

A COMPARISON OF CALCIUM, VITAMIN D, OR BOTH FOR NUTRITIONAL RICKETS IN NIGERIAN CHILDREN

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ABSTRACT

Background Nutritional rickets remains prevalent in many tropical countries despite the fact that such countries have ample sunlight. Some postulate that a deficiency of dietary calcium, rather than vitamin D, is often responsible for rickets after infancy.

Methods We enrolled 123 Nigerian children (median age, 46 months) with rickets in a randomized, double-blind, controlled trial of 24 weeks of treatment with vitamin D (600,000 U intramuscularly at enrollment and at 12 weeks), calcium (1000 mg daily), or a combination of vitamin D and calcium. We compared the calcium intake of the children at enrollment with that of control children without rickets who were matched for sex, age, and weight. We measured serum calcium and alkaline phosphatase and used a 10-point radiographic score to assess the response to treatment at 24 weeks.

Results The daily dietary calcium intake was low in the children with rickets and the control children (median, 203 mg and 196 mg, respectively; $P=0.64$). Treatment produced a smaller increase in the mean (\pm SD) serum calcium concentration in the vitamin D group (from 7.8 ± 0.8 mg per deciliter [2.0 ± 0.2 mmol per liter] at base line to 8.3 ± 0.7 mg per deciliter [2.1 ± 0.2 mmol per liter] at 24 weeks) than in the calcium group (from 7.5 ± 0.8 mg per deciliter [1.9 ± 0.2 mmol per liter] to 9.0 ± 0.6 mg per deciliter [2.2 ± 0.2 mmol per liter], $P<0.001$) or the combination-therapy group (from 7.7 ± 1.0 mg per deciliter [1.9 ± 0.25 mmol per liter] to 9.1 ± 0.6 mg per deciliter [2.3 ± 0.2 mmol per liter], $P<0.001$). A greater proportion of children in the calcium and combination-therapy groups than in the vitamin D group reached the combined end point of a serum alkaline phosphatase concentration of 350 U per liter or less and radiographic evidence of nearly complete healing of rickets (61 percent, 58 percent, and 19 percent, respectively; $P<0.001$).

Conclusions Nigerian children with rickets have a low intake of calcium and have a better response to treatment with calcium alone or in combination with vitamin D than to treatment with vitamin D alone. (N Engl J Med 1999;341:563-8.)

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NUTRITIONAL rickets causes considerable disability among children.¹ Though virtually eliminated from Europe and North America by the fortification of foods with vitamin D, nutritional rickets remains prevalent in many parts of the world, including Africa, the Indian subcontinent,² Asia,³ and the Middle East.⁴ Rickets has been ranked among the five most prevalent diseases among children in developing countries.⁵

Because there is ample sunlight in tropical countries, the cause of rickets in these areas remains an enigma. In Africa, rickets has been thought to result from inadequate endogenous production of vitamin D because of increased skin pigmentation or insufficient exposure to sunlight. Consequently, vitamin D is still given as primary therapy for rickets in African children. Studies in South Africa and Nigeria suggest that a dietary deficiency of calcium may cause rickets,⁶⁻¹¹ and there are case reports of rickets caused by dietary calcium deficiency in North America.^{12,13} Most of the children in these studies had normal serum 25-hydroxyvitamin D concentrations and high serum 1,25-dihydroxyvitamin D concentrations, indicating adequate intake of vitamin D. In both regions, calcium supplementation alone resulted in healing of the rickets. However, not all authorities agree with the conclusion that calcium deficiency alone causes rickets.^{14,15} We report the results of a 24-week controlled trial to test the hypothesis that calcium supplementation with or without vitamin D is superior to vitamin D alone for the treatment of rickets in Nigerian children.

METHODS**Subjects**

Children with deformities characteristic of rickets (genu varum, genu valgum, and widened wrists) were recruited within and around Jos, Nigeria (population, 360,100), through posters, ra-

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dio announcements, and word of mouth. Each child was examined, and a parent or guardian was interviewed. Children who were 1 to 14 years of age and who had clinical evidence of rickets underwent radiography of the wrists and knees. Rickets was considered active if the epiphyseal plate was wider than normal and there was concave cupping or fraying of the metaphyseal margins on the radiographs. Children were excluded if they were reported to have taken vitamin D or calcium supplements during the 12 weeks before screening or a multivitamin or cod-liver oil (both of which contain some vitamin D) less than 4 weeks before screening. Children were also excluded if they had a history of renal disease, tuberculosis, or liver disease or evidence of any of these disorders on physical examination or laboratory testing.

For each child who was enrolled, a parent or guardian was asked to recruit a control child from among the child's playmates. A child was eligible to serve as a control if he or she was the same sex, age (within three months), and weight (within 1.0 kg for children who were less than two years of age and within 2.0 kg for those who were at least two years of age) as the subject and had no clinical evidence of rickets. Children over the age of five years were not matched for weight because the short stature of children with rickets would have led to the selection of malnourished control children. For children for whom a matched control child could not be recruited, control children were recruited among outpatients receiving primary care at Jos University Teaching Hospital. These were children who returned for follow-up of acute illnesses (e.g., malaria, pneumonia) from which they had recovered and who had no illness likely to affect the metabolism of vitamin D or calcium.

Participation was voluntary, and written informed consent was obtained from the parents or guardians of all the children. The study was approved by the Nigerian Ministry for Health and the ethics review boards of Jos University Teaching Hospital and the University of Utah.

Data and Sample Collection

Using food-composition tables designed for African food-stuffs,¹⁶⁻¹⁸ we calculated dietary calcium intake by asking parents or guardians on two occasions about the children's food intake on the preceding day. Dietary intake of vitamin D was not determined. Parents and guardians were not instructed to modify their children's diet during the study. Height and weight were measured at base line and at 24 weeks while the children were standing, and the intercondylar or intermalleolar distance was measured while the children stood with their legs together. We calculated z scores for weight for height, weight for age, and height for age, which permit comparison of nutritional status in age and sex groups, using the nutritional anthropometric program of Epi Info software (version 6.03, Stone Mountain, Ga.).

Radiographs of the wrists and knees were obtained 12 and 24 weeks after treatment was started and were compared with the base-line radiographs. We used a 10-point scoring system to assess the radiographic changes in the wrists and knees.¹⁹ The radius and ulna were each given a score of 2 if the width of the growth plate was increased and was accompanied by fraying and concave cupping of the metaphyseal margins; a score of 1 was given if fraying was present but concave cupping was absent. The femur and tibia were each given a score of 3 if the distal femoral epiphysis or the proximal tibial epiphysis appeared widely separated from its metaphysis by a lucent region. A score of 2 was given if the lucency was only partial and the metaphyseal margin was frayed. A score of 1 was given if there was partial lucency with a smooth metaphyseal margin. If only one of the femoral condyles or tibial plateaus was affected, the score was halved. The scores for the more severely involved wrist and the more severely involved knee were calculated. The maximal score was 10 (2 points for the radius, 2 for the ulna, 3 for the femur, and 3 for the tibia), indicating severe rickets. A score of 1.5 or less after 24 weeks of treatment was considered to indicate nearly complete resolution of the abnormalities. Each radiograph was independently scored

by three physicians who were unaware of the child's treatment assignment, and the mean value of the three scores was used for the analysis. The reproducibility of the scoring method was tested in a subgroup of 67 radiographs and has been reported elsewhere.¹⁹ The intraclass correlation of scores between observers was 0.82, and the correlation within observers was 0.89 or greater, indicating good reproducibility.

Study Protocol

Eligible children were randomly assigned in blocks of nine to receive vitamin D, calcium, or both. Medication kits were serially numbered and contained the complete 24-week treatment for each child. The randomization code was kept at the University of Utah and was not broken until all data had been collected. The medications were dispensed in sealed, opaque packets, and vitamin D or placebo was administered intramuscularly on two occasions by a nurse while the investigators were in a different room.

Children assigned to the vitamin D group received an intramuscular injection of 600,000 U of vitamin D at enrollment and after 12 weeks. They were also provided chewable placebo tablets (candy containing no calcium but similar in appearance to calcium tablets) and instructed to take two in the morning and three in the evening at least 30 minutes before eating. Children assigned to the calcium group were supplied chewable 200-mg tablets of calcium carbonate and were instructed to take two tablets in the morning and three in the evening at least 30 minutes before eating (total dose, 1000 mg of elemental calcium daily). They were given an injection of placebo (light mineral oil) at enrollment and after 12 weeks. The combination-therapy group received both vitamin D and calcium in the doses given above. The children returned every four weeks for a new packet of tablets, and tablet counts were used to assess compliance.

Biochemical Measurements

Serum samples were obtained from the children at base line and at 12 and 24 weeks. All samples were stored at -70°C until they were transported on dry ice to the University of Utah. All samples from an individual child and the samples from the matched control child were assayed together to exclude the effect of interassay variability.

Serum calcium, phosphorus, alkaline phosphatase, and albumin were measured with the use of standard methods. Serum 25-hydroxyvitamin D was measured by radioimmunoassay after acetonitrile extraction. Serum 1,25-dihydroxyvitamin D was measured by radioreceptor assay after extraction on C-18 columns. Biochemical testing was performed by Associated Regional University Pathologists (Salt Lake City).

Statistical Analysis

The primary outcome variables were changes in serum calcium and alkaline phosphatase concentrations and radiographic scores. The primary comparison between the children with rickets and the control children was the dietary intake of calcium. Normally distributed data are reported as means \pm SD; data that were not normally distributed are reported as medians, with interquartile ranges. Dichotomous variables were compared with use of the chi-square test. The Mann-Whitney U test was used to compare variables that were not normally distributed. The two-tailed Student's t-test for paired samples was used to compare mean values of normally distributed continuous variables within treatment groups and between children with rickets and matched control children. Repeated-measures analysis was used to compare mean values among treatment groups during follow-up.

RESULTS

Of the 297 children who were screened, 174 were excluded for the following reasons: 116 had clinical features of rickets that were considered radiographi-

cally to indicate inactive disease, 23 had recently taken vitamin D or calcium, 20 did not return for enrollment, 13 had been given a diagnosis other than rickets, and 2 were outside the eligible age range. A total of 123 children were enrolled in the trial between July 1996 and December 1996, and follow-up was completed in May 1997. Of the 123 children who were enrolled in the treatment trial, 110 completed the full 24 weeks of treatment. The remaining 13 children were lost to follow-up. One child in the calcium group was excluded from the final analysis because the child was given calcitriol by another physician six weeks after enrollment. Among the 123 children who were recruited as controls, 5 were not precisely matched for age, 6 were not matched for weight, and 9 were not matched for sex. The base-line characteristics of the two groups of children are shown in Table 1. The children with rickets were shorter and weighed less than the control children. The children with rickets also had a lower mean z score for weight for height, primarily because the children were matched for weight rather than for height and because the children with rickets were shorter.

The median daily intake of calcium in the children with rickets (203 mg) was well below the daily allowance of 800 mg recommended by the National Institutes of Health, but it was not significantly different from that in the control children (196 mg). The serum alkaline phosphatase and 1,25-dihydroxyvitamin D concentrations were higher and the serum calcium, phosphorus, and 25-hydroxyvitamin D concentrations were lower in the children with rickets than in the control children (Table 1). However, only 46 children with rickets (37 percent) had serum 25-hydroxyvitamin D concentrations of less than 12 ng per milliliter (30 nmol per liter), suggesting depletion of vitamin D. The children with low serum 25-hydroxyvitamin D concentrations did not differ from those with normal concentrations with respect to age, duration of rickets, or calcium intake. The initial radiographic scores represented all degrees of severity of rickets and correlated with serum alkaline phosphatase concentrations ($r=0.53$, $P<0.001$) and with calcium intake (expressed as milligrams per kilogram of body weight; $r=0.18$; $P=0.04$).

There were no significant differences in base-line characteristics among the three treatment groups. The responses of the children in each treatment group are summarized in Table 2. The increase in the serum calcium concentration was greater in the two groups that received calcium supplements than in the group that received vitamin D alone. The serum alkaline phosphatase concentration decreased more in the group that received a combination of calcium and vitamin D than in the group that received vitamin D alone ($P<0.001$) or the group that received calcium alone ($P=0.008$); the decrease was not significantly different between the calcium group

TABLE 1. BASE-LINE CHARACTERISTICS OF THE CHILDREN.*

CHARACTERISTIC	CHILDREN WITH RICKETS (N=123)	CONTROL CHILDREN (N=123)	P VALUE
Age (mo)			0.14
Median	46	42	
Interquartile range	34-63	25-70	
Sex (no.)			0.37
Male	55	62	
Female	68	61	
Religion (no.)			0.001
Christian	82	57	
Muslim	41	66	
Age when breast-feeding stopped (mo)	16±5	17±5	0.04
Dietary intake of calcium (mg/day)			0.64
Median	203	196	
Interquartile range	160-257	152-254	
Dietary intake of calcium (mg/kg of body weight/day)			0.01
Median	16	15	
Interquartile range	13-21	10-20	
Height (cm)	88.4±11.9	98.1±15.4	<0.001
Weight (kg)	12.7±3.4	14.5±5.1	<0.001
Height for age (z score)†	-3.6±1.5	-1.5±1.1	<0.001
Weight for age (z score)†	-2.3±0.9	-1.6±0.8	<0.001
Weight for height (z score)†	-0.3±0.8	-0.9±0.8	<0.001
Serum calcium (mg/dl)	7.7±0.9	9.0±0.6	<0.001
Serum phosphorus (mg/dl)	5.2±1.9	6.0±1.8	0.002
Serum alkaline phosphatase (U/liter)	812±415	245±78	<0.001
Serum albumin (g/dl)	4.1±0.4	4.2±0.5	0.37
Serum 25-hydroxyvitamin D (ng/ml)	13.9±10.2	20.5±6.2	<0.001
Serum 1,25-dihydroxyvitamin D (pg/ml)	134±40	116±38	<0.001

*Plus-minus values are means ±SD. Data were missing for some variables. To convert values for serum calcium to millimoles per liter, multiply by 0.25. To convert values for serum phosphorus to millimoles per liter, multiply by 0.32. To convert values for serum 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.50. To convert values for serum 1,25-dihydroxyvitamin D to picomoles per liter, multiply by 2.40.

†The z scores were calculated with use of the following formula: (actual value - median reference value) ÷ standard deviation of the reference values.

and the vitamin D group ($P=0.06$). However, the final serum alkaline phosphatase concentrations were similar in the calcium group and combination-therapy group. The mean serum 1,25-dihydroxyvitamin D concentrations fell more in the combination-therapy group than in the vitamin D group ($P=0.002$). Similarly, the extent of healing as assessed radiographically was greater in the combination-therapy group than in the vitamin D group ($P=0.002$). The percentages of children with a combined outcome of a serum alkaline phosphatase concentration of 350 U per liter or less and a radiographic score of 1.5 or less (indicating nearly complete resolution of the abnormalities) after 24 weeks of treatment (Fig. 1) were similar in the calcium and combination-therapy

TABLE 2. RESPONSES OF 109 CHILDREN WITH ACTIVE RICKETS TO TREATMENT WITH VITAMIN D, CALCIUM, OR A COMBINATION OF VITAMIN D AND CALCIUM.*

CHARACTERISTIC	VITAMIN D (N=37)			CALCIUM (N=34)			VITAMIN D AND CALCIUM (N=38)		
	BASE LINE	12 WK	24 WK	BASE LINE	12 WK	24 WK	BASE LINE	12 WK	24 WK
Height (cm)†	88.7±11.6		91.8±11.1	89.9±13.0		93.1±12.8	86.5±11.0		90.9±10.7
Height for age (z score)‡	-3.8±1.5		-3.6±1.4	-3.5±1.4		-3.4±1.4	-3.7±1.8		-3.3±1.9
Weight (kg)§	12.6±2.7		13.5±2.8	13.2±4.4		14.2±4.7	12.4±3.4		13.5±3.6
Intercondylar or intermalleolar distance (cm)§	10.2±5.0		9.9±4.3¶	11.2±5.8		10.1±6.2	9.2±4.5		8.0±4.1
Serum calcium (mg/dl)	7.8±0.8	8.2±1.0	8.3±0.7	7.5±0.8	8.8±0.8	9.0±0.6	7.7±1.0	8.8±0.9	9.1±0.6
Serum phosphorus (mg/dl)§	5.0±2.1	5.2±1.4	5.1±1.0	5.4±1.7	5.8±1.6	5.5±1.0	5.1±1.7	5.7±1.3	5.9±0.8
Serum alkaline phosphatase (U/liter)**	765±381	623±338	510±238	761±309	544±262	362±159	922±512	500±312	355±134
Serum albumin (g/dl)§	4.1±0.4	4.3±0.6	4.1±0.5	4.1±0.3	4.3±0.5	4.2±0.5	4.2±0.6	4.3±0.6	4.3±0.5
Serum 25-hydroxyvitamin D (ng/ml)††	14±6	26±12	35±16	16±17‡‡	18±13	21±11	13±5	36±13	41±17
Serum 1,25-dihydroxyvitamin D (pg/ml)§§	137±43	123±33	127±29	130±36	118±42	109±36	133±43	108±37	88±25
Radiographic score¶¶	4.8±2.7	2.9±2.3	1.5±1.6	5.1±3.0	2.5±2.0	1.0±0.9	5.7±3.2	2.0±1.9	0.5±0.7

*Plus-minus values are means ±SD. The analysis includes children who completed 24 weeks of treatment. Data were missing for some variables. To convert values for serum calcium to millimoles per liter, multiply by 0.25. To convert values for serum phosphorus to millimoles per liter, multiply by 0.32. To convert values for serum 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.50. To convert values for serum 1,25-dihydroxyvitamin D to picomoles per liter, multiply by 2.40.

†P=0.66 for the comparison of vitamin D with calcium, P<0.001 for the comparison of vitamin D with combination therapy, and P=0.002 for the comparison of calcium with combination therapy for pairwise comparisons of the difference in responses between groups over time.

‡P=0.96 for the comparison of vitamin D with calcium, P<0.001 for the comparison of vitamin D with combination therapy, and P=0.002 for the comparison of calcium with combination therapy for pairwise comparisons of the difference in responses between groups over time.

§There was no significant difference between the three groups by global analysis of variance.

¶The 24-week value was not significantly different from the base-line value.

||P<0.001 for the comparison of vitamin D with calcium, P<0.001 for the comparison of vitamin D with combination therapy, and P=0.76 for the comparison of calcium with combination therapy by repeated-measures analysis of the difference in responses between groups over time.

**P=0.06 for the comparison of vitamin D with calcium, P<0.001 for the comparison of vitamin D with combination therapy, and P=0.008 for the comparison of calcium with combination therapy by repeated-measures analysis of the difference in responses between groups over time.

††P<0.001 for the comparison of vitamin D with calcium, P=0.007 for the comparison of vitamin D with combination therapy, and P<0.001 for the comparison of calcium with combination therapy by repeated-measures analysis of the difference in responses between groups over time.

‡‡The standard deviation is large because of a single outlier (110 ng per milliliter [275 nmol per liter]). When the outlier was excluded, the value was 13±4 ng per milliliter (32±11 nmol per liter), which was significantly different from the 24-week value (P<0.001).

§§P=0.35 for the comparison of vitamin D with calcium, P=0.002 for the comparison of vitamin D with combination therapy, and P=0.08 for the comparison of calcium with combination therapy by repeated-measures analysis of the difference in responses between groups over time.

¶¶P=0.26 for the comparison of vitamin D with calcium, P=0.002 for the comparison of vitamin D with combination therapy, and P=0.12 for the comparison of calcium with combination therapy by repeated-measures analysis of the difference in responses between groups over time.

groups (61 percent and 58 percent, respectively) and were significantly greater than the percentage in the vitamin D group (19 percent, P<0.001).

The seven children in the calcium and combination-therapy groups with radiographic scores of more than 1.5 did not differ significantly with respect to age, compliance, or initial serum 25-hydroxyvitamin D concentration from those who had scores of 1.5 or less. The decreases in serum alkaline phosphatase concentrations and radiographic scores were similar among children with serum 25-hydroxyvitamin D concentrations of less than 12 ng per milliliter at base line and those with normal serum 25-hydroxyvitamin D concentrations at base line.

Overall, compliance ranged from 92 to 96 percent

in the three groups. The base-line characteristics of children who were lost to follow-up did not differ significantly from those who completed the trial. Subjective improvement at 24 weeks was reported by 83 percent of the parents of children in the vitamin D group, 86 percent of the parents of children in the calcium group, and 93 percent of the parents of children in the combination-therapy group (P=0.42). Six children had fractures during treatment, four in the vitamin D group and one in each of the other two groups.

DISCUSSION

Nutritional rickets in children is usually considered to be due primarily to a deficiency of vitamin D,

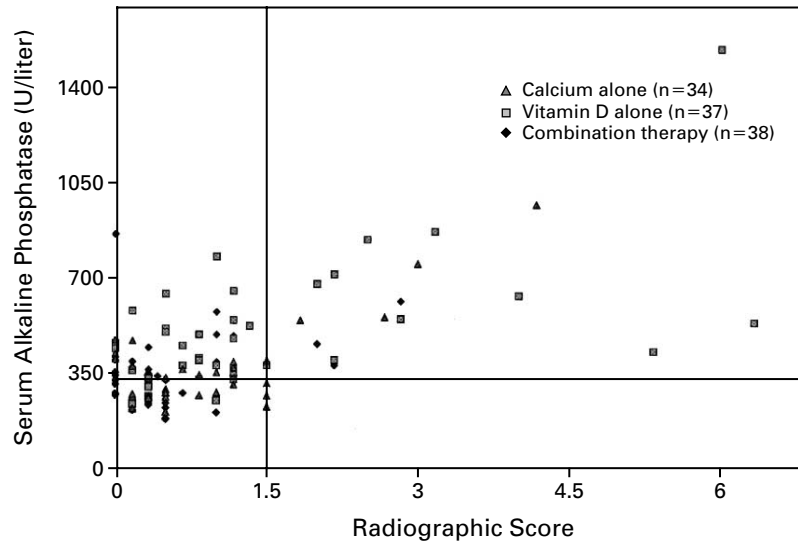


Figure 1. Serum Alkaline Phosphatase Concentrations and Radiographic Scores after 24 Weeks of Treatment with Vitamin D, Calcium, or a Combination of Vitamin D and Calcium.

The horizontal line represents the upper limit of the normal range of serum alkaline phosphatase concentrations (350 U per liter). The vertical line represents a radiographic score of 1.5, the value considered to indicate that resolution of the abnormalities was nearly complete.

but several small studies in tropical and subtropical countries (Nigeria and South Africa) have suggested that in these countries, a low dietary intake of calcium has an important role. These studies reported that children with rickets had a response to calcium therapy,^{6-8,10,11} but none objectively compared the response with that to a combination of calcium and vitamin D. We found that calcium supplementation with or without vitamin D therapy was more effective than supplementation with vitamin D alone in healing active rickets in a cohort of Nigerian children.

About one third of the children with rickets had low serum 25-hydroxyvitamin D concentrations at base line, but the response of these children to calcium supplementation was no different from that of the children with normal concentrations of vitamin D at base line. This finding supports the contention that vitamin D deficiency is not the primary cause of rickets in these children. The age at onset of rickets resulting from a deficiency of vitamin D peaks between 4 and 12 months,²⁰ whereas the age at onset of rickets among Nigerian children peaks between 15 and 25 months.

The serum 25-hydroxyvitamin D concentrations rose significantly during treatment in the children in the calcium group, and the increases were accompanied by a significant decrease in serum 1,25-dihydroxyvitamin D concentrations. These data support previous studies suggesting that a low dietary intake

of calcium increases the hepatic catabolism of 25-hydroxyvitamin D, thereby lowering its serum concentration, by raising serum parathyroid hormone and 1,25-dihydroxyvitamin D concentrations.²¹ We believe that treatment with calcium supplements in our study reduced serum 1,25-dihydroxyvitamin D concentrations (by decreasing the secretion of parathyroid hormone), with a consequent reduction in 1,25-dihydroxyvitamin D–stimulated hepatic catabolism of 25-hydroxyvitamin D and an increase in serum 25-hydroxyvitamin D concentrations. There is a possibility that vitamin D deficiency could lead to rickets in younger children, whereas a deficiency of calcium could be the chief factor in sustaining the disease in older children.²² However, we found no correlation between serum 25-hydroxyvitamin D concentrations and age to support this possibility, nor did we find that the response to calcium differed according to the child's serum 25-hydroxyvitamin D concentration at base line.

The calcium intake in the children with rickets was estimated on the basis of dietary recall to be approximately 200 mg per day, well below the recommended dietary allowance of 800 mg per day.²³ The absence of a difference in dietary calcium intake between the children with rickets and the control children may imply that a low calcium intake alone cannot by itself cause rickets. However, a short duration of breast-feeding, reduced calcium content of breast milk,²⁴ high intake of dietary inhibitors of calcium

absorption, or impaired physiologic adaptation could also reduce available dietary calcium among children with rickets.

In conclusion, we found that Nigerian children with rickets had a low calcium intake and that dietary supplementation with calcium or a combination of calcium and vitamin D healed the rickets. Although our findings do not prove that calcium deficiency by itself causes rickets, vitamin D deficiency does not appear to be an important cause of rickets in these children. Enriching their diet with inexpensive, locally acceptable food sources of calcium may prevent rickets in such children.

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