o+}$ was overcome by a lesser increase in $v_{o-}$ than in $v_{o+}$.

Figure 4 shows that urinary calcium excretion, $v_{o-}$, in this population contributes to the regulation of pool size and bone calcium deposition only to a minor degree, because a mere 11% of an increase in calcium absorption was excreted in the urine. No direct measurements of endogenous fecal calcium excretion, $v_{endo}$, were made in this population; however, on the assumption that $v_{endo}/v_{o-}$ approximates unity in humans (Bronner 1982, Heaney et al. 1977), it is apparent that only about a quarter of the calcium input into the body was handled by excretion, the remainder going to the skeleton.

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1 Values describing the rates of true calcium absorption, $v_{o+}$, and of bone calcium deposition, $v_{o+}$, have previously been reported (Abrams et al. 1996) for some of the subjects.

2 For discussion of the role of muscle mass and function in determining bone mass, see Frost (1990a, 1990b and 1997).
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FIGURE 3  Correlation between calcium absorption (v_a) and age (panel A) and bone calcium deposition (v_o, panel B) and removal (v_o0, panel C), and with BCaC (panel D). (A) True calcium absorption, v_a, as a function of age in 68 girls (100 studies), 5–18 y. The age range and significance of the box plots are as in the legend of Figure 2. (B and C) Correlation between bone calcium deposition, v_o, or bone calcium resorption, v_o0, and true calcium absorption, v_a, mg/d, in 68 girls (100 studies), aged 5–18 y.

(B) \[ v_o = 1050 (140) + 1.74 (0.4) v_a \] (df = 99; F = 18.4; P < 0.0001; \( r^2 = 0.16 \))

(C) \[ v_o0 = 1165 (141) + 0.93 (0.4) v_a \]

Numbers in parentheses are standard errors of their respective means. (D) Correlation between the size of the exchangeable bone calcium compartment, BCaC, and true calcium absorption, v_a, mg/d, in 68 girls (100 studies), aged 5–18 y.

\[ BCaC = 1964 (245) + 2.7 (0.7) v_a \] (df = 98; F = 14.3; P = 0.0009; \( r^2 = 0.13 \))

Numbers in parentheses are standard errors of their respective means.

5, the response by [Ca_s] to changes in v_a is very small indeed, whereas BCaC responds significantly.

All three components of calcium metabolism, BCaC, v_o, and v_o0 vary with age in similar fashion and peak at about the same time, at or near the menarche (Leitch and Aitken 1959, Mitchell 1939; Fig. 2). This suggests that all three are developmentally regulated in the same fashion. With the bone calcium compartment in equilibrium with the mass of the bone mineral, it seems reasonable to infer that the various processes that cause bone mass to grow also regulate the deposition and removal rates.

In turn, these rates, together with the excretion rates, regulate the size of the bone calcium compartment by feedback mechanisms. At any given developmental time, an increase in calcium absorption would tend to increase the body calcium pool and therefore the bone calcium compartment. To maintain the compartment size constant, calcium excretion and/or the difference between bone calcium deposition and removal must be increased. In girls (Fig. 4; Wastney et al. 1996) and in adult women (Bronner 1982, Wastney et al. 1996), urinary calcium output accounts for only a small fraction of the calcium input from the intestine, with endogenous fecal calcium responding in a comparably modest fashion (Bronner 1982, Heaney et al. 1977). No direct measurements of endogenous fecal calcium excretion, v_ndo, were made in the population of girls studied here, but, on the assumption that v_u/v_u0 approximates unity in humans (Bronner 1982, Heaney et al. 1977), it is apparent that only about a quarter of the calcium input into the body was handled by excretion, the remainder going to the skeleton.
The bone calcium compartment, BCaC (Fig. 3D), and \( v_{0.4} \) (Fig. 3A) increased in response to an increase in \( v_a \). However the rates of increase of BCaC and of \( v_{0.4} \) far exceeded the rate of increase of \( v_a \). That can only mean that the bone calcium compartment in the girls turned over much more quickly than the rate per unit time at which calcium entered the body via intestinal absorption. The impetus for this high turnover must, we think, be sought in the developmental history of our subjects. One observation in support of this inference is that when the data from girls in Tanner stages 1–5 were analyzed separately by Tanner stage, the slopes of the correlations between \( v_a \) and \( v_{0.4} \) increased in each of the first four stages, exceeding unity at stage 4, and thereafter fell below unity. However, the number of studies per stage was insufficient for statistical significance.

The steady-state plasma calcium level is the resultant of net intestinal calcium input, urinary calcium excretion and net bone uptake, with the bone calcium compartment serving as the first storage compartment. Plasma calcium can therefore remain closer to its “set value.” This was certainly true in our population. Serum calcium increased by only 0.65% for an increase in calcium absorption, \( v_a \), of 100 mg/d (Fig. 5), whereas the much larger bone calcium compartment, BCaC, increased by 14% (Fig. 3D).

The high rate of turnover of the bone calcium compartment and the high rate of skeletal growth at menarche notwithstanding, the mechanisms of response by \( v_{0.4} \) and \( v_{0.40} \) to an increase in calcium input from the gut, \( v_a \), seem similar in girls and women. The justifications for this statement come from a comparison of the slopes of the two correlations, \( v_{0.4} \) with \( v_a \), and \( v_{0.40} \) with \( v_a \) (legends Figs. 3B and 3C). The fact that the slope of the correlation between \( v_a \) and \( v_{0.4} \) is only half of the value of the slope of the correlation between \( v_a \) and \( v_{0.40} \) means that when the calcium load from the gut increases, \( v_{0.40} \) goes up less rapidly than does \( v_{0.4} \), so that the bone balance, i.e., \( v_{0.4} - v_{0.40} \), increases.

Qualitatively, the same process occurs in adults, with the bone calcium balance increasing as intestinal calcium input rises. In adults, however, the rates of change are slower than in the girls (Figure 7; Bronner 1982, Schwartz et al. 1985).\(^8\)

It stands to reason that as the skeletal mass approaches its programmed maximum in the third decade of life (Bronner 1994), the rate of bone calcium deposition approaches a low

\[ v_{0.4} = 56 (15) + 0.11 (0.04) v_a \quad (df = 89; F = 7.47; P = 0.008; r^2 = 0.08) \]

Numbers in parentheses are standard errors of their respective means.

\[ v_{0.40} / BCaC = 0.95 (0.06) - 0.03 (0.004) y \]

Numbers in parentheses are standard errors of their respective means.

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\(^8\)The bone calcium balance equals the body calcium balance, provided the body calcium pool is constant at a given moment. Therefore, body calcium balance = \( v_{0.4} - v_{0.40} \). In adults, this relationship is (Bronner 1982) as follows: \( v_{0.4} - v_{0.40} = -113 + 0.77 S_i \), where \( S_i \) is the net calcium absorption, i.e., \( v_a - v_{0.4} \). A portion of \( v_a \) is subject to regulation (Bronner 1987), but much is not. Therefore, \( v_{0.4} \) like \( S_i \), can be considered to be a disturbing signal.
exchangeable calcium compartment of bone, and the rates of bone calcium deposition and removal, peak at or near the time of menarche, as does calcium absorption. The developmental course affects the regulatory role in that in this population of girls, the bone formation rate appears to respond strongly to increased calcium input from the gut, whereas this is not the case in adults. Quantitative analysis reveals, however, that the rate of bone formation, which in turn is tied to the size of the exchangeable calcium compartment, is so much greater than the rate of calcium input that turnover must be linked more strongly to development than to calcium regulation. Nevertheless, the underlying pattern of regulation is preserved; the disturbance due to a calcium load is overcome by a greater decrease in bone calcium removal than by a corresponding increase in bone calcium deposition. As a result, plasma calcium increases by less than 4% when calcium absorption increases 600 times.11

LITERATURE CITED


11 Data analysis has been based on the totality of studies. Exclusion of the second studies conducted on 32 subjects, yielding 68 instead of 100 data points, would not alter the relationships. For example, the slope of the equation describing \( \frac{v_{e}}{BCaC} \) as a function of age remains at \(-0.03\), the slope of the equation correlating \( v_{o} \) with \( v_{e} \) is 1.5 instead of 1.7, and the slope of the correlation between \( v_{o} \) and \( e \) is 0.6, instead of 0.9.

\( \frac{v_{o}}{BCaC} \) decreases monotonically until the age of 18 y at the rate of 3%/y. This means that with time, \( v_{o} \) plays a diminishing role in maintaining the size of the compartment containing the calcium in solution that is in rapid exchange with bone calcium in the solid state. After the age of 18 y, the ratio \( \frac{v_{o}}{BCaC} \) no longer decreases at the rate of 3%/y. In postmenopausal women, in their sixth decade, \( \frac{v_{o}}{BCaC} \) approximates 0.23 (Bronner and Lemaire 1969), about half the value for 18-y-old girls (Fig. 6). This represents a rate of decrease of about 0.5%/y.

In their analysis of calcium kinetics, Wastney et al. (1996) indicated that the fraction of calcium deposited in bone, equivalent to \( \frac{v_{o}}{BCaC} \), did not vary with postmenarcheal age. Figure 6 covers only about 5 postmenarcheal years. If one eliminates four low values that may be outliers, from the data of Wastney et al. (1996) (their Fig. 6F), their data also show a downward trend between \(-1\) and 5 y postmenarche. Their value for women 20 y after menarche is 0.18, a value actually about half the value for 18-y-old girls (Fig. 6). This represents a rate of decrease of about 0.5%/y.

In conclusion, it is of interest that maturation of the skeleton finds different expressions, depending on which compartment of calcium metabolism is analyzed. Thus, size of the

10 Wastney et al. (1996) explain the discrepancy between their data and the earlier data by Abrams (1993), which also showed a decrease of \( \frac{v_{o}}{BCaC} \) as a function of postmenarcheal age, as due to an overestimation of \( v_{o} \) and \( BCaC \). If a four-compartment model is collapsed into a two-compartment model, compartment sizes are overestimated, but this overestimation is both small and constant (Bronner and Lemaire 1969) and cannot explain the discrepancy. In the current report, moreover, compartment sizes and turnover rates were derived from a three-compartment model with the aid of the SAAM (Simulation, Analysis and Modeling) program (Abrams et al. 1996), similar to the model utilized by Wastney et al. (1996).