

Increased bone fracture prevalence in postmenopausal women suffering from pollen-allergy

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Received: 6 April 2005 / Accepted: 13 September 2005

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Abstract *Introduction:* Our aim was to investigate whether pollen-allergy can affect bone mass and fractures in postmenopausal women. *Methods:* A total of 125 postmenopausal pollen-allergic women (mean age: 61.26 yr) were split into four groups: (1) treated with neither H1 histamine receptor (H1R) antagonist nor inhaled corticosteroid ($n=43$); (2) treated only with H1R antagonist ($n=53$); (3) treated with both H1R antagonist and inhaled corticosteroid ($n=17$); (4) treated with only inhaled corticosteroid ($n=12$). Treatment, in the appropriate groups, had occurred for at least 5 years, seasonally. One-hundred non-allergic postmenopausal subjects matched for age, body mass index (BMI), and age at menopause served as

controls. *Results:* Overweight and obesity ($25 \text{ kg/m}^2 \leq \text{BMI}$) were common among the allergic women (76%). Allergic patients without treatment had a slightly lower bone density than their non-allergic counterparts. The rate (34.9%) of prevalent low-energy fractures (distal forearm, hip, and clinical vertebral fractures) in untreated allergic patients was almost triple that observed in non-allergic women (13%, $\chi^2 p=0.003$). Bone fracture occurred more often in H1R-only treated patients (30.19%) than in controls ($\chi^2 p=0.01$); however, clinical vertebral or hip fractures developed neither in those treated only with H1R antagonist nor in those who received both H1R antagonist and inhaled corticosteroid. Bone fractures were more frequent among patients with inhaled steroid treatment than among patients with a combined treatment of inhaled steroid and antihistamine (50 versus 29.4%). BMI predicted prevalent fractures at 1.278 (95% CI: 1.047–1.559, $p=0.016$) for a 1 kg/m^2 increase among untreated allergic patients. *Conclusion:* In conclusion, we found a high prevalence of low-energy fractures among pollen-allergic postmenopausal women which was associated with obesity. It is possible that the H1R antagonists compensate for both the negative effect of pollen-allergy and the adverse effect of inhaled corticosteroid treatment on bone fracture risk.

Keywords Bone mineral density · Fractures · H1 histamine receptor antagonist · Obesity · Pollen-allergy

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Introduction

Some data suggest that enhanced histamine release may have an adverse effect on bone metabolism, however the pathomechanism is not fully understood. In mast cell disorders, clinical symptoms are caused by the extracellular release of chemical mediators from the mast cells (such as histamine), the pathologic infiltration of neoplastic mast cells in tissues, or both. In patients with mastocytosis, increased bone resorption, normal or decreased bone formation and, consequently, decreased bone mass have been described [1–3]. It has been postulated that mast cells

function as accessory cells in bone resorption [4]. The most abundant of the inflammatory mediators released during degranulation by the mast cells is histamine [5–7], and the possible role of mast cell-derived histamine in the pathogenesis of idiopathic male osteoporosis has been described [8]. Several studies have shown that H1 or H2 histamine receptor (H1R, H2R) antagonists are able to arrest osteoclast differentiation and function in vivo and to decrease bone resorption in animal models [4, 9–16].

The mast cell is one of the important cells in the pathogenesis of allergic disorders [17], and most allergic symptoms are associated with histamine release [18]. The purpose of this study was to investigate how pollen-allergy with seasonally increased histamine secretion changes bone mass and bone fracture development and how H1R antagonist treatment influences bone mass and fracture prevalence among pollen-allergic postmenopausal patients.

Material and methods

Patients

One hundred and twenty-five postmenopausal women with pollen-allergy [mean age $\pm$ standard error (SE): 61.26 ± 0.57 years] were recruited from an allergologist's practice for this cross-sectional study. The diagnosis of allergy was based on characteristic clinical and laboratory findings (skin prick tests, specific IgE assays). The 125 women were

placed into four cohort groups on the basis of type of allergy treatment, or the lack of treatment. One group consisted of 43 allergic women who received neither inhaled corticosteroids nor H1R antagonist; the average duration of the pollen-allergy among these women was 22.3 years (range: 7–45 years). A second group consisted of 53 allergic women who were being treated only with an H1R antagonist [either cetirizine (10 mg/day), loratidine (10 mg/day), or ketotifen (2 and 4 mg/day)]; the duration of pollen-allergy among these women was 16.5 years (range: 7–15 years). The third group consisted of 17 allergic patients who received an H1R antagonist (at the same doses mentioned above) and inhaled a corticosteroid [either budesonide (maximal 512 μ g/day), fluticasone (maximal 400 μ g/day), or mometasone (maximal 36 μ g/day)]; the allergic disease had existed for 8.5 years (range: 5–16 years) in this group of patients. The fourth group consisted of 12 allergic women who were treated only with an inhaled corticosteroid (at the doses mentioned above); the average duration of the pollen-allergy was 7.4 years (range: 5–14 years) among these women. The minimal duration of allergic symptoms in each of the patients participating in the study was 5 years and, where relevant, the treatment had been seasonally used for 5 years or more. The allergic symptoms were: sneezing, sniffing, rhinorrhoea, nasal blockage, reddening of conjunctivae, swelling of eyelids, keratoconjunctivitis, reduced taste or smell, reduced hearing, headaches. Most symptoms occurred in every group, however they were of a shorter duration

Table 1 Age, body mass index (BMI), age at menopause, and dual-energy X-ray absorptiometry (DXA) and quantitative ultrasound (QUS) parameters in control and allergic groups

Treatment	Control –	Allergic –	H1R antagonist	H1R antagonist, inhaled corticosteroid	Inhaled corticosteroid
Investigated parameter ^a	n=100, mean $\pm$ SE	n=43, mean $\pm$ SE	n=53, mean $\pm$ SE	n=17, mean $\pm$ SE	n=12, mean $\pm$ SE
Age (year)	61.84 $\pm$ 0.85	60.19 $\pm$ 1.29	62.06 $\pm$ 1.29	60.41 $\pm$ 1.91	59.33 $\pm$ 2.08
BMI (kg/m ²)	28.61 $\pm$ 0.52	28.03 $\pm$ 0.69	29.43 $\pm$ 0.67	28.35 $\pm$ 0.96	30.73 $\pm$ 1.64
Age at menopause (year)	48.52 $\pm$ 1.19	48.07 $\pm$ 0.71	49.38 $\pm$ 0.55	47.35 $\pm$ 1.31	48.75 $\pm$ 1.16
L2-4 BMD (g/cm ²)	0.899 $\pm$ 0.019	0.894 $\pm$ 0.023	0.924 $\pm$ 0.027	0.857 $\pm$ 0.043	0.895 $\pm$ 0.042
T-score	–1.48 $\pm$ 0.15	–1.65 $\pm$ 0.14	–1.47 $\pm$ 0.16	–1.89 $\pm$ 0.26	–1.68 $\pm$ 0.26
Z-score	–0.34 $\pm$ 0.14	–0.56 $\pm$ 0.15	–0.33 $\pm$ 0.16	–0.79 $\pm$ 0.25	–0.54 $\pm$ 0.28
Femoral neck BMD (g/cm ²)	0.768 $\pm$ 0.015	0.732 $\pm$ 0.017	0.764 $\pm$ 0.017	0.756 $\pm$ 0.032	0.711 $\pm$ 0.032
T-score	–1.93 $\pm$ 0.12	–2.33 $\pm$ 0.13*	–2.09 $\pm$ 0.14	–2.17 $\pm$ 0.26	–2.33 $\pm$ 0.19
Z-score	–0.27 $\pm$ 0.10	–0.67 $\pm$ 0.13**	–0.34 $\pm$ 0.13	–0.51 $\pm$ 0.23	–0.73 $\pm$ 0.23
Forearm BMD (g/cm ²)	0.273 $\pm$ 0.007	0.269 $\pm$ 0.009	0.283 $\pm$ 0.009	0.277 $\pm$ 0.019	0.279 $\pm$ 0.017
T-score	–2.3 $\pm$ 0.17	–2.31 $\pm$ 0.22	–1.99 $\pm$ 0.23	–2.17 $\pm$ 0.48	–2.13 $\pm$ 0.45
Z-score	–0.26 $\pm$ 0.11	–0.37 $\pm$ 0.13	–0.06 $\pm$ 0.13	–0.26 $\pm$ 0.26	–0.16 $\pm$ 0.34
Estimated calcaneus BMD (g/cm ²)	0.468 $\pm$ 0.016	0.452 $\pm$ 0.016	0.468 $\pm$ 0.021	0.455 $\pm$ 0.032	0.450 $\pm$ 0.046
T-score	–0.97 $\pm$ 0.14	–1.13 $\pm$ 0.14	–1.01 $\pm$ 0.19	–1.13 $\pm$ 0.29	–1.16 $\pm$ 0.40
QUI	88.3 $\pm$ 9.9	83.5 $\pm$ 2.5	86.1 $\pm$ 3.3	84.0 $\pm$ 5.1	83.3 $\pm$ 7.2
SOS (m/s)	1543.1 $\pm$ 6.5	1532.4 $\pm$ 3.9	1535.5 $\pm$ 5.0	1533.5 $\pm$ 8.4	1537.2 $\pm$ 10.2
BUA (dB/MHz)	64.2 $\pm$ 2.4	64.1 $\pm$ 2.5	67.7 $\pm$ 3.2	63.9 $\pm$ 4.9	58.7 $\pm$ 7.9

* $p=0.032$, ** $p=0.016$; unmatched two-tailed t -test for comparisons between untreated allergic and control subjects; no statistical differences were assessed between other groups

^aBMD, Bone mineral density; SOS, speed of sound; BUA, heel broadband ultrasound attenuation; QUI, quantitative ultrasound index

among the untreated allergic patients (2–3 weeks) than among the H1R antagonist- and/or inhaled corticosteroid-treated allergic subjects (1–2 months). H1R antagonists or inhaled corticosteroids were not recommended for use in patients with symptoms that were relatively less severe or of a shorter duration.

One hundred non-allergic subjects from general practice served as controls; these were matched for age, body mass index (BMI), and age at menopause to the allergic subjects. Potential participants in both the allergic and non-allergic control groups with secondary causes of osteoporosis (asthma, thyroid or parathyroid dysfunction, history of renal stones, impaired renal function, diabetes mellitus, hepatic disorders, gastrointestinal diseases, ovariectomy) or those on medication likely to affect skeletal metabolism (vitamin D, bisphosphonates, sexual steroids, selective estrogen receptor modulators, calcitonin, fluorides, thiazide diuretics, anticoagulants, anticonvulsive drugs, antacids, oral or intravenous corticosteroids, with the exception of inhaled corticosteroids and H1R antagonists) were excluded. All of the participating women were informed about the study and were asked to give written informed consent. The study was authorized by the Ethical Committee of the participating institution.

Bone densitometry, quantitative ultrasound, and fracture assessment

Bone mineral density (BMD, g/cm²) was measured for all of the allergic patients and controls at lumbar 2–4 vertebrae, left femoral neck [XR-46, Norland, Fort Atkinson, Wis.; coefficient of variation (CV %): 0.9 on vertebrae; 1.3 on femoral neck] and at the radius of the non-dominant side (P-DEXA, Norland; CV%: 0.464) by the dual-energy X-ray absorptiometry method (DXA). Broad-band ultrasound attenuation of the heel (BUA, dB/MHz, CV%: 1.92), speed of sound (SOS, m/s, CV%: 0.14), quantitative ultrasound index (QUI, CV%: 1.85) and estimated calcaneal BMD (CV%: 2.19) and its T-score were assessed by the quantitative ultrasound (QUS) method (Sahara bone sonometer, Hologic, Waltham, Mass.). According to the World Health Organization (WHO) guidelines [19], BMD measurements were categorized as normal (T-score 1.0 or above), osteopenia (T-score between -1.0 and -2.5), or osteoporosis (T-score 2.5 or below). Diagnosis of osteopenia or osteoporosis was set up if T-score values were lower than -1.0 or ≤-2.5 at one or more measured sites.

Distal forearm, hip and validated (by morphometry according to McCloskey method [20]) vertebral fractures with clinical symptoms that resulted from mild to moderate trauma (typically a fall to the floor from standing height or less) and had occurred within the past 10 years, and were confirmed by medical record were considered to be low-energy fractures. Fractures following severe trauma (a fall from greater than standing height, traffic accidents) and other fracture sites that are not listed above were excluded. Morphological vertebral fractures without relevant clinical

symptoms were not considered. The patients were asked about skeletal pain, especially about back pain, by means of a questionnaire.

Statistics

Statistically significant differences were analyzed by the unpaired *t*-test and the Mann-Whitney test. The frequency of bone fractures in the allergic and non-allergic groups were compared using standard Chi-squared tests. Pearson's correlation test was applied to determine the relationship between BMD values and BMI and between DXA and QUS parameters. The relationship between osteodensitometric and QUS values, adjusted for BMI, and the risk of having at least one fracture at the distal forearm, spine, or hip were determined by multivariate logistic regression analysis. The results were described using Odds ratio (OR) and the 95% confidence intervals (CI). A *p* value of 0.05 or

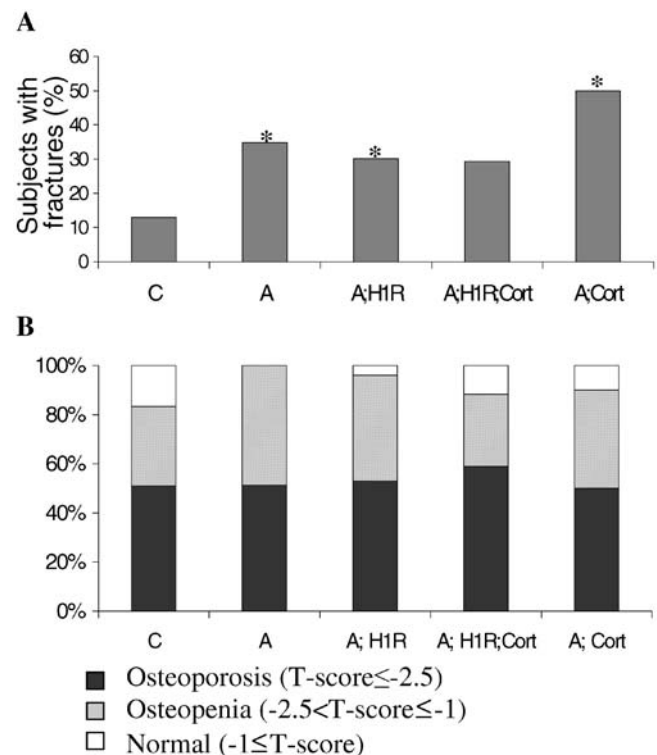


Fig. 1 **a** Percentage distribution of all documented low-trauma bone fractures (distal forearm, clinical vertebral, hip fractures) in non-allergic and allergic groups. **b** Diagnosis of osteoporosis, osteopenia [at one or more measured sites (femoral neck, lumbar 2–4 vertebrae, forearm)] and normal bone density in non-allergic and allergic groups. C Non-allergic controls (*n*=100), A allergic women receiving neither H1R antagonist nor an inhaled corticosteroid (*n*=43), A;H1R allergic women receiving H1R antagonist (*n*=53), A; H1R; Cort allergic women receiving both H1R antagonist and inhaled corticosteroid (*n*=17), A;Cort allergic women receiving inhaled corticosteroid (*n*=12). **p*<0.05, Chi-squared test for the comparison of allergic groups to non-allergic subjects

less was considered to be significant for all statistical tests. Data were presented as the mean $\pm$ SE. Statistical analyses were performed with the SPSS statistical software (version 10.0, SPSS Inc., Chicago, Ill.).

Results

Descriptive statistics

Forty-six allergic patients (36.8% of all allergic) were obese ($\text{BMI} > 30 \text{ kg/m}^2$), and 49 allergic women (39.2% of all allergic) were overweight ($25 \leq \text{BMI} \leq 30 \text{ kg/m}^2$). Of the non-allergic postmenopausal women that had been matched with the allergic ones for age, BMI, and age at menopause, 35% were obese and 41% were overweight. Anthropometric values and age at menopause are shown in Table 1.

Fracture prevalence and back pain

Allergic women who did not receive any treatment for pollen-allergy had almost triple the rate of prevalent fractures [34.9% (15/43): 12 distal forearm, 1 clinical vertebral, 2 hip fractures] compared to non-allergic women [13% (13/100), $p=0.003$] and a 1.6-fold higher rate of back pain [72.1% (31/43) versus 44% (44/100), respectively; $p=0.002$]. Distal forearm fracture occurred more often among H1R-antagonist-only treated allergic women than among non-allergic controls [30.19% (16/53) versus 9% (9/100), respectively; $p=0.001$], and back pain was more frequent among H1R-antagonist-only treated allergic than among controls [73.6% (39/53) versus 44% (44/100), respectively; $p<0.001$]. Neither allergic patients treated only with H1R antagonist nor allergic patients treated with both an antagonist as well as an inhaled steroid had clinical

vertebral or hip fractures. The bone fractures [50% (6/12) versus 29.4% (5/17), respectively] and the clinical vertebral and hip fractures in particular [8.3% (1/12) versus 0% (0/17), respectively] were more frequent in those receiving only inhaled steroid treatment than in those receiving both an inhaled steroid and antihistamine. Back pain appeared more often in allergic patients receiving only an inhaled steroid than in those on an inhaled steroid and H1R antagonist treatment [91.6% (11/12) versus 64.7% (11/17), respectively], however the differences were not statistically significant. Compared to the controls, both the H1R-only treated group and the inhaled-corticosteroid-only group had significantly more low-trauma bone fractures (Fig. 1a). No documented hip or clinical vertebral fracture was found in those pollen-allergic women who received only H1R antagonist or both H1R antagonist and inhaled corticosteroid.

Densitometric and quantitative ultrasound findings

DXA and QUS results are presented in Table 1. Allergic patients who received neither inhaled corticosteroids nor H1R had significantly lower T- and Z-scores at the femoral neck than the non-allergic controls, and in most of the allergic patients the other DXA and QUS parameters were lower (not statistically significant) than those of the non-allergic controls. Osteopenia was diagnosed more often among untreated pollen-allergic women than among the controls, and normal bone density was not found at all in the former group (Fig. 1b). No differences were found with respect to the DXA nor in QUS results between allergic patients receiving H1R antagonist treatment and the non-allergic controls. Furthermore, some results of the allergic patients were slightly higher. A modest correlation was found between QUS and DXA results at all measurement sites (range: $r=0.276$ – 0.584) in the non-allergic controls, the untreated allergic women, and the H1R-only treated

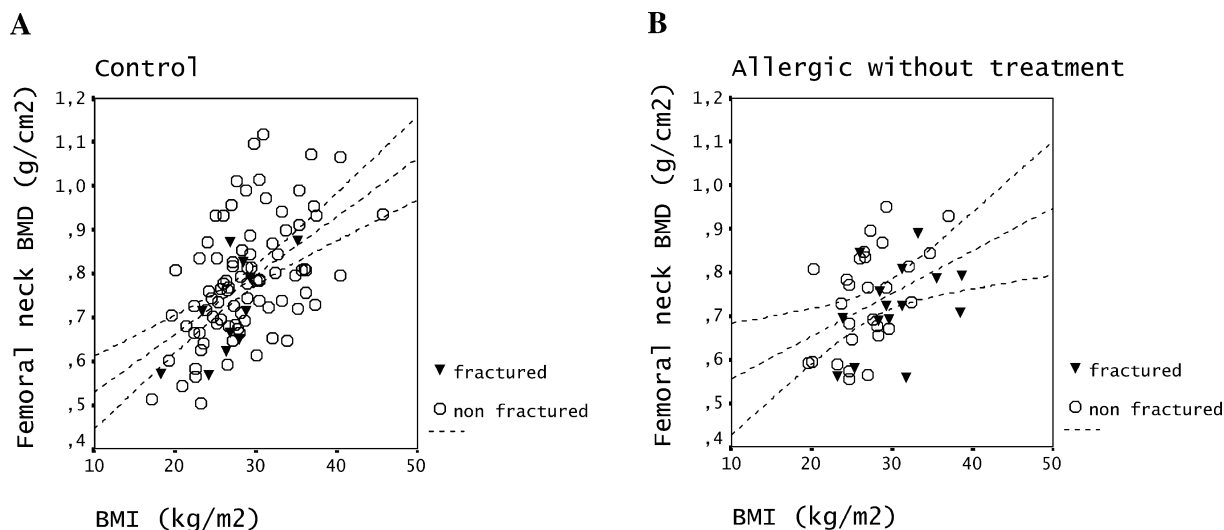


Fig. 2 Correlation of body mass index (BMI) with femoral neck bone mineral density (BMD) in non-allergic controls (**a**) ($r=0.533$, $p<0.001$) and in allergic women receiving neither H1R antagonist

nor inhaled corticosteroid (**b**) ($r=0.41$, $p=0.006$). The line reflects the regression with a 95% confidence interval

Table 2 Age, body mass index, age at menopause, and DXA and QUS parameters in fractured and non-fractured controls and untreated allergic women

Investigated parameter	Control			Allergic receiving neither H1R antagonist nor inhaled corticosteroid		
	Non-fractured (<i>n</i> =87, mean ± SE)	Fractured (<i>n</i> =13, mean ± SE)	<i>p</i>	Non-fractured (<i>n</i> =28, mean ± SE)	Fractured (<i>n</i> =15, mean ± SE)	<i>p</i>
Age (year)	61.91±0.89	61.38±2.74	0.538	58.14±1.44	64.00±2.30	0.036
BMI (kg/m ²)	28.78±0.57	27.54±1.17	0.545	26.84±0.77	30.24±1.23	0.027
Age at menopause (year)	48.00±1.47	50.60±0.60	0.585	49.21±0.78	45.93±1.31	0.03
L2-4 BMD (g/cm ²)	0.917±0.020	0.777±0.038	0.013	0.878±0.031	0.910±0.036	0.476
T-score	-1.34±0.16	-2.39±0.24	0.012	-1.71±0.19	-1.55±0.22	0.516
Z-score	-0.21±0.15	-1.19±0.27	0.015	-0.70±0.18	-0.46±0.12	0.143
Femoral neck BMD (g/cm ²)	0.783±0.014	0.658±0.067	0.059	0.743±0.222	0.722±0.025	0.693
T-score	-1.91±0.13	-2.10±0.35	0.568	-2.28±0.18	-2.44±0.21	0.619
Z-score	-0.22±0.10	-0.70±0.30	0.244	-0.74±0.17	-0.53±0.19	0.499
Forearm BMD (g/cm ²)	0.279±0.008	0.234±0.015	0.031	0.281±0.121	0.262±0.010	0.193
T-score	-2.15±0.19	-3.14±0.38	0.068	-2.14±0.30	-2.59±0.28	0.242
Z-score	-0.14±0.12	-1.01±0.28	0.008	-0.32±0.21	-0.46±0.12	0.681
Estimated calcaneus BMD (g/cm ²)	0.480±0.016	0.399±0.052	0.016	0.473±0.021	0.424±0.033	0.227
T-score	-0.86±0.14	-1.63±0.47	0.013	-1.03±0.16	-1.35±0.32	0.239
QUI	101.9±10.8	74.7±14.0	0.127	85.8±2.8	79.1±4.8	0.221
SOS (m/s)	1546.8±7.2	1520.6±12.3	0.015	1535.7±4.8	1524.8±7.1	0.265
BUA (dB/MHz)	65.6±2.4	55.6±8.1	0.026	66.2±2.6	59.9±5.6	0.24

p= Mann-Whitney test for comparisons between fractured and non-fractured individuals. Non-fractured controls differed from non-fractured allergic patients in age (*p*=0.036) and in femoral neck Z-score (*p*=0.021). Fractured controls differed from fractured allergic in lumbar spine BMD (*p*=0.018) and in lumbar spine T-score (*p*=0.018)

allergic women. However, no correlation was revealed between the QUS and DXA results in corticosteroid-treated allergic subjects, irrespective of the H1R antagonist treatment.

Prediction of fractures

In the control group, BMI-adjusted values for a 1 SD reduction in the lumbar 2–4 vertebral T-score predicted prevalent low-energy fractures with a significant (*p*=0.034) odds ratios of 2.01 (95% CI: 1.06–3.817). In allergic patients receiving no treatment, only the body mass index was able to predict prevalent fractures at 1.278 (95% CI: 1.047–1.559, *p*=0.016) for a 1 kg/m² increase in BMI, and this effect remained significant after an adjustment for age (OR=1.193; 95% CI: 1.017–1.4; *p*=0.031). The femoral neck BMD positively correlated with BMI in both the control group and in untreated allergic subjects (Fig. 2), with a higher number of fractured patients found with higher BMD in the untreated allergic group. Neither DXA nor QUS values were able to predict bone fractures in any of the allergic groups. No significant differences were observed in age, BMI, and age at menopause between fractured and non-fractured subjects in the control group. Fractured patients had lower lumbar and forearm BMD and QUS values. In contrast, the fractured untreated pollen-allergic patients did not differ from non-fractured untreated

allergic women with respect to BMD at any of the skeletal sites tested and QUS values. The fractured allergic women were, however, older and more obese, and they had earlier menopause than their non-fractured counterparts (Table 2). The fractured untreated allergic women had a higher lumbar BMD and a higher lumbar T-score than the non-allergic non-fractured women. The non-fractured allergic patients were younger, and they had a lower femoral neck Z-score than the non-fractured control patients.

Discussion

In this cross-sectional analysis, we have found a high bone fracture rate in pollen-allergic postmenopausal women who had not been receiving treatment for pollen-allergy. Fractures developed more often in allergic patients receiving only an inhaled corticosteroid than in those receiving only antihistamine or antihistamine in combination with an inhaled steroid. Neither hip nor clinical vertebral fractures were diagnosed among the antihistamine-treated allergic patients, irrespective of whether they used inhaled corticosteroid for their pollen-allergy. There was no relationship between low-energy bone fractures and the bone mass and quantitative ultrasound results, however a higher body mass index was found to be associated with fractures among untreated allergic women.

The moderately decreased bone mass among allergic patients using inhaled corticosteroids was not surprising as similar results have been found in earlier studies [21–23]. Although our study was conducted on only a limited number of patients treated only with inhaled corticosteroids, we found that this patient cohort showed an increased fracture rate, which is in contrast to the results of Vertergaard et al. [24], who found that there was no increase in the risk of fractures among users of inhaled corticosteroids. The higher fracture rate in untreated pollen-allergic patients, however, can not be explained by the possible unfavorable effects of inhaled corticosteroids. Our results show that an allergy, independent of corticosteroid administration, has an adverse effect on fracture risk. There are some possible explanations for this increased fracture rate in pollen-allergic patients. It is well known that allergic symptoms are associated with enhanced histamine production and that histamine induces osteoclastogenesis [5, 6, 18]. These observations suggest that histamine oversecretion may enhance bone resorption, which could be related to increased fracture rate in people with an allergy. We hypothesize that postmenopausal women who are at a higher risk for bone fractures due to allergic rhinitis and inhaled steroid therapy could be protected by an H1R antagonist since neither clinical vertebral nor hip fracture was found in the antihistamine-treated patient group. With respect to the DXA results and most of the QUS results, patients treated with antihistamines had moderately increased values. Some studies have demonstrated that histamine deficiency and histamine receptor inhibition prevent bone resorption. A previous study by our group showed that histamine deficiency in transgenic mice causes increased bone mass [9]. Histamine deficiency and promethazine, an H1R antagonist, have been shown to inhibit ovariectomy-induced bone loss in rats [9, 14]. Furthermore, promethazine can induce a modest increase in vertebral bone mass in postmenopausal women [25].

Our study confirms previously reported data concerning the association of fracture risk with BMD in postmenopausal non-allergic control patients; however, in allergic subjects, fracture risk is not related to bone density. In comparison with non-allergic subjects, untreated allergic patients had almost a threefold increase in low-energy fracture rate despite only a mild difference in bone mass. Since this result suggests an involvement of bone in pollen-allergic postmenopausal patients that is independent of mineral density, we subsequently investigated a number of non-mass bone characteristics by means of the QUS method. There is evidence documenting the ability of QUS to give further BMD-independent information on bone and to predict osteoporotic fracture risk [26–28]. QUS parameters are associated with several non-mass bone parameters, such as architecture, histomorphometrical parameters, trabecular separation, connectivity, alignment, mechanical properties (Young's modules and strength), etc. SOS is influenced by the elasticity of bone as well as by its density. BUA is determined by mechanisms of diffraction, scattering, and absorption in the bone, marrow, and soft tissue [29]. Our data confirm the previously reported low correlation be-

tween QUS and DXA results. QUS at the heel, with respect to SOS values, showed an ability to discriminate between women with or without fractures in the postmenopausal control group; this result is in concordance with that of other studies [30, 31]. However, this finding was not confirmed among allergic postmenopausal women. We found only moderately lower QUS values among non-treated fractured allergic patients in comparison with non-treated, non-fractured allergic women. A novel finding of this study is the moderately decreased QUS results in every allergic group. An earlier study reported that QUS parameters at calcaneus and at phalanges are decreased in systemic glucocorticoid-treated patients compared with controls [32], however, to date, no QUS data have been reported for patients being treated with inhaled corticosteroids. Fracture risk could be estimated by QUS in postmenopausal osteoporosis [33], however, the clinical usefulness of the method in different patient groups, such as in those with an allergy, has not established.

Low BMI is one of the main determinants of low bone mass according to previous results – and confirmed by our study – and it was found to be associated with low-energy fractures as an independent risk factor [34, 35]. Despite the fact that overweight and obesity were very common among allergic postmenopausal women, we found a high prevalence of fractures in this group. The greater BMI by 1 kg/m² was accompanied by almost a 1.3-fold higher risk for bone fractures among non-treated, pollen-allergic, postmenopausal women. The prevalence of obesity is also very high in asthma patients and increases with increasing asthma severity [36]. Obesity has been suggested to be a risk factor for asthma, but the mechanism is unclear [37]. While leptin and leptin-associated cytokines might play roles in overweight-related asthma [38], it is not known whether obesity really predisposes asthma and pollen-allergy or whether asthma and allergy cause obesity as a secondary consequence of the disease. Similar observations were published in type 2 diabetes mellitus: a higher BMI was strongly associated with a higher BMD, however the fracture risk was found to be increased [39].

Several limitations should be considered when interpreting the results of this study. The authors tried to avoid the confounding effect of BMI by using a BMI-matched, non-allergic control group; consequently, most control patients were obese or overweight. Surprisingly, several non-allergic controls were osteoporotic or osteopenic, which explains the relatively high prevalence of fractures among them. We presume that the controls do not accurately represent a cross section of the healthy Hungarian population. The range of disease severity for individual patients was quite broad, which may have influenced the applied treatment. Therefore, our findings are not exclusively the consequences of the therapy; for example, the more serious pollen-allergy symptoms could be associated with the more serious osseous disorders, irrespective of corticosteroid administration. We have not included non-clinical vertebral fractures, which could potentially reduce the performance of spinal BMD. The seasonal variation of vitamin D status and potential vitamin D deficiency were also not

considered. However, allergic and control subjects were simultaneously recruited. The small number of cases in some patient groups and the large SE values did not enable us to draw conclusions from several of the results. Unfortunately, we did not measure bone turnover markers and mast cell activity, and histamine metabolism was also not estimated in this study.

In conclusion, we found a high rate of low-energy bone fractures which were associated with obesity in postmenopausal women with untreated pollen-allergy. We also found that neither bone mineral density nor quantitative ultrasound parameters could predispose prevalent bone fractures among postmenopausal pollen-allergic women. Appreciation of the DXA and QUS results in allergic patients was not established. Since the question remains of whether significant bone mineral improvement can be achieved by H1R antagonist therapy, further studies are needed to investigate the effects of H1R antagonists on fracture risk reduction in postmenopausal osteoporosis.

Acknowledgements This study was supported by The Medical Research Council of Hungary (ETT 226/2003) and The Hungarian Scientific Research Fund (OTKA T038067).

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