Calcium balance in 1–4-y-old children[1-4]

Mary Frances Lynch, Ian J Griffin, Keli M Hawthorne, Zhensheng Chen, Maria Hamzo, and Steven A Abrams

ABSTRACT

Background: Few calcium balance data are available from young children on which to base dietary recommendations.

Objective: The objective of the study was to evaluate the relation between calcium intake and balance in healthy children aged 1–4 y consuming typical American diets.

Design: Subjects were assigned to a diet with nutrient intakes similar to those of their usual diet. Calcium absorption was assessed by using a dual-tracer stable-isotope technique. Endogenous fecal excretion was measured in a subset of children, and net calcium balance was calculated.

Results: Mean calcium intake was 551 mg/d (range: 124–983 mg/d), and mean ($\pm$SEM) calcium retention was 161 ± 17 mg/d. Both linear and nonlinear modeling of balance data showed that a calcium intake of $\approx$470 mg/d led to calcium retention of 140 mg/d, which is the amount that meets expected bone growth needs in children of this age. No evidence was found that calcium intakes of 800 to 900 mg/d reached the threshold intake beyond which no additional increase in calcium retention would occur.

Conclusions: Bone growth needs in 1–4-y-old children following American diets are met by a daily calcium intake of $\approx$470 mg/d, which suggests that the current Adequate Intake of 500 mg/d is close to the actual Estimated Average Requirement. The benefits and risks of higher calcium intakes consistent with threshold values should be evaluated in a controlled trial before those intakes could be used as a basis for dietary recommendations.   *Am J Clin Nutr* 2007;85:750–4.

KEY WORDS   Calcium absorption, stable isotopes, bioavailability, nutrient requirements

INTRODUCTION

In 1997, new dietary guidelines for minerals (including calcium) were released by the Institute of Medicine. At that time, because a perception existed of limited available data on which to base an Estimated Average Requirement (EAR) and a Recommended Dietary Allowance (RDA) for calcium, intake recommendations were limited to the use of an Adequate Intake (AI) and a Tolerable Upper Limit (UL) (1). Since 1997, considerable data on calcium requirements have been reported for most population groups, and it is reasonable to believe that an EAR could be established for adults and adolescents (2, 3). This possibility has clear importance because the EAR is an important aspect of food labeling and dietary planning guidelines (4, 5).

One group for which minimal data have been available is young children, especially those who are <4 y old (1, 6). It is well recognized that dietary patterns are different in this age group than in infants or older children (1, 2, 4, 7), and because of this difference, special food-labeling guidelines are in place for these age groups (4). However, no data are available on which to rationally base a calcium EAR for this age group. Essentially, all recommendations have adapted data obtained in other age groups (1) or have combined the <4-y-old group with children aged 4–8 y to estimate calcium requirements for prepubertal children (8, 9). The minimal available data on calcium balance in young children were generated many years ago; those data may have substantial systematic errors and do not reflect current typical diets (6, 10).

The principal reason for the absence of data in this age group is the impracticality of prolonged dietary regulation and complete urine and fecal collections that are required for traditional balance studies especially in active children who are often not toilet-trained. Studies in this age group are now more feasible with stable-isotope methods in which calcium absorption can be directly assessed with a short-term urine collection (11).

Further complicating the understanding of dietary calcium requirements for young children is the fact that the usual daily intake in the United States (median: 766 mg/d) is much higher than the AI of 500 mg/d (1). Therefore, in the current study, our goals were to evaluate the relations among calcium intake, absorption, and retention in healthy young children across a range of dietary calcium reflecting both the AI and typical intakes and to relate these data to bone growth needs so as to develop a candidate EAR.

SUBJECTS AND METHODS

Subjects

Healthy children aged 12–48 mo residing in the greater Houston area were recruited through public advertising. Subjects were selected to reflect the approximate racial and ethnic distribution of

the greater Houston area. No subjects aged 12–14 mo were enrolled, and thus the final age range for the subjects was 15–48 mo.

Written informed consent was obtained from each subject's parents for all studies. The Institutional Review Board of Baylor College of Medicine and Affiliated Hospitals approved the protocol.

Methods

Screening visit

Children were eligible for enrollment if they were healthy, were not taking any medications except multivitamins, were born at term ($\geq$37 wk gestation), and had a birth weight $\geq$2500 g. Children were excluded from participating if they had chronic health problems, were below the 3rd or above the 97th percentile of weight or height-for-age, or were below the 5th or above the 95th percentile of weight-for-height. Those subjects taking multivitamins were required to discontinue their use 2 wk before their participation in the mineral absorption study. Families were offered the option of participating in a 2-d calcium absorption study or a 5-d study in which fecal samples would also be collected and endogenous excretion would be measured.

The research dietitian met with each subject's parents and obtained a 24-h diet history to evaluate the usual daily micronutrient and calorie intake. To reflect the marketplace, dietary intake data were analyzed with the use of NUTRITION DATA SYSTEM FOR RESEARCH software (versions 5.0 and 2005; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). Final calculations were completed with the use of version 2005.

A plan was developed for the diet that each child would consume at home for the 7 d before the inpatient mineral absorption study. This step was taken to ensure that children did not alter their eating habits immediately before the mineral absorption study. All foods and beverages to be consumed during these 7 d were provided by the research center and were weighed before delivery to the family for the period before the mineral absorption study (the prestudy period). Parents were instructed to return all uneaten food and beverage items from the first 3 d of the weeklong prestudy period so that the unconsumed items could be weighed.

Isotope preparation and mineral absorption study

We purchased ^{42}Ca (94% enrichment) and ^{46}Ca (6% enrichment) from Trace Sciences (Toronto, Canada), and they were prepared for human use as the chloride salt by the Investigational Pharmacy Service of Texas Children's Hospital (TCH), Houston, TX. All isotopes were tested for sterility and pyrogenicity before use.

At the end of the home pack-out period, patients were admitted to the General Clinical Research Center at TCH for the calcium absorption study. On the morning of the inpatient study, a heparin-lock intravenous catheter was placed with the use of topical 4% lidocaine cream (L-M-X-4; Ferndale Laboratories, Ferndale, MI) as an analgesic. Subsequently, 15 μg ^{46}Ca was given intravenously over 1 min. The subgroup of subjects in whom endogenous fecal calcium was being measured received a larger dose, 40 μg ^{46}Ca, which was given intravenously. Subjects were then given breakfast that included 30 mL calcium-fortified apple juice (Minute Maid; Coca-Cola Company, Atlanta, GA). The juice contained 15 mg Ca to which a

further 2 mg ^{42}Ca had been added. After the subject consumed the isotope-containing juice, the subject consumed another 30 mL calcium-fortified apple juice without isotope from the same cup as a rinse to ensure that none of the isotope was left in the cup. This process was repeated at lunch with the use of the same amount of isotopes as at breakfast.

Each breakfast provided approximately one-third of the daily mineral intake of the subject. The remaining intake was divided between lunch, dinner, and 2 small snacks. Menus for the inpatient study visit were based on each subject's usual mineral intake that he or she had received at home for the previous 7 d. All foods and beverages provided during the inpatient visits were weighed before the visit, and the unconsumed foods and beverages were weighed after the visit to measure intake. Dietary intakes used in the results section were based on these intakes.

Subjects remained in the inpatient unit for 48 h, and their urine was collected in 24-h pools for the duration of their hospitalization. If the subject was not well toilet-trained, urine bags were used for the sample collection. The subset of subjects in whom endogenous fecal excretion was measured remained in the inpatient unit for 120 h, during which time their urine and stools were collected in 24-h pools.

Calculation of mineral absorption

Urine samples were prepared for mass spectrometric analysis by using an oxalate precipitation technique as previously described (11). Samples were analyzed for isotopic enrichment with the use of a magnetic sector thermal ionization mass spectrometer (Finnigan MAT 261; Finnigan, Bremen, Germany). Each sample was analyzed for the ratio of ^{42}Ca to ^{43}Ca and ^{46}Ca to ^{43}Ca with correction for fractionation to the reference ^{44}Ca to ^{43}Ca. The accuracy and precision of this technique for natural abundance samples compared with those of standard data are $\geq$0.15%, depending on the ratio being measured.

Calcium absorption was calculated as the relative recovery in the urine of the oral isotope divided by the recovery of the intravenous isotope during the 24 h after isotope administration (from time of the first oral dose until 24 h after the last oral dose). The endogenous fecal excretion of calcium was calculated as the ratio of urinary to fecal recovery of the intravenously administered isotope by using the equations described previously (12, 13). Mineral balance was calculated as the difference between total dietary absorption (the product of intake and fractional absorption) and the sum of urinary and endogenous fecal excretion.

Sample size and statistical analysis

Data were analyzed by using SPSS for WINDOWS software (version 13; SPSS Inc, Chicago, IL. Power calculations were carried out by using DSTPLAN (version 4.2; MD Anderson Cancer Center, Houston, TX). All results are shown as means $\pm$ SEMs.

Previous studies suggested a correlation coefficient (r) of 0.5 between calcium intake and net calcium balance in this age range (6). A sample size of 25 has an 80% power of detecting this degree of correlation at $P < 0.05$.

RESULTS

Subject demographics

Calcium absorption was measured in 28 subjects (14 boys and 14 girls). The ethnic distribution of the study population was 46%

TABLE 1
Subject characteristics[1]

Characteristic	Value ($n = 28$)
Age (mo)	30 ± 2 (15–48)
Weight (kg)	12.6 ± 0.4 (9.5–16.3)
Height (cm)	88.9 ± 1.6 (74.2–102.3)
Calcium intake (mg/d)	551 ± 41 (124–983)

[1] All values are $\bar{x}$ ± SEM; range in parentheses.

white, 29% Hispanic, 18% African American, and 7% multiethnic. Ethnicity and sex were initially considered as a covariate in each analysis but did not significantly affect the relations between calcium intake and absorption or excretion and were omitted from further analyses. The baseline characteristics of the study group are shown in **Table 1**. Eight subjects agreed to and completed the 5-d studies in which endogenous fecal calcium excretion was measured. The baseline characteristics of this subgroup did not differ significantly from those of the group as a whole (mean age: 26 ± 3 mo; weight: 12.5 ± 0.8 kg; height: 87.0 ± 2.8 cm; calcium intake: 563 ± 70 mg/d). No significant correlation was found between calcium intake and body weight, height, or age for the study subjects ($P > 0.10$ for each).

Relation between calcium absorption and retention

Average calcium intake in study subjects during the mineral absorption study was 551 ± 41 mg/d (median: 513 mg/d). Calcium intakes during the prestudy home dietary period did not differ significantly from those during the study and are not shown. Calcium fractional absorption was significantly and negatively correlated to intake ($r = -0.50$, $P = 0.006$) (**Figure 1**). The use of nonlinear modeling did not increase the correlation between intake and retention. Mean calcium absorption was 45.6 ± 2.5% of intake.

To determine calcium retention, measurement of endogenous fecal excretion in each subject was necessary. We used the mean value obtained from the 8 subjects in whom endogenous fecal excretion was measured (ie, 3.5 mg · kg^{-1} · d^{-1}) for the other 20 subjects, in whom it was not measured. A fixed value was used rather than one based on calcium intake, because no significant
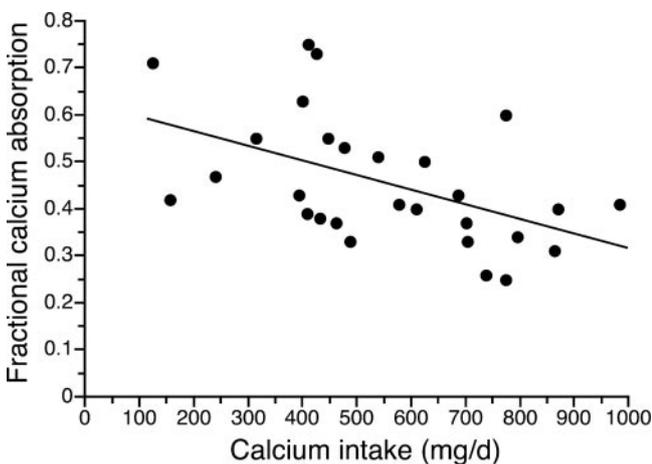

FIGURE 1. Calcium fractional absorption was significantly negatively correlated to intake ($r^2 = 0.26$, $P = 0.006$). The equation for the linear relation was $y = -0.00031 \times x + 0.626$.
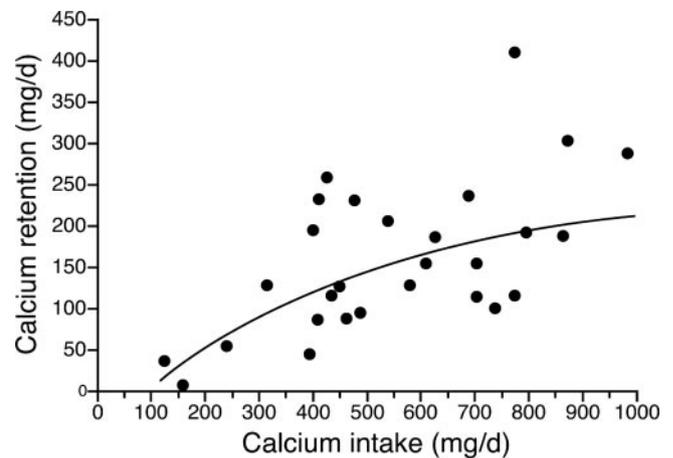

FIGURE 2. In a linear model, the relation between calcium intake and retention was fitted by using the equation $y = 0.25 \times x + 23.6$ ($r^2 = 0.36$, $P < 0.001$). An improved fit was obtained by using an S-curve relation: $y = \text{Exponent}[5.732 + (-373/x)]$ ($r^2 = 0.55$, $P < 0.001$).

relation was found between either calcium intake or total absorption and endogenous fecal calcium excretion in the 8 subjects in whom it was measured. Urinary calcium excretion was that obtained during the first 24 h of the inpatient study. Urinary calcium averaged 2.2 ± 0.2 mg · kg^{-1} · d^{-1} (median: 1.1 mg · kg^{-1} · d^{-1}); 6 subjects had values >4 mg · kg^{-1} · d^{-1}. Mean calcium retention was 161 ± 17 mg/d (median: 142 mg/d) for the whole cohort. For the 8 subjects in whom endogenous fecal excretion was directly measured, the mean calcium retention was 159 ± 29 mg/d. (See Appendix 1 under Supplemental Data in the current issue at www.nutrition.org.)

Relation between calcium intake and retention

We evaluated the relation between calcium intake and calcium retention by using both linear and nonlinear models. With the use of linear regression analysis, the relation between intake and retention was fitted by the following equation:

$$\text{Calcium retention} = 0.25 \times (\text{calcium intake}) + 23.6 \quad (1)$$

where $r = 0.60$. An improved fit ($r = 0.75$) was obtained by using an S-curve relation (**Figure 2**). No close relation was found between calcium intake and fractional retention ($r = 0.05$).

Relations between calcium retention, requirements for growth, and the threshold value

Available data, including weight-based estimates published in the 1950s (14) and dual-energy X-ray absorptiometry (DXA) bone mineral data, showed that calcium accretion to the whole skeleton averages 100–120 mg/d from 1–4 y of age (15, 16). Because calcium balance as performed with isotopes or by using traditional mass-balance techniques does not include dermal (sweat) losses, the dermal loss value must be estimated and added to the skeletal accretion value to determine the requirement for daily calcium retention (1, 8). Estimates of dermal losses of 20 to 40 mg are generally used for prepubertal children (1, 8). Therefore, a mean value of 140 mg/d can be estimated as the required average calcium balance (110 mg/d bone calcium accretion and 30 mg/d dermal loss).

TABLE 2
Calcium intakes needed to achieve various calcium retention (balance) values[1]

	Retention of 100 mg/d	Retention of 140 mg/d	Retention of 180 mg/d	Retention of 200 mg/d
		mg/d		
Linear (this study)	305	465	625	705
S curve (this study)	332	472	691	857
Matkovic and Heaney (6)	603	771	939	1023

[1] Values are derived in which calcium intake values (x, mg/d) are shown to achieve various levels of calcium retention (y, mg/d). The equation for the linear relation was $y = -0.00031 \times x + 0.626$ ($r^2 = 0.36$), and that for the *S* curve was $y = \text{Exponent}[5.732 + (-373/x)]$ ($r^2 = 0.55$); $P < 0.001$ for each.

The calcium intake, calculated from our data and the earlier data (6), needed to achieve a range of calcium retention values is shown in **Table 2**. Both models of our data show that an intake of ≈470 mg/d is required to achieve the 140 mg/d calcium retention needed to meet bone accretion needs and to offset dermal losses.

Another measurement of interest is the calcium intake at which calcium retention reaches or approaches a maximum (1, 2, 8). This value is referred to as a threshold value. Too few subjects in our study had intakes high enough to allow us to estimate this value. Our data (Table 2 and Figure 2) suggest that the threshold intake is ≥850–900 mg/d.

DISCUSSION

We have shown that calcium absorption in 1–4-y-old children is inversely related to usual dietary intake. The amount of retained calcium needed for bone growth according to average rates of bone mineral accretion is achieved at calcium intakes of ≈470 mg/d. This intake is much lower than the amount needed by adolescents for bone growth or the amount needed by adults to prevent bone loss (1, 14, 17). Compared with adults, young children have significantly higher calcium absorption efficiency and significantly lower rates of total calcium excretion (1, 14, 17).

The lack of data in this age group has led to a wide range of estimates for the recommended calcium intake. In the United States, the reference calcium intake is 500 mg/d, which is an AI; and at the time that the AI was set, it was believed that data were not available from which to establish EAR and RDA values (1). However, the AI concept is very limiting for setting dietary policy, and EAR values are available for many other minerals, such as magnesium, for which far fewer balance data are available than for calcium. It is important that an EAR be established for use in processes including revision of food labels and meal planning (4, 5). Establishment of an EAR is likely possible at this time in older age groups because of the large amount of new data generated since the Dietary Reference Intakes process of the mid-1990s, but no similar data have been generated for young children (2, 3, 17).

In general, despite the disparity of techniques and populations studied, estimates of calcium accretion by the skeleton in early childhood have a reasonable consistency over the past 50 y. Mean calcium accretion averages ≈80 mg/d during the first year of life,

increases slightly to ≈100 mg/d during the second year of life (15), and increases to ≈120 mg/d during the preschool and early school years (1, 8, 14–16).

Calcium's absorptive efficiency averaged 46% for a population mean intake of 551 mg/d. This is ≈1.5 SD above the value for estrogen-replete premenopausal women (ie, ≈30 ± 10%) at the same calcium intake (18, 19). Thus, although calcium's absorptive efficiency has been shown to be greater in adolescents than in adults, it appears that, at low calcium intakes, the same is true for infants and young children (20, 21).

Our data indicate that the current AI of 500 mg/d is very close to the actual "average requirement" needed to meet average bone growth requirements. Reasonable rounding of our value would lead to a candidate EAR of 500 mg/d for children 1–4 y of age. Assuming that an additional 30% calcium retention (a total retention of ≈180 mg/d) would meet the needs of 97.5% of the population, the best fit of our data would suggest a candidate RDA of ≈700 mg/d.

Around the world, wide ranges of dietary recommendations exist for calcium in young children. Recommendations generally are expressed as a value whose definition is similar to the RDA—ie, an intake that meets the needs of nearly all members of the population. In the United Kingdom, this value is 350 mg/d, whereas, for the European Union, it is 400 mg/d. A much higher value of 800 mg/d is recommended in Ireland. The calcium intake recommended by the FAO/WHO is 500 mg/d (9, 22). In the United Kingdom, as in the United States, mean calcium intakes are far above the recommended amount, which makes it difficult to assess the consequences of low intakes (22). Ultimately, however, this range of recommendations, more than fundamental variations in diets or genetics, reflects the lack of usable data in this age group.

Another possible approach toward establishing dietary intake recommendations for calcium in children is to identify the threshold intake value—rather than using the average bone growth requirement—as the goal. Various methods may be used to estimate an approximate threshold or determine an intake at which near-threshold retention may reliably be achieved (1, 2, 6, 19). We cannot apply such approaches to our dataset, which is limited by both the small number of studies and the range of intakes. Our data, however, do not provide any evidence for a threshold at intakes of ≈850–900 mg/d.

With the use of a large database of studies mostly performed in the early part of the 20th century, a threshold of 1390 mg/d in children aged 2–8 y was reported (6). The threshold balance of 246 mg/d achieved at this intake was much higher than the usual rate of bone mineral calcium accretion by the skeleton. Although earlier balances likely had falsely elevated retention values for most intakes, the threshold calcium intake may not be affected by systematic errors related to short-term intake transients across the range of intakes (6). Therefore, in contrast to adolescents, in whom there is reasonable convergence between the calcium intake that meets growth needs and the threshold intake, these 2 values in infants (6, 21) and young children (the current study) are markedly different. It is important to note that no data have suggested any short or long-term benefit from high rates of calcium retention in children of this age. Thus, until further data are available, the goal of meeting average bone growth requirements is appropriate (1).

Ultimately, identifying an "optimal" intake in young children, as in infants, can be accomplished only by long-term studies

evaluating the benefits and potential risks of intakes that are above the usual growth needs (23). Such data are extremely difficult to generate, however, and doing so requires studies that begin in the first few years of life and provide follow-up to at least early adolescence. Therefore, revision of the dietary requirements to establish an EAR for calcium cannot await data that may not be available for many decades.

A limitation of our data is the lack of endogenous fecal excretion data in all subjects. However, results in the subjects in which it was obtained are similar to those in previous reports in children (11, 12). It is extremely unlikely that substantial variation occurs in endogenous fecal excretion in young children, and the use of the mean data for nonmeasured subjects should lead to a small potential error in calculated balance. Other limitations are the use of databases to measure the calcium content of the ingested food and the lack of assessment of vitamin D status in these children. We did not find a relation between vitamin D status and calcium absorption in vitamin D–nondeficient older children, and it is unlikely that any of these children were vitamin D deficient (24).

Because of the global existence of both vitamin D and calcium deficiency rickets in the age group we studied, it is important also to consider the effects of very low calcium intakes. Our data indicate that calcium intakes of ≈300 mg/d are consistent with retention of ≈80–100 mg/d, an amount that is likely to represent an approximate minimum for bone growth (after dermal losses) in young children. In areas where large amounts of inhibitors of calcium absorption are present in the diet, a higher minimal intake may be needed. However, in some of those areas, urinary calcium excretion is very low, and, therefore, in the presence of adequate vitamin D, intakes of 300 mg/d likely are adequate (24, 25). Further data are needed in these settings to assess calcium requirements in populations with habitual intakes of high amounts of inhibitors of calcium absorption, and our data cannot be reliably used as a basis for dietary guidelines there.

In summary, we have shown that calcium intake and absorption efficiency are inversely related in young children and that a calcium intake of ≈470 mg/d meets the usual bone growth needs of such children. This value, or the rounded value of 500 mg/d, may be considered as a candidate EAR value for 1–4-y-old children.

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