Research letter

Adaptation of Inuit children to a low-calcium diet

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Abstract

FOR INUIT CHILDREN, A TRADITIONAL DIET contains 20 mg of elemental calcium per day, well below the recommended daily intake. To identify alterations in intestinal or renal calcium absorption, 10 healthy Inuit children (5 to 17 years of age) were given a standardized calcium load (Pak test). Five had hypercalciuria (hyperabsorptive in 3 and renal leak in 2), a frequency markedly different from that for white children ($p < 0.004$) and not explained by calcitropic hormone and serum calcium levels, which were normal. There was a preponderance of the *bb* vitamin D receptor genotype (8 of 10 subjects; $p < 0.01$ for comparison with white populations). Dietary calcium absorption appeared to be more efficient in these Inuit children, with an increased frequency of hypercalciuria associated with the *bb* genotype. This may represent a genetic adaptation to dietary constraints and may predispose to nephrolithiasis or nephrocalcinosis if standard nutritional guidelines are followed.

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Recommended elemental calcium intakes for North American children are 800 mg/d for those 4 to 8 years old and 1300 mg/d for those 9 years of age and older.[1] With a traditional diet, Inuit children in northern Canada ingest only 20 mg of elemental calcium per day.[2] After presumably adapting to this constraint over millennia, the Inuit are now adopting a more southern "market" diet, with appreciably higher calcium intakes. Having observed cases of severe hypercalciuria and nephrocalcinosis in children from northern communities, we hypothesized that adaptation to a restricted calcium intake might be associated with altered intestinal or renal tubular calcium absorption, which might be maladaptive as the traditional diet is supplanted. In this situation, increased dietary calcium absorption might lead to hypercalciuria, nephrocalcinosis or nephrolithiasis. We used a standardized oral calcium challenge to examine intestinal calcium absorption and renal calcium handling in healthy Inuit children.

Six female and 4 male Inuit children, 5 to 17 years of age, were recruited at random from clinics of the Montreal Children's Hospital. These otherwise healthy children had come from remote Northern Quebec communities for follow-up after appendectomy ($n = 4$), cutaneous infection ($n = 2$), tonsillectomy ($n = 1$) and healed fracture ($n = 2$) and for evaluation of mild developmental delay ($n = 1$). The children, their parents and the treating physicians were approached at the Northern Children's Clinic to obtain informed consent; the services of a translator were used when required.

Each child underwent a pediatric Pak test with standardized oral calcium load. Urine was collected before and after a standard calcium meal, and blood was drawn for determination of vitamin D receptor genotype, serum calcium level and levels of calcitropic hormones. One patient (subject 2) did not receive the full calcium load and was excluded from the associated analyses.

Urinary calcium excretion of less than 0.56 μmol/mol creatinine before loading and less than 0.76 μmol/mol creatinine after loading is considered normal. A normal fasting urinary calcium:creatinine ratio combined with post-load urinary calcium excretion greater than 0.76 μmol/mol creatinine is consistent with absorptive hypercalciuria, indicating increased intestinal calcium absorption. Elevated pre- and post-load urinary calcium:creatinine ratios identify patients with so-called renal leak hypercalciuria, although the 2 forms of hypercalciuria may not be distinct etiologically.[3]

The pediatric Pak test has been well validated in multiple studies examining the frequency of hypercalciuria in North American and European children.[4,5] In North American children, absorptive hypercalciuria occurs in 2.0% and renal leak in 4.1% ($n = 48$);[4] in European children these conditions occur in 1.20% and 0.83% respectively ($n = 236$).[5] In general, urinary calcium:creatinine ratios above 0.56 to 0.76 μmol/mol are considered potentially injurious and are associated with risk of renal complications, such as nephrocalcinosis, stones and tubular dysfunction.

Serum and urine calcium and creatinine were measured with a Vitros 950 analyzer (Ortho-Clinical Diagnostics, Rochester, NY). Hormone assays included 25-hydroxy vitamin D (25(OH)D), 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) (both by radioimmunoassay, Dia Sorin, Stillwater, Minn.) and intact parathyroid hormone (by chemiluminescence assay, Nicols Institute, San Juan Capistrano, Calif.). Restriction fragment length polymorphisms for the

vitamin D receptor gene at the *Bsm*I site were analyzed by polymerase chain reaction as previously described, with *B* designating the absence and *b* the presence of this site.[6] Norms for white populations are *bb* 33%, *Bb* 49.6%, and *BB* 17% (*n*= 572).[6,7]

Fisher's exact test for proportions was used to compare calcium absorption and the *Bsm*I polymorphism with published standards.

Approval for this project was obtained from the Research Ethics Board of the Montreal Children's Hospital.

Fasting and post-load urinary calcium:creatinine ratios are shown in Table 1. Hyperabsorptive hypercalciuria was observed in 3 of 9 children (subjects 4, 5 and 6); 2 of 10 children (subjects 1 and 7) manifested renal-leak hypercalciuria before calcium loading. In 4 of 9 children, the pattern was normal. These results differ significantly from published norms for white and black children[4,5] (Fisher's exact test, $p < 0.004$).

Intact parathyroid hormone, serum calcium and vitamin D levels were normal, with 2 exceptions (Table 1): subject 9 had slightly higher than normal intact parathyroid hormone and subject 7 had higher than normal $1,25(OH)_2D$. In addition, 2 subjects (1 and 6) had borderline low levels of 25(OH)D.

The study participants had a preponderance of the *bb* genotype for the vitamin D receptor gene (8 children had this genotype and 2 had the *Bb* genotype; $p < 0.01$ compared with North American norms).[6,7]

Compared with reference populations,[4,5,8] hypercalciuria was significantly more common among study participants, and observed urine calcium levels were highly elevated. Our results support both more efficient calcium absorption and increased renal losses, effects that were not explained by the normal levels of intact parathyroid hormone and $1,25(OH)_2D$. The distribution of vitamin D receptor genotypes was significantly different from that in the white population ($p < 0.01$) but was similar to that of some Asian populations. In other groups with low calcium intakes (e.g., Chinese and Thai people), *bb* is also the predominant genotype.[9,10] This genotype is believed to be adaptive because of its association with more efficient intestinal calcium absorption. In general, these Asian populations did not demonstrate hypercalciuria with their usual diets,[11] and it appears that they were able to mineralize their bones and maintain eucalcemia with a significantly lower calcium intake than recommended for the standard North American diet.

While limited by both the cross-sectional nature of this study and the small sample size, our data are nonetheless consistent with a genetic adaptation to a traditionally low-calcium diet, whereby the *bb* genotype appears to be associated with a high rate of hypercalciuria. Dietary calcium intakes based on North American guidelines may therefore result in iatrogenic hypercalciuria and renal damage. A cautious approach to implementing such guidelines, with recognition of genetically distinct target populations, is thus warranted. Given the dangers, these findings should also motivate more extensive longitudinal evaluation.

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Table 1: Results of laboratory tests for 10 Inuit children

Subject	Sex	Age, yr	Serum Ca^{2+}, mmol/L*	Urinary Ca:cr ratio, µmol/mol		Interpretation of Pak test result§	Vitamin D receptor genotype	Intact PTH, pg/mL ¶	Form of vitamin D; serum level	
				Pre-load†	Post-load‡				25(OH)D, nmol/L**	$1,25(OH)_2$, pmol//L††
1	F	13	2.48	0.82	1.01	Renal leak	*bb*	24	20 (W)	67
2	M	11	2.40	0.23	No data		*bb*	15	30 (W)	50
3	M	16	2.41	0.40	0.67	Normal	*bb*	12	100 (W)	50
4	M	17	2.34	0.31	0.76	Hyperabsorption	*bb*	47	95 (W)	106
5	F	5	2.58	0.23	1.50	Hyperabsorption	*bb*	20	55 (S)	82
6	M	7	2.54	0.45	0.93	Hyperabsorption	*bb*	20	35 (S)	72
7	F	9	2.58	0.69	1.41	Renal leak	*Bb*	23	65 (S)	122
8	F	6	2.58	0.20	0.53	Normal	*Bb*	21	45 (S)	58
9	F	12	2.42	0.12	0.44	Normal	*bb*	62	45 (W)	77
10	F	13	2.43	0.21	0.47	Normal	*bb*	33	50 (W)	106

Note: Ca:cr ratio = calcium to creatinine ratio, PTH = parathyroid hormone, 25(OH)D = 25-hydroxy vitamin D, $1,25(OH)_2D$ = 1,25-dihydroxy vitamin D.
*Normally 2.25–2.76 mmol/L.
†Normally < 0.56 µmol/mol.
‡Normally < 0.76 µmol/mol.
§Normal is defined as pre-load urinary Ca:cr ratio < 0.56 µmol/mol and post-load ratio < 0.76 µmol/mol. Hyperabsorption is defined as pre-load urinary Ca:cr ratio < 0.56 µmol/mol and post-load ratio > 0.76 µmol/mol. Renal leak is defined as pre-load urinary Ca:cr ratio > 0.56 µmol/mol and post-load ratio > 0.76 µmol/mol.
¶Normally 10–60 pg/mL (1 pg/mL = 0.1053 pmol/L).
**Normally 25–100 nmol/L in winter (W), 37–199 nmol/L in summer (S).
††Normally 36–108 pmol/L.

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