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Risk factors for reduced bone mineral density measurements in milk-allergic patients

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Abstract

Background: Earlier studies noted that young adults with IgE-mediated cow's milk allergy (IgE-CMA) have significantly lower bone mineral density (BMD) than age- and gender-matched controls. We sought to identify additional risk factors contributing to the low BMD in IgE-CMA patients.

Methods: Postpubertal (defined by Tanner stage V) IgE-CMA patients (n = 78; 16- to 30-year-old females and 17.5- to 30-year-old males) were evaluated prospectively for BMD using a DXA scan, serum values of bone turnover factor, and dietary and lifestyle questionnaires. Patients receiving > 2 short courses of systemic steroid treatments were excluded.

Results: Abnormal BMD measurements (T- or Z-scores < -1.0) of the lumbar vertebrae, femoral neck, or hip were noted in 60 patients, while normal BMD values were present in 18 patients, despite similarly decreased calcium intakes between the groups ($P = 0.92$). Patients with abnormal BMD were more likely to be asthmatic ($P = 0.014$), have a lower weight z-score ($P = 0.007$), have a decreased percent caloric intake derived from fat ($P = 0.01$), and have an increased carbohydrate intake ($P = 0.03$), in comparison with the normal-BMD group. Serum values of bone turnover were similar between the groups. On multivariate regression analysis, only asthma significantly ($P = 0.006$) increased the risk for osteopenia and osteoporosis (OR 38.5, 95% CI 2.8-500). Fitting continuous z-scores into a regression model, both asthma and weight z-score were significant (adjusted $r^2 = 0.272$). Asthma was significantly overrepresented in osteopenic and osteoporotic subpopulations while decreased weight only in patients with osteoporosis.

Conclusions: In the context of a low calcium intake, asthma and weight are independent risk factors for decreased BMD in IgE-CMA patients.

KEYWORDS

asthma, bone mineral density, cow's milk allergy, osteoporosis

1 | BACKGROUND

The maintenance of healthy bones in young adults may be disturbed by many factors including poor nutrition or local systemic inflammation resulting in abnormal bone structure and function.¹ Milk is a

superior source of bioavailable calcium, the main mineral of skeletal bones providing their physical strength.² In addition to calcium, other proteins present in milk are important for establishing healthy bone mineral density. Milk-derived ribonuclease, for example, promotes angiogenesis within bone tissue. In addition, lactoferrin present in

milk is a bone growth factor capable of stimulating osteoblast differentiation and can reduce bone resorption.³ Not surprisingly, therefore, randomly controlled trials demonstrated a significantly positive association between dairy food intake and bone health (for review, see 4).

In order to analyze the role of dairy intake in bone health, we chose a model utilizing postpubertal IgE-mediated cow's milk allergy (IgE-CMA) patients who, by definition, cannot consume even minor amounts of dairy foods since infancy due to the threat of anaphylaxis.⁵ We previously demonstrated that bone mineral density (BMD) of lumbar spine (SP), femoral neck (FN), and hip was significantly decreased in IgE-CMA patients compared to an age- and gender-matched control group.⁶ Furthermore, the BMD of IgE-CMA patients who became desensitized by milk oral immunotherapy (OIT) was comparable to the control group, suggesting that the osteopenia and osteoporosis in these patients may be reversible. We observed, however, a subgroup of IgE-CMA patients that were able to maintain their BMD in the normal range despite a decreased calcium intake. Hereby, we use this group to look for additional risk factors contributing to a low BMD in IgE-CMA patients.

2 | METHODS

2.1 | Study design

Patients were recruited between July 2012 and February 2017 at a food allergy referral center at the Assaf Harofeh Medical Center (Zerifin, Israel). The study was approved by the institutional ethics committee, and all patients signed written consent. Postpubertal males and females diagnosed with IgE-CMA were eligible for inclusion, and >90% agreed to participate in the study. IgE-CMA was diagnosed as previously described.⁷ Since their diagnosis in infancy, all had strictly avoided dairy products, including those containing baked milk.

Puberty in both sexes was determined by signs of Tanner stage V. Females were at least 2 years after menarche. The minimal age for girls and boys was 16 and 17.5 years, respectively, up to a maximum of 30 years. Height and weight were determined barefoot. Exclusion criteria included a female's history of pregnancy, and in both genders, any bone affecting disease/treatment, systemic steroid treatment for a period longer than 4 weeks, or >2 short courses of systemic (oral or IV) steroid treatments. For those entering the study, a medical history for ascertainment of other medical conditions was obtained. Asthmatic patients were physician-diagnosed based on evidence of reversible airway obstruction.

Each asthmatic patient was tested with a baseline spirometry and was followed up for their asthma at each clinic visit. Patients reporting to have asthma were again contacted by phone in May 2017 regarding the past use of inhaled steroids. A total of 78 IgE-CMA patients were recruited to the study. Data from the first 34 patients recruited were previously analyzed in comparison with the control and post-OIT groups.⁶

2.2 | Bone health and bone mineral density assessment

The BMD was determined in the SP (L1-L4), FN, and trochanteric and intertrochanteric regions of the hip using a DXA scan (Hologic Explorer Series QDR; Hologic Inc., Bedford, MA, USA). The BMD results for each group were compared to an age- and gender-matched population (Z-score) and to the average results obtained from a gender-matched 20-year-old population (T-score). A normal BMD (termed BMD 0) was defined as a z-score (Z) ≥ -1.0 . A decrease in the BMD of either the hip, SP, or FN of more than 1-2.4 SD below the mean (Z - or T-score = 0) defines a patient with osteopenia. We further divided this group into those with mild osteopenia (BMD 1, $-1.0 > Z \geq -1.8$) and moderate osteopenia (BMD 2, $-1.8 > Z \geq -2.4$). A decrease in BMD of -2.5 SD or greater below the mean in the hip, SP, or FN (BMD 3) defines a patient with osteoporosis.¹ Patients were grouped into their severity level (BMD 0, BMD 1, BMD 2, or BMD 3) by their minimal SP, FN, or hip T- or Z-score measurement.

For our analyses, those with BMD measurements in the osteopenic range (< -1.0 T- or Z-score in the hip, SP, or FN) or less formed the abnormal group. Blood values of bone turnover such as calcium, phosphorus, magnesium, parathyroid hormone (PTH), and vitamin D-OH 25 levels were drawn from each patient.

2.3 | Nutritional intake

Patients were assessed by a dietician for their nutritional intakes using the average of the 3-day (2 midweek and 1 weekend day) intake record ($n = 28$). If a patient did not have the 3-day dietary intake documentation, then a 24-hour recall assessment similar to that used by the Ministry of Health, Israel (http://www.health.gov.il/PublicationsFiles/Mabat_1999-2001-b.pdf), was used for data analysis ($n = 34$). A computer program based on local food tables was used to determine the total calories, protein, fat, carbohydrate, and essential vitamins and minerals (Israeli Ministry of Health, Tzameret Program; <https://www.health.gov.il/Subjects/FoodAndNutrition/Nutrition/professionals/Pages/Tzameret.aspx>).

The % dietary reference intake (DRI) calculated by this program utilizes the recommended daily allowance cutoff method.

2.4 | Statistical analysis

Statistical analysis was performed utilizing SPSS. Categorical variable data are presented as N (%), and chi-square analysis was utilized for test of statistical significance. For continuous variables, tests for normality (Kolmogorov-Smirnov) were performed. Data that were normally distributed are presented as mean $\pm$ standard deviation and were analyzed by t test. Data that were not normally distributed are presented as median (IQR) and were analyzed by the Mann-Whitney U test. Variables that differed significantly between patients with normal and those with reduced BMD on univariate analysis were inputted into multivariate logistic regression analysis.

In addition, a linear regression analysis using bone z-scores (minimum of the 3 measured values) as continuous variables fitted by a linear regression model with the 5 variables (weight z-score, height z-score, asthma, % intake from fat, and carbohydrate intake) was performed. All tests were 2-tailed, and statistical significance was set at $P < 0.05$.

3 | RESULTS

3.1 | Bone densitometry

The baseline characteristics of the patient population ($n = 78$) are presented in the online repository (OR Table S1). In confirmation of our original findings,⁶ abnormal BMD scores (< -1.0 in T- and Z-scores of either the hip, SP, or FN) were found in 77% (60/78) of the patient cohort. However, the presence of a normal bone densitometry (≥ -1.0 in all measurements of T- and Z-scores) in 18 patients (23.0%) suggested that there are likely additional risk factors playing a role in the reduced BMD seen in IgE-CMA patients. An analysis comparing the IgE-CMA patients with decreased densitometric values to the IgE-CMA patients with normal BMD was performed. As presented in Table 1, both groups were matched for age, gender, height z-score, smoking, and amount of exercise (hours/week) performed. However, they differed significantly in 2 parameters. First, patients with decreased BMD were more likely to be asthmatic ($P = 0.014$). Conversely, asthmatic IgE-CMA patients exhibited consistently poorer BMD z-score measurements as compared to nonasthmatic IgE-CMA patients (Figure 1). However, it should be noted that even nonasthmatic IgE-CMA patients were more likely to have abnormal BMD (< -1.0 Z-scores) in the hip when compared to the control cohort from the initial phase of the study⁶ ($P = 0.022$). Decreased FN T- and Z-scores were also noted, but statistical significance was not reached (T-score, mean: -0.392 vs 0.042 , $P = 0.062$; Z-score, mean: -0.354 vs 0.05 , $P = 0.094$, for nonasthmatic IgE-CMA patients vs control cohort,

respectively). In a post hoc analysis, we evaluated the BMD in IgE-CMA patients who completed milk OIT,⁷ stratified by their asthma status. There were no significant differences in Z-scores for asthmatics completing milk OIT ($n = 9$) vs IgE-CMA patients without asthma completing milk OIT ($n = 14$) (L1-L4: -1 [-2.0 to 0.0] vs -1 [-1.75 to 0.0]; FN: 0 [-1.0 to $(+1.0)$] vs -1 [-1.0 to $(+0.75)$]; hip: 0.0 [-1.0 to $(+0.5)$] vs 0 [-1.0 to 0.0] [median (IQR), 25%-75%], respectively). Thus, it appears that asthma alone is not sufficient for a decreased BMD, but exacerbates the condition in the context of decreased calcium intake.

Controller inhaled steroid use in the past was reported by $>95\%$ of the asthmatics. None received >500 mg/day. At study inclusion, their baseline spirometric values (% predicted of normal values) for FVC, FEV₁, FEV₁/FVC, and FEF₂₅₋₇₅ were 103.4 ± 4.14 , 96.6 ± 5.1 , 93 ± 3.4 , and 64.5 ± 8.7 , respectively (mean $\pm$ 95% CI), suggestive of only a mild smaller airways obstruction in some patients. In each case of obstruction ($n = 14$), a bronchodilator was administered and reversibility was noted. None were hospitalized over the 5-year reporting period (2012-2017).

An additional difference between the abnormal- and normal-BMD groups was that IgE-CMA patients in the abnormal group weighed significantly less on average when compared to the IgE-CMA patients with normal BMD ($P = 0.007$; Table 1). Asthma and decreased weight, however, associated differently within each BMD severity level. Asthma occurrence is presented in Figure 2 for each BMD severity level. Asthma was underrepresented in the normal-BMD group (BMD 0), whereas in each of the remaining BMD levels (BMD 1, 2, and 3) the majority of patients were asthmatics. We did not observe any incremental increase in the occurrence of asthma within these 3 groups. In contrast, decreased weight seems to get stronger with BMD severity, and reaches statistical significance only for patients with BMD in the osteoporotic range (BMD 3, $n = 13$) as compared to those with a normal BMD ($P \leq 0.002$; Figure 3). Interestingly, 8 out of these 13 patients in BMD 3 were asthmatic.

TABLE 1 Comparison of IgE-CMA patients with normal vs decreased bone mineral density values

Parameter	Decreased BMD	Normal BMD	P-value
Age (years)	20 ± 3.5	21.2 ± 2.94	0.16
Gender (males)	28 (46.7)	5 (27.8)	0.18
Height (z-score)	-0.74 ± 0.91	-0.33 ± 0.74	0.087
Weight (z-score)	-0.49 ± 1.15	0.09 ± 0.61	0.007
Smoking	13 (23.2)	3 (18.8)	1.00
Exercise (H/W), median (IQR)	3.0 (0.25-4.5)	3.0 (0.0-5.25)	0.91
Asthma	35 (58.3)	4 (22.2)	0.014

For continuous variables, data are presented as mean $\pm$ standard deviation if normally distributed and as median (IQR) if not normally distributed. For categorical variables, data are presented as N (%). Decreased BMD, < -1.0 in any T- and Z-scores of the hip, SP, or FN ($n = 60$). Normal BMD, ≥ -1.0 in all measurements of T- and Z-scores ($n = 18$). Significant values are presented in bold print.

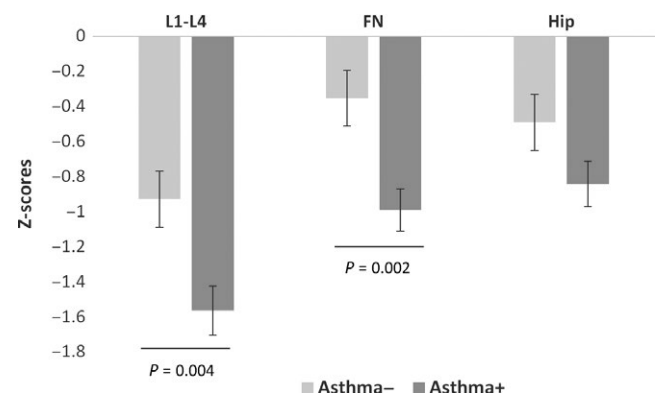


FIGURE 1 Bone mineral density (BMD) measurements of study participants categorized by their asthma status. Mean Z-score $\pm$ standard error bars of z-score measurements for L1-L4, FN, and hip are presented. Pairwise comparisons were significant for L1-L4 ($P = 0.004$) and FN ($P = 0.002$)

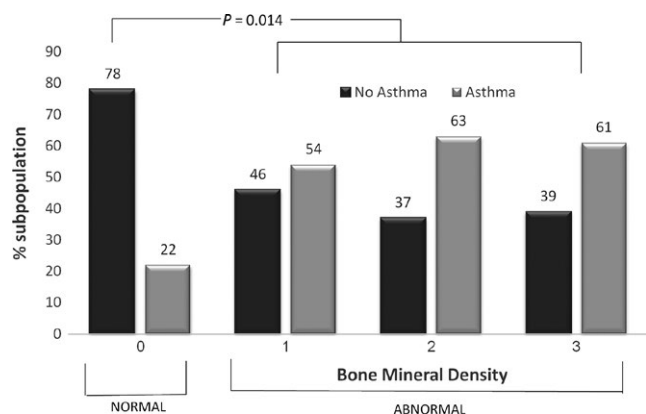


FIGURE 2 Composition of asthmatic IgE-CMA patients within each bone mineral density (BMD) severity level. The percent patient composition with regard to their asthmatic status for each severity level is presented. Normal: BMD 0, $n = 18$; abnormal: BMD 1, $n = 28$, BMD 2, $n = 19$, and BMD 3, $n = 13$. Patients with decreased BMD were more likely to be asthmatic ($P = 0.014$)

With respect to serum values reflective of bone turnover, there were no differences between the groups in the levels of vitamin D, parathyroid hormone, calcium, phosphorus, or magnesium (OR Table S2).

3.2 | Nutritional assessment

Patients were evaluated for their nutritional intakes by a dietician. The total energy intake (Kcal) was similar between those with an abnormal BMD vs those with a normal BMD (Table 2). Both groups had similarly decreased calcium intakes and decreased calcium intake presented as the percent of the recommended intake adjusted for age and gender (%DRI) as well (Table 2). Comparing the asthmatic IgE-CMA and nonasthmatic IgE-CMA groups, the total energy intake and the %DRI calcium were similar. Interestingly, patients with a decreased BMD had an increased carbohydrate intake and a decreased percent caloric intake from fat ($P = 0.03$ and $P = 0.01$, respectively),

as compared to the normal-BMD group (Table 2), but this effect does not persist in multivariate analysis (see below). Therefore, the differences in BMD between the groups are unlikely to be due to these differences in nutrition.

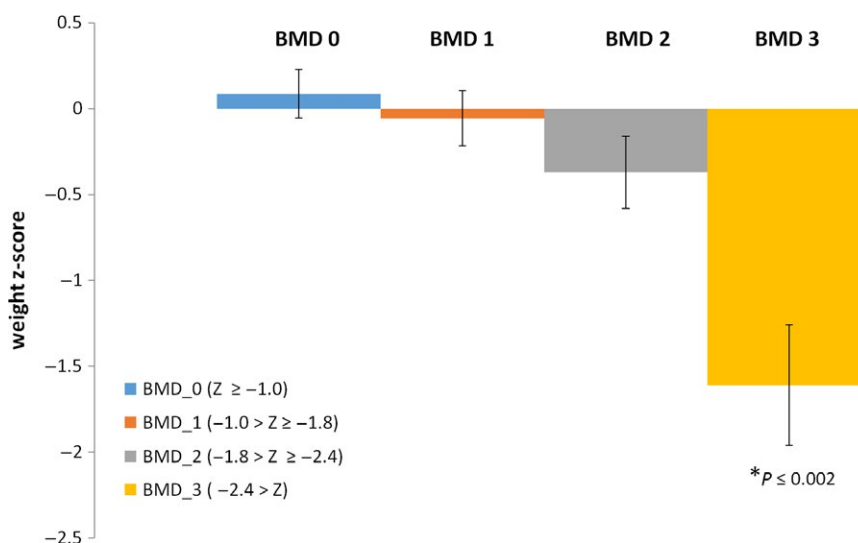
3.3 | Multivariate analysis

Multivariate logistic regression analysis was next performed to evaluate the contribution of the variables above to the decreased BMD in our cohort. Asthma remained a significant independent risk factor for the difference between the groups (OR 38.5, 95% CI 2.8-500, $P < 0.006$), as well as to a lesser extent the percent fat intake (OR 0.9, 95% CI 0.82-0.996, $P = 0.042$) (Table 3). This analysis, grouping together all abnormal BMD patients, cannot pick up the contribution of decreased weight, which appears to be a relevant factor mainly for the severe BMD cases (see above). Thus, we performed an additional analysis, using bone z-scores (minimum of the 3 measured values) as continuous variables fitted by a linear regression model with the same 5 variables (weight z-score, height z-score, asthma, % intake from fat, and carbohydrate intake). Both weight and asthma were found to be significant ($P = 0.0009$ and 0.0037 , respectively; adjusted $r^2 = 0.272$), but not any of the other 3 factors. Repeating the regression with only these 2 variables improves the statistical significance further (adjusted $r^2 = 0.290$; weight, beta coefficient 0.45, 95% CI 0.19-0.46, $P < 0.001$; asthma, beta coefficient -0.3 , 95% CI -0.75 to -0.16 , $P = 0.003$). Thus, we conclude that low BMD is correlated with a lowered weight and with asthma.

4 | DISCUSSION

The multitude of consequences of persistent IgE-CMA go beyond the obvious ever-present risk of anaphylaxis and include effects on the quality of life,⁸⁻¹⁰ nutrition,¹¹ growth,^{12,13} and BMD.⁶ In addition, the inherent atopy of these patients makes them more likely to experience other manifestations of the atopic march.¹⁴ Indeed,

FIGURE 3 Weight z-scores stratified by bone mineral density (BMD) status. The mean weight z-score $\pm$ standard error bars for each BMD severity level are presented. BMD 3 vs BMD 0 ($P < 0.001$), BMD 1 ($P < 0.001$), and BMD 2 ($P = 0.002$). Comparisons of BMD 0 to BMD 1 and BMD 2 were not statistically significant [Colour figure can be viewed at wileyonlinelibrary.com]



Nutritional intake	Abnormal BMD (median [IQR])	Normal BMD (median [IQR])	P-value
Calories (Kcal)	1683 (1399-2067)	1318 (1212-2059)	0.21
% recommended caloric intake	78 (58.8-94)	66 (48-85.5)	0.26
Protein (g)	70.9 (48.3-99.9)	65.1 (51.6-101.7)	0.82
% caloric intake from protein	15.6 (11.5-22.6)	17.0 (14.7-26.1)	0.18
Fat (g)	56.5 (42.4-83.2)	61.5 (44.5-90.9)	0.63
% caloric intake from fat	30.4 (24.7-36.6)	36.7 (32.7-42.3)	0.01
Carbohydrate (g)	209.1 (160.4-271.8)	153 (116.9-199.8)	0.03
% caloric intake from carbohydrate	50.4 (40.1-56.8)	40.3 (35.4-48.2)	0.02
Calcium ^a (mg)	338.6 (205.4-429.8)	239 (195-647.6)	0.92
%DRI calcium	30 (19-42)	23.9 (17.5-57)	0.88
Iron (mg)	12.7 (8.8-18.4)	11.6 (9.1-16.5)	0.75
Magnesium (mg)	245.8 (174.8-288.6)	287.5 (210.3-365.4)	0.14
Phosphorus (mg)	863.7 (581.9-1190.5)	897.1 (751.1-1638.5)	0.24
Potassium (mg)	1998.7 (1582-2771.5)	2150.2 (1803.1-3294.4)	0.24
Zinc (mg)	7.4 (5.0-10.4)	7.8 (5.2-11.9)	0.52
Vitamin C (mg)	78.5 (39.6-99.6)	69.5 (31.6-133.1)	0.98
Thiamine (mg)	0.98 (0.66-1.45)	0.97 (0.61-1.37)	0.8
Riboflavin (mg)	1.0 (0.72-1.65)	1.13 (0.83-1.75)	0.68
Vitamin B6 (mg)	1.7 (1.2-2.3)	1.68 (1.4-2.6)	0.35
Vitamin B12 (mg)	3.2 (1.7-4.7)	2.5 (1.4-6.5)	0.87
Vitamin A (mg)	262.3 (145.3-436.7)	181.9 (132.4-449.6)	0.41
Vitamin E (mg)	5.7 (3.2-8.7)	5.7 (4.8-9.4)	0.7

Normal BMD, n = 13; decreased BMD, n = 49.

Values are median (IQR).

DRI, dietary reference intake.

^aSix patients reported taking calcium supplements on a regular basis. Due to questions of their compliance, however, it was not incorporated into their calcium intake calculation.

TABLE 2 Nutritional intake information stratified by bone mineral density (BMD) results

TABLE 3 Risk factors associated with decreased bone mineral density (BMD) on multivariate analysis

Variable	OR	95% CI	P-value
Weight, z-score	0.41	0.13-1.28	0.125
Height, z-score	0.49	0.16-1.5	0.210
Asthma	38.5	2.8-500	0.006
% caloric intake from fat	0.9	0.82-0.996	0.042
Carbohydrate intake (g)	1.0	0.99-1.01	0.632

approximately half of the IgE-CMA patients in our cohort were diagnosed with asthma. The latter, whose treatment often requires the use of steroids, can have its own influences on bone health and disease depending on the dose, length of treatment, and mode of steroid delivery, that is, inhaled or systemic. For this reason, an exclusionary criterion for our cohort was receiving >2 courses of

systemic steroids, which has been shown to have cumulative deleterious effects on bone health.¹⁵

We previously observed a significant reduction in the BMD of young adult IgE-CMA patients associated with their decreased calcium intake.⁶ As we expanded our analysis, we noted that decreased weight and asthma were additional independent variables associated with poor bone health. Interestingly, asthma was a risk factor across all BMD severity levels, with a wide CI on the logistic regression analysis likely reflecting the small sample size of patients with asthma and a normal BMD. Decreased weight, on the other hand, was only significantly associated with patients with osteoporosis.

The finding of an association of low weight and decreased BMD is supported in the literature in the elderly,¹⁶ in adolescents and adults with anorexic nervosa,^{17,18} and controversially in diet-induced weight loss in obese patients (reviewed in 19). Decreased weight, however, may not be solely a consequence of decreased nutrition. The balance between nutritional intake and nutritional expenditures, the latter being based on one's individual metabolic rate, plays a role.

One of the sensing inputs for this rate homeostasis is the leptin/melanocortin pathway in the central nervous system. Of interest, there was an association of low BMD with a decreased percent intake of calories from fat. A role for leptin in bone health is illustrated by the findings that long-term leptin treatment was shown to increase BMD in lean hypoleptinemic women.²⁰

More surprisingly, asthma increased the risk for osteopenia and osteoporosis, despite our exclusionary criteria of receiving >2 courses of systemic steroids. The etiology for decreased BMD in asthmatics is likely multifactorial. In our study, the asthmatic and nonasthmatic subpopulations did not differ in their total energy intake, and both groups had similarly decreased calcium intakes, and thus, this could not in or by itself explain our findings. Decreased exercise tolerance can contribute to decreased BMD in asthmatics,²¹ but at least in our IgE-CMA cohort both asthmatics and nonasthmatics did not differ significantly in the hours exercised/week. An important limitation to that mentioned above is that both for nutritional intake and for the exercise tolerance, the information obtained was reflective of their current status and may not be representative of their lifetime habits. Two additional explanations, the intrinsic inflammatory state of asthma per se and the potential impact of inhaled steroid treatment in IgE-CMA patients, require some attention.²² In both of these scenarios, a first hit of a reduced calcium intake would be required in conjunction with a second risk factor, to lead to a decreased BMD. Regarding the role of the asthma disease state, a neutrophilic airway inflammatory phenotype was shown to be associated with systemic inflammation in asthmatic patients.^{23,24} Systemic inflammation, furthermore, has been associated with decreased BMD in diverse clinical disease states (for reviews, see 22,25,26).

A second potential risk factor may be related to the treatment regimen received by these asthmatic patients. The effect of inhaled steroids on BMD in patients with asthma has been the subject of some disagreement over the past 2 decades.²⁷ After excluding studies evaluating densitometry in growing children in whom there are no growth parameter-adjusted standards²⁸ and those grouping adult asthmatic and chronic obstructive pulmonary disease patients together, a more recent meta-analysis suggests that the use of inhaled steroids at currently prescribed doses does not reduce the BMD of asthmatic subjects.²⁷ It appears, however, that at higher doses (>than 1 mg per day), inhaled steroids can reduce T- and Z-scores.²⁹

There are several limitations to this study. Although all participants were postpubertal, and at the minimal ages to enter this study, more than 93% and 98% of the BMD values on average are achieved for girls and boys, respectively,³⁰ the possibility exists that for individual patients, this percentage level of peak bone mass was not reached. Furthermore, since we are dealing with an atopic population, other atopic conditions such as atopic dermatitis and allergic rhinitis could additionally be significant factors, considering that their treatment often requires topical steroid use. Finally, an important limitation is that we do not have data on the duration or severity of asthma, or the lifetime cumulative dosing of steroids. A prospective study providing cumulative data since early childhood on hospitalizations, frequent exacerbations, and steroid use (systemic,

inhaled, and topical) would be required to characterize the association between the asthmatic status and BMD taken in adulthood. However, since this was not the primary outcome of the study, we were not able to reliably obtain these data, retrospectively.

In terms of our patients, the exclusionary criteria of >2 lifetime steroid bursts suggest the asthmatics were of mild-moderate severity. While the cumulative lifetime dosing in this population was not recorded and the compliance to their inhaled steroid regimen was unknown, none of the patients were given >500 µg/day of inhaled steroids over the past 5 years, suggesting the doses received should not have deleterious bone effects, in or by itself. Further prospective studies are required to test directly the contributory roles of being asthmatic vs its treatment with inhaled steroids, on their BMD effects. Nevertheless, while the current literature does not report implied risk to bone strength in asthmatics on routine doses of inhaled steroids, the risks/benefits of such treatments should be carefully evaluated in IgE-CMA patients due to their inherent low calcium intake.

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CONFLICT OF INTEREST

The authors have no conflict of interests relevant to this article to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table 1s. Baseline characteristics of IgE-CMA patients

Characteristic	IgE-CMA Group (n=78)
Age (y)	19.5 (17.3-22.8)
Sex (males)	33 (42.3)
Smoking*	16 (22.2)
Exercise (H/W)*	3 (0-4.5)
Asthma	39 (50)

* data from 72 patients are available

For categorical variables (sex, smoking, and asthma) data are presented as N (%). For continuous variables (age and exercise) data are presented as median (IQR) H/W, Hours per week.

Table 2s. Serum values of IgE-CMA patients at time of analysis for BMD (stratified by BMD results)

Serum Value	Decreased BMD median, (IQR)	Normal BMD median, (IQR)	p-value
Calcium (mg/dL, n=63)	9.4 (9.0-9.6)	9.4 (8.9-9.9)	NS
Magnesium (mg/dL, n=60)	1.94 (1.87-2.08)	1.99 (1.85-2.15)	NS
Pi (mg/dL, n=60)	3.25 (3.10-3.7)	3.4 (2.93-3.7)	NS
PTH (pmol/L, n=65)	3.9 (3.1-4.70)	3.80 (3.15-4.9)	NS
Vitamin D (ng/ml, n=50)	28.4 (23.0-39.65)	26.3 (21.5-35.1)	NS

IQR, Interquartile range; Pi, inorganic phosphorous; PTH, Parathyroid Hormone; NS=not significant.