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ORIGINAL ARTICLE

Fractures during growth: potential role of a milk-free diet

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Abstract
Summary Dietary calcium deficiency may increase fracture risk. In girls, 29.4% of fracture cases and 11.8% of controls without fracture had a history of milk-free diet. The odds ratio (OR) for fracture with a milk-free diet in girls was 4.6, $p<0.01$. In boys, 23% of cases and 19% of controls had a history of a milk-free diet; OR=1.3, NS). A milk-free diet due to cow's milk allergy is associated with increased fracture risk in girls.
Introduction An intake of calcium below the reference daily intake (RDI) of 800–1200 mg/day during growth is thought to increase fracture risk even though convincing evidence for this view is scarce. The paucity of evidence may be partly due to many trial participants being calcium replete. Children and adolescents with cow's milk allergy (CMA) avoid milk and have a calcium intake below the RDI. The aim of this study was to examine the association between consumption of a milk-free diet and fracture risk.
Methods In this case-control study conducted in Poland, 57 boys and 34 girls aged 2.5–20 years with fractures (cases) were randomly matched by age and sex with 171 boys and 102 girls without fractures (controls). Weight and height were examined using standard methods. Bone mineral density (BMD) and body composition were measured using dual-energy X-ray absorptiometry. Conditional logistic regression and Bayesian analyses were used to determine the proportion of the fracture risk attributable to a milk-free diet.
Results In girls, 29.4% of cases and 11.8% of controls had a history of milk-free diet producing an odds ratio (OR) for fracture associated with a milk-free diet of 4.6 (95% confidence interval [CI]: 1.4–15.5, $p<0.01$). In boys, 23% of cases and 19% of controls had a history of a milk-free diet; OR=1.3 (95% CI: 0.6–2.7, NS). If the prevalence of CMA in the population is 5%, only 6.7% of the fractures occurring are attributable to CMA and the associated nutritional deficit.
Conclusions Cow's milk allergy is associated with increased fracture risk in girls. Whether this association is due to the illness, calcium deficit or a deficit in other milk nutrients is uncertain. These data suggest that the contribution of milk-free diet to fracture liability among children and adolescents is modest.

Keywords Adolescents · Bone mineral density · Children · Cow's milk allergy · Fractures · Milk-free diet

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Introduction

A low dietary calcium intake during growth is regarded as a risk factor for fractures [1–6]. The rationale for this view is that assembly of a mineralized skeleton requires a positive calcium balance so there should be a level below which a 'deficiency' state exists. A low intake of milk and dairy produce is associated with lower bone mineral density (BMD) and a higher prevalence of fractures in childhood [7–10]. Some, but not all, meta-analyses support an association, albeit a weak one, between fracture or BMD and dietary calcium intake during growth [11, 12]. Several randomized double blind placebo controlled trials report a reduction in bone resorption and higher BMD during supplementation, with benefits in BMD found in children taking under 800 mg calcium daily [13–17]. Sustained intakes of calcium may be necessary to suppress bone remodeling as some [18–20], but not all [21, 22], studies suggest that the benefit is lost when supplementation is stopped. For example, Chevalley et al. report a residual skeletal benefit of calcium-enriched food in pre-pubertal boys one year after supplementation, but these changes were confined to the appendicular skeletal sites [22].

Thus, a deleterious effect of calcium 'deficiency', and a beneficial effect of calcium 'sufficiency', on fracture risk or BMD is really based on retrospective and prospective cohort and case-control studies [11, 12, 23–29]. Lack of randomized double blind placebo-controlled prospective trials demonstrating that a low calcium intake during growth results in higher fracture rates during growth or during adulthood is the result of the view that allowing children to consume a calcium intake under the reference daily intake (RDI) is unethical, a notion that begs the question [11, 30].

If a deficiency state exists, the negative results in case control and prospective studies and equivocal results in meta-analyses may be partly the result of methodological constraints. These studies included subjects with a calcium intake within the RDI. The lack of power to detect a true association between calcium 'deficiency' and fractures or low BMD may reflect under representation of subjects with intakes below the RDI [31]. The reference daily intake (RDI) is the intake level considered sufficient to meet requirements of nearly all (97–98%) individuals in the healthy population in each age category. Polish RDI values vary by age and only slightly differ from those in other European countries. The following are the recommended intakes for Polish population during growth: 400 mg daily from 0 to 1 year, 600 mg for children aged 1–3 years, 800 mg for 3–10 years, 1000 mg for boys 10–18 years and 1200 mg for girls 10–18 years [32, 33].

The study of children with cow's milk allergy (CMA) offered an opportunity to examine the effect of a low milk intake on the skeleton. We examined the association between intakes of calcium below the RDI, as referred to Polish recommendations, fractures and BMD in children with a history of CMA and 2.5 to 14 years of a milk-free diet, a model of calcium 'deficiency' that partly over comes this methodological problem [34, 35].

Methods

A total of 1,198 Caucasian children and adolescents aged 2–20 years were enrolled between 1999–2003. They were residents of north eastern Poland and most were followed as patients of the clinics in the Medical University Children's Hospital 'Dr. Ludwik Zamenhof' in Bialystok. In addition, 220 healthy children and adolescents were recruited from a local public school. All participants received 400 IU of vitamin D supplements during the first year of life, which is mandatory for prevention of nutritional rickets in Poland.

In this case-control study, fracture was the outcome and a milk-free diet due to CMA was the risk factor. Cases were 34 Caucasian girls and 57 Caucasian boys aged from 2.5 to 20 years, recruited from the Bialystok Medical University Children's Hospital, with one or more fractures involving the wrist, forearm (radius or ulna), tibia, humerus, fibula, ankle, clavicle or femoral shaft. Fractures of fingers or due to severe trauma, e.g., road accidents, were excluded. Of all fracture cases, 29 (32%) were in the first decade and 62 subjects (68%) were in the second decade of life. Fractures were ascertained by interview and from medical records. All study participants were screened for CMA and subjects with CMA were followed in clinics at the Bialystok Medical University Children's Hospital. CMA was diagnosed based on symptoms and laboratory results [skin prick-tests with modified food allergens, serum immunoglobulin E (milk-protein specific IgE)] and double blind placebo-controlled food challenge.

Clinical manifestations of cow's milk protein hypersensitivity and intolerance comprised: atopic dermatitis, atopic asthma, chronic allergic rhinitis, lactose intolerance with or without malabsorption. The number of subjects on a milk-free diet diminished as children became older (of all 230 subjects with CMA, 179 were in the first decade of life and 51 were in the second one). About 78% of the children with CMA were under 11 years (the median was 7.0 years). All children with a diagnosis of CMA were treated with a restrictive milk-free diet from 2.5 to 14 years (median 3.6 years). The majority of CMA patients were diagnosed during babyhood and the milk-free diet was introduced during their first year/first months of life. Specific hypoallergenic formulas were used in this group, including extensively hydrolysed casein formulas (e.g., Nutramigen), 77%; soy-based formulas (e.g., Prosobee), 21%; rice-based hydrolysate formulas or amino acid-based formulas free of antigens (2%).

For each fracture case, three controls without fracture were randomly sampled from 884 controls aged 2–20 years. Individuals with a daily intake of ≥2 servings of milk (a serving defined as a cup equivalent to 200 ml of whole milk) or other dairy products were considered as having a normal milk intake. Both cases and controls were free of chronic diseases or prolonged use of any medication known to affect bone metabolism. Cases and controls were matched for age and sex using standard methods [36]. Assessment of calcium intake was conducted in a subset of participants aged 7–17 yr on a milk-free diet (n=46). The assessment was based on direct interview of participants, from which 24-hour recall of calcium intake was obtained. A modified version of youth-adolescent questionnaire (YAQ) [37] was used in the interview. The questionnaire has previously been validated in older children and adolescents [38]. Informed consent was obtained from participants and their parents or guardians. The study was approved by the ethical committee at the Medical University of Bialystok.

Weight was measured using an electronic scale and height (±0.1 cm) was measured with an anthropometer. Bone mineral content (BMC, g), bone mineral density (BMD, g/cm^2), in the total body and lumbar spine, lean mass (kg) and fat mass (percent) were measured by dual-energy X-ray absorptiometry (DPX-L, version 1.3z GE-Lunar Radiation Corp., Madison, WI, USA). The coefficient of variation was 1.1% based on repeated scans in 32 pediatric subjects.

We estimated the OR for fracture and the absolute fracture risk associated with a milk-free diet due to CMA. To assess the association between exposure and fracture risk, a conditional logistic regression used the PHREG procedure in SAS system (SAS Institute Inc, Cary, NC) with a discrete logistic model stratified by matching variables (age and sex). Univariate analyses identified potential confounders. Those associated with fracture ($P<0.1$) were used in a multivariate model with the primary exposure variable. Likelihood ratio tests were used for all tests of significance.

In a case-control study, the measure of association is the odds ratio, an estimate of relative risk of an outcome given exposure to a risk factor. However, the odds ratio does not convey absolute risk of fracture which is of more interest to clinicians. The following question was asked: Given that an individual is exposed to CMA, what is the risk of sustaining a fracture? To answer this question, a Bayesian analysis was carried out [39]. Let π be the annual incidence of fracture in the general population, P(CMA|Fracture) be the proportion of children and adolescents with fracture who were exposed to CMA, and P(CMA|no fracture) be proportion of subjects without fracture who were exposed to CMA, then the risk (probability) of sustaining a fracture given that the individual is exposed to CMA, denoted by P (Fracture|CMA), can be shown to be:

$$P(Fracture|CMA) = \frac{\pi P(CMA|Fracture)}{\pi P(CMA|Fracture) + (1-\pi)P(CMA|NoFracture)}$$

Since we cannot determine the incidence π in a case-control study, it was assumed that π varied between 1% and 3% per year.

Results

In girls, 29.4% of fracture cases and 11.8% of controls were exposed to a milk-free diet (p=0.013). The OR of fracture associated with CMA was 4.6 (95% CI: 1.4–15.5) (p=0.013). In boys, about 23% of cases and 19% of controls were exposed to a milk-free diet (OR=1.30 (95% CI: 0.61–2.73, p=0.5) (Table 1).

There were no differences in the duration of the milk-free diet between boys and girls. The duration of milk-free diet was longer in 34 girls with than without fractures (1.94 yr vs 0.73 yr, p=0.002), no such association occurred in boys (1.08 vs 0.9 yr, p=0.57 NS, respectively). The daily calcium intake in a subset of 46 subjects on a milk-free diet was 388 mg (range: 240–770) and over 95% of these subjects had an intake below 500 mg per day. No association was found between calcium intake, BMD or fracture prevalence. There were no significant differences in age-, weight-, height and BMI-adjusted BMC or BMD between CMA patients and those on normal diets.

Higher lean mass was associated with lower risk of fracture in boys (OR per 15 kg: 0.52; 95% CI: 0.3–1.0), not girls (OR per 10 kg: 0.56; 95% CI: 0.2–1.6). Higher BMC was associated with lower risk of fracture in boys (OR per 15 g: 0.65; 95% CI: 0.4–1.0), not girls (OR per 10 kg: 0.62; 95% CI: 0.3–1.5). Body fat was not associated with fractures. The association between CMA, milk-free diet and fracture remained significant in girls after adjusting for these potential confounders (Table 2).

If the background annual incidence of fracture was 1%, given the OR of about 4, the fracture incidence in girls with a milk-free diet was 2.45% producing an excess risk of 1.45%. If the annual fracture incidence was 3%, the excess risk was 4.15%. For boys, the excess risk attributable to milk-free diet was less than 1% (Table 3). If the prevalence of CMA is 5%, given the above excess risk, 6.7% of the incident fracture in the population are attributed to CMA. If the prevalence of CMA is 10%, the population attributable fraction is 12.7%.

Table 4 shows the number of fractures in the community preventable under a range of assumptions. Assuming a

Table 1 Characteristics of participants

	Controls	Cases with fractures	P-value
Girls	**n=102**	**n=34**	
Age (yr)	13.0±4.3	13.0±4.2	0.991
Weight (kg)	46.7±18.2	43.5±15.7	0.326
Lean mass (kg)	30.9±9.9	30.1±9.6	0.678
Fat mass (kg)	12.3±8.9	10.2±6.6	0.146
Height (cm)	150.9±21.2	150.6±20.9	0.942
Body mass index (kg/m^2)	19.5±4.2	18.3±3.3	0.110
Spine BMD (g/cm^2)	0.93±0.29	0.90±0.28	0.601
Spine BMC (g)	31.3±14.9	30.0±14.3	0.729
Total BMD (g/cm^2)	0.869±0.21	0.852±0.26	0.213
Milk-free diet	12 (11.8)[a]	10 (29.4) [a]	0.016
Normal diet	90 (88.2)[a]	24 (70.6)[a]	
Boys	**n=171**	**n=57**	
Age (yr)	13.2±3.9	13.1±3.9	0.896
Weight (kg)	50.1±21.0	47.5±19.0	0.502
Lean mass (kg)	38.1±15.2	35.7±14.1	0.405
Fat mass (kg)	8.5±7.6	8.3±6.6	0.884
Height (cm)	156.0±23.3	155.0±23.1	0.826
Body mass index (kg/m^2)	19.5±4.2	18.8±3.5	0.340
Spine BMD (g/cm^2)	0.87±0.26	0.79±0.26	0.128
Spine BMC (g)	31.5±17.5	28.9±17.2	0.448
Total BMD (g/cm^2)	0.894±0.22	0.874±0.16	0.450
Milk-free diet	32 (18.7) [a]	13 (22.8) [a]	0.501
Normal diet	139 (81.3) [a]	44 (77.2) [a]	

[a] Number (percent) of total for each group.

fracture incidence in adolescents of 1% per year, that 30% of the population have a calcium intake under 600 mg daily, and that milk or calcium supplementation reduces fracture risk by 30%, then 15% of the fractures will be prevented. With a prevalence of calcium deficiency of 20% and the same assumptions, the number of fractures prevented ranged from 6% to 13%.

Discussion

This study supports the hypothesis that a milk-free diet increased the risk for fracture in girls. The incremental or excess risk associated with a milk-free diet varied between 1 and 4%, which suggests that most fractures in childhood and adolescence are not attributable to a milk-free diet. The null association in boys may not necessarily indicate that a milk-free diet is safe; trauma may make a larger contribution to fracture than bone fragility associated with CMA in boys. Fractures occurred mainly in the older children and adolescents at a time when trauma associated with exercise and physical activities at school increase. Thus, in the face of this increased risk, any small effect of calcium deficiency may have been obscured.

The study focused on children with CMA to ensure that there was a low calcium intake due to milk-free diet [29, 34, 35, 40–47]. However, this introduced several limitations. CMA has a prevalence of about 5–7% and about 11% in New Zealand [40, 44, 45]. Thus, the attributable risk for

Table 2 Association between milk-free diet and fracture risk

	Girls	Boys
Unadjusted model	4.61 (1.38–15.47)	1.30 (0.61–2.73)
Adjusted for lean mass	4.32 (1.26–14.75)	1.19 (0.56–2.54)
Adjusted for lean mass and BMC	4.26 (1.24–14.69)	1.18 (0.56–2.53)

Values are odds ratio and 95% confidence intervals.

Table 3 Estimates of excess risk for fracture conferred by a low milk intake due to cow's milk allergy

	Background fracture incidence (in the population)		
	1%	2%	3%
Girls			
Fracture incidence for subjects exposed to CMA	2.45%	4.84%	7.15%
Excess risk	1.45%	2.84%	4.15%
Boys			
Fracture incidence for subjects exposed to CMA	1.21%	2.42%	3.63%
Excess risk	0.21%	0.42%	0.63%

Table 4 Modeling of effectiveness of calcium supplementation in a population: Percent of reduction in fracture incidence in the population for a population prevalence of calcium deficiency of 30% and 20%

Relative risk of fracture associated with calcium deficiency	Relative risk reduction of fracture associated with calcium supplementation		
	20%	25%	30%
Prevalence=30%			
1.1	6.4	8.0	9.6
1.2	6.8	8.5	10.2
1.5	7.8	9.8	11.7
2.0	9.4	11.8	14.1
2.5	10.3	12.9	15.5
3.0	11.2	14.0	16.8
Prevalence=20%			
1.1	4.3	5.4	6.5
1.2	4.6	5.8	6.9
1.5	5.5	6.9	8.2
2.0	6.8	8.5	10.2
2.5	7.7	9.6	11.6
3.0	8.6	10.8	12.9

fracture in the community will be small. Moreover, the increased risk may have been due to the disease or a deficiency in milk products other than calcium. It is not clear whether CMA itself and related factors (e.g., inadequate intestinal calcium absorption, lower energy/protein intake, estrogen status or disorders of neuromuscular coordination) also contributed to fracture risk. However, this seems unlikely as these children do not have severe protein malnutrition or reduced lean or fat mass. It is also possible that older patients with CMA may have had a higher calcium intake from other foods, such as fruits, grains, vegetables, meat or fish. Whether the parents tried to increase calcium intake is not known. The point is, if the calcium intake was higher, then the error is conservative, the real deficit would produce an even greater fracture risk.

If the offending deficit in the milk-free diet was calcium, then this may contribute to the population burden of fractures in communities where the calcium intake is below 600 mg or even 500 mg daily in children as reported in 5% in some communities but 20–40% in others [46–50]. Approximately half of Polish prepubertal children have average intake less than 600 mg calcium per day [48]. Harel et al. reported that daily calcium intake in US population was 536 +/− 19 mg (45% of RDI) in girls and 681 +/− 28 mg (57% of RDI) in boys [49]. Another US study reported a large proportion of 10-year-old children did not meet the RDI for calcium intake (54% below 600 mg) [50]. Even a small excess risk of 1–4%, when common as in these communities, contributes a substantial burden of fractures in that community [34, 35]. For instance, given a 1% annual incidence, assuming a risk reduction of 30% produced by calcium supplementation, the population-based incidence of fractures will be reduced by 10 to 17%.

In general, milk and dairy produce are safe and free of side effects, except for those populations who have CMA, food allergy or lactose intolerance. Thus, provided supplementation with milk reduces fracture risk -and this remains unproven- then treatment targeted to high risk individuals, particularly adolescent girls with a low milk intake or to whole communities with a high prevalence of a low milk intake should theoretically prevent ~15% of these fractures in children. Tobacco use in adults confers a similar attributable risk for fracture [51].

Although deficits in BMD are reported in CMA [38], we did not detect significantly lower bone mass in the cases, nor in studied subjects with milk-free diet. Supplementation with milk extract or calcium supplements increases BMD in children with an intake of under 800 mg daily [4, 52]. The increments of 1–3% in BMD observed during supplementation are probably the result of remodeling suppression. When remodeling is suppressed, the many remodeling sites active before supplementation complete the remodeling cycle with bone formation producing an increase in BMD and a slowing of endocortical expansion. From this higher BMD, remodeling continues at a lower rate provided the supplement is continued. When the supplement is stopped the remodeling rate increases producing a decline in BMD [18, 21]. Whether the increment in BMD achieved with continued intake of the supplement will reduce bone fragility is not known, but it is possible.

In summary, although obtained using case-control methodology, rather than from a randomized controlled trial, these data are consistent with previous reports and support the view that a milk-free diet increases fracture risk in girls. It is unclear whether milk-free diet alone, CMA or both contributed to bone fragility in these girls. Given this limitation, we infer that long-term deprivation of milk and dairy products during growth is likely to increase the risk of fracture, perhaps due to low calcium intake. Under the assumption that milk or calcium supplementation through milk prevents fractures, supplementing this group of high risk individuals with calcium is appropriate. As most fractures in children are not due to a milk-free diet, supplementation of whole communities seems unjustified unless large portions of children and adolescents in the community have a low milk intake, then supplementation using milk or calcium-enriched foods may reduce the fracture burden by 15%.

In conclusion, a milk-free diet is associated with an increased risk of fracture in girls. Whether this risk is the result of the calcium content under 500 mg daily, and can be reversed by supplementation, will not be definitively established until randomized placebo controlled trials using milk or calcium supplements are undertaken in individuals with calcium intakes below the RDI. Although these trials are regarded as unethical, an alternate view is that it is unethical to make recommendations regarding widespread milk supplementation based on low levels of evidence that are easily challenged. Supplementation of whole communities in whom most fractures are not the result of calcium deficiency is questionable, even if there is a perception of ‘doing no harm’.

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