

Bone mineral status in children with cow milk allergy

Jensen VB, Jørgensen IM, Rasmussen KB, Mølgaard C, Prahl P. Bone mineral status in children with cow milk allergy.

Pediatr Allergy Immunol 2004; 15: 562–565. © 2004 Blackwell Munksgaard

To investigate bone mineral status in children with verified cow milk allergy for more than 4 yr compared with a large reference population of 343 local healthy controls. Whole body bone mineral content (BMC), projected bone area and bone mineral density (BMD) were determined by dual energy x-ray absorptiometry in nine children (8–17 yr old, one girl and eight boys). All children had cow milk allergy for more than 4 yr. All children had asthma and was treated with corticosteroids. BMC and BMD were reduced for age ($p < 0.01$). Height for age was significantly reduced ($p < 0.01$), indicating 'short' bones. BMC for bone area was borderline reduced ($p = 0.05$), indicating reduced bone mineralization. The growth of the children was reduced compared with their parents and siblings ($p < 0.01$), and the bone age was retarded (mean 1.4 yr, $p < 0.01$). Calcium consumption calculated from food intake was about 25% of the recommended. All laboratory tests were normal. Short bones were the main reason for reduced BMC and BMD for age in children with cow milk allergy, but a borderline low BMC for bone area indicated reduced bone mineralization of the bones. A supplementation of calcium to children with cow milk allergy is recommended.

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Key words: bone mineral content; bone mineral density; children; cow milk allergy

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Accepted 7 June 2004

A Danish cohort study from 1990 showed that 2.2% of all children developed cow milk allergy or intolerance in the first year of life. When older than 3 yr 13% of these children still not tolerated milk (1, 2). Children with cow milk allergy or intolerance will grow up without milk products and so has a potential risk of eating an insufficient quantity of calcium by the diet, because milk foods are the greatest source of calcium in a common Danish diet (3). Many children with cow milk allergy suffers from asthma. Inhaled corticosteroid is an effective and frequent used treatment of asthma in children (4, 5). It is known that systemic treatment with corticosteroid will result in reduced bone mineral density (BMD) (6, 7). Inhaled corticosteroid 504 µg daily for 3–6 yr does not result in either reduced whole body mineral content (BMC) or BMD (8). Studies from Denmark and the USA have shown that 70–80% of the calcium intake by children comes from milk products (3, 9). However,

evaluation of bone mass in children is difficult because both BMC and BMD are strongly influenced by bone size. We have therefore earlier proposed that bone mineralization is assessed in three steps: height for age, bone area for height and BMC for bone area. These three steps reflect three different causes of reduced bone mass; short bones, narrow bones and light bones (10). The aim of this study was to evaluate bone mineral status in children with verified milk allergy for more than 4 yr.

Material and methods

Patients

Nine children of white origin (8–17 yr of age, one girl and eight boys) with verified cow milk allergy for more than 4 yr were recruited from the outpatient allergy clinic, Department of Paediatrics, Gentofte University Hospital. Cow milk

allergy was verified by prick test, elimination and provocation test. Children with bone diseases, endocrine diseases, collagen diseases and cerebral palsy were excluded.

Questionnaire

The children and their parents answered a questionnaire concerning asthma symptoms, bone fractures and use of inhaled corticosteroids in the child. The calcium intake was estimated using a food frequency questionnaire (FFQ) with 88-items recording the usual daily intake (mg/day) during the last month. The FFQ was previously validated against food records, and the reproducibility and validity have previously been described in detail (11).

Serum analyses

Peripheral venous blood was obtained from all nine subjects for analysis of serum calcium, phosphate, alkaline phosphatase, total protein, albumin, calcitonin, PTH (parathyroid hormone), 25-hydroxy-vitamin D and 1,25-dihydroxy vitamin D. The results were compared with local references used in the clinic.

Anthropometry

Standing height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured on a digital electronic scale with a precision of 0.1 kg. Patients only wore underpants and cotton T-shirt when weighed.

Bone mineral assessment

Whole body BMC was measured in gram hydroxyapatite, bone size expressed as anterior-posterior projected bone area measured in cm². BMD, g/cm² (=BMC/bone area) and fat percentage (%) were determined by dual energy x-ray absorptiometry (DEXA) using a Hologic 1000/W (Hologic, Inc., Waltham, MA, USA). For analyses, software version 5.61 was used. Subjects wore only underpants and cotton T-shirt during the scan. For quality control, spine phantoms were scanned daily. DEXA measurement and height were compared with local references for healthy schoolchildren and adolescents of white origin living in Copenhagen (201 girls and 142 boys, aged 5–19 yr). None of these controls got medication that might affect bone mineralization (10). The data were analysed as age- and sex-specific SDSs [SDS = (observed – predicted)/s.d.]. Whole body DEXA-measurement was also ana-

lysed using the three-step approach as described earlier (10).

Statistical analysis

Growth Vision was used to compare childrens expected final adult height with their parents. The data were analysed by paired t-test and Student's t-test by MICROSOFT ACCESS software. The other statistical analyses were performed using the statistical package SSPP/PC+. The Wilcoxon signed rank sum test was used for comparing SDSs.

Ethics

Our study was carried out in accordance with the Helsinki II declaration and was approved by the local ethics committee of Copenhagen County, Denmark (approval no. KA 97110). Written informed consent was obtained from both participant and the parents.

Results

Both BMC and BMD for age was significantly reduced (Table 1). Height for age was significantly lower in patients with cow milk allergy compared with normal controls, indicating 'short bones' (Table 1). Bone area for height was normal, i.e. bone width was normal. BMC for bone area was borderline reduced ($p = 0.05$), indicating reduced bone mineralization. Fat percentage for age was quite normal. The growth of all the children was significantly reduced compared with their parents and siblings ($p < 0.01$). Bone age ad modum Greulich was retarded ($p < 0.01$, mean 1.4 yr). All the children had asthma and was treated with inhaled corticosteroids (mean 567 µg/day) (Table 2). All had at least one skin prick

Table 1. Bone mineral status in children with cow milk allergy

Z-score	Mean (s.d.)	s.e.m.
BMC for age	-1.53 (0.58)*	0.19
BMD for age	-1.65 (0.78)*	0.26
BA for age	-1.56 (0.60)*	0.20
Height for age	-1.53 (0.75)*	0.25
BA for height	-0.16 (1.00)	0.33
BMC for BA	-0.73 (0.95)**	0.32
FAT% for age	-0.03 (1.05)	0.35

Height, bone measurements and body composition in children with milk allergy aged 8–17 yr. Figures are sex-specific Z-scores ($n = 9$).

Significantly different from 0: * $p < 0.001$, ** $p = 0.05$.

BMC, bone mineral content; BA, bone area; BMD, bone mineral density; FAT%, whole body fat percentage.

Table 2. Use of inhaled corticosteroids

Gender	Age (yr)	Asthma debut (months)	Use of corticosteroids (months)	Accumulated corticosteroids (mg)*	Mean dose of corticosteroids ($\mu\text{g}/\text{day}$)*
M	12	17	12	73	203
M	15	48	131	2352	598
M	11	16	99	1854	624
M	8	3	59	609	341
F	12	42	111	1646	494
M	9	11	30	420	466
M	11	12	101	3820	1260
M	17	6	132	2394	604
M	16	24	132	2044	516

*These estimates may be inaccurate considering a variable compliance.

test-positive to inhalant allergens and five were allergic to eggs (Table 3). Seven children had Prurigo Besnier and six children had rhinitis (Table 3). Calcium consumption was only 25% of recommended (mean 217 mg/day, range: 79–482). For all the children serum calcium, phosphate, alkaline phosphatase, total protein, albumin, calcitonin, PTH, 25-hydroxy-vitamin and 1,25-dihydroxy-vitamin D correlated age standardized reference intervals.

Discussion

Only two studies concerning the bone mineralization in patients with verified cow milk allergy are known (12, 13). In a study from the USA BMD was estimated in 55 children and young adults with cow milk allergy. It was concluded that the calcium intake is important for the optimal mineralization of the growing bones (12). In another study, BMC and BMD were measured in 240 children and young adults with cow milk allergy; here, BMC and BMD were not found to differ from a standard material (13). The reduced BMC in our study is mainly due to a reduced height and a possible reduced mineralization. In a Spanish study, 30 children aged 2–13 yr on a low-milk diet were examined. Fifty

percentage of these had either osteoporosis or osteopenia (14). All our nine patients had a very low calcium intake (mean 217 mg/day). Other studies have shown a correlation between calcium intake and BMC. Chan et al. showed in his study that BMC in children is correlated to age, weight, height and calcium intake (15). BMC raised exponential with age, weight and height. Children who ingested more than 1000 mg calcium a day had a higher BMC than children who ingested <1000 mg. Johnston et al. carried out for a 3-yr period a double-blind, placebo-controlled study among twins. The aim of the study was to investigate if calcium supplement could increase BMD in children aged 6–14 yr (16). The children who received calcium supplement ingested in average 719 mg more calcium per day than those who did not receive supplement and they obtained about 3% higher BMD during 3 yr. In children who were in puberty or beyond the puberty, calcium supplement had a little effect on BMD. Bonjour et al. showed that BMD in girls before the puberty was increased by ingesting food which was enriched by extra calcium (17). Lee et al. found that the calcium intake in children was positively correlated to BMD, and that it is necessary with a sufficient calcium intake in childhood to ensure optimal bones (18). Stalling et al. examined 19 children aged 6–12 yr with verified intolerance to lactose; this study had the same conclusion (19). All our patients had asthma and were treated with inhaled corticosteroid (estimated mean 567 $\mu\text{g}/\text{day}$). It should be noted that these estimates might be rather inaccurate considering a most variable compliance in children treated with inhaled corticosteroids for asthma. This fact may of course result in a much lower dose of inhaled corticosteroids than estimated and may tend to support our conclusion of no or little influence of inhaled corticosteroids on BMC. Agertoft et al. showed that Danish children

Table 3. Other atopic diseases

Gender	Age (yr)	Asthma debut (months)	SPT inhalant allergens	SPT egg	Prurigo Besnier	Rhinitis
M	12	27	+	+	+	–
M	15	48	+	+	+	+
M	11	16	+	–	+	+
M	8	3	+	+	+	+
F	12	42	+	–	–	–
M	9	11	+	–	+	+
M	11	12	+	–	–	+
M	17	6	+	+	+	–
M	16	24	+	+	+	+

SPT, skin prick test.

treated with inhaled corticosteroid (mean 504 $\mu\text{g/day}$) had a normal BMD and BMC (8). These authors showed in another study that children with asthma during childhood (whatever they got corticosteroids or not) were lower than expected, but would obtain a normal final adult height (20). We also found that our patients were lower than expected.

In conclusion, short bones were the main reason for the reduced BMC and BMD for age in our patients. The borderline low BMC for bone area may indicate a reduced mineralization of the bones. It cannot be ruled out that the treatment with inhaled corticosteroids may in part cause the low BMC; but we think that the low intake of calcium may be the major cause. To avoid later osteoporosis a sufficient calcium supplement to children with cow milk allergy is still recommended.

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