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Bone ultrasonometric features and growth hormone secretion in asthmatic patients during chronic inhaled corticosteroid therapy

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Abstract

Background: Quantitative ultrasound bone densitometry (QUBD) is a new method to assess bone mineral density and bone microarchitecture. Corticosteroid (CS) therapy may diminish bone mass, alter bone quality and may influence growth hormone (GH) secretion and bone metabolism markers. Therefore, the aim of this study was to evaluate the effects of long-term therapy with inhaled CSs (ICSs) on structural bone characteristics and their correlations with GH secretion and bone markers in asthmatic patients.
Methods: In a cross-sectional study, we enrolled 60 adult patients with mild to moderate persistent asthma: 22 on chronic (>1 year) ICS therapy, 10 naive to ICSs treatment and 28 healthy control subjects. The groups were matched for age and BMI. Each subject underwent to QUBD at the phalanxes to assess bone microarchitecture by ultrasound bone profile index (UBPI), bone density by amplitude-dependent speed of sound (AdSos); test with GH-releasing hormone (GHRH) injection with calculation of peak GH and the Δ GH (peak GH–basal GH); and hormonal and bone markers measurements.
Results: Asthmatics treated with long-term ICS therapy showed a lower UBPI ($P < 0.01$) compared to controls (49.8 ± 19.3 vs. 77.0 ± 10.1, respectively) and to asthmatics never taking ICSs (73.2 ± 9.6). In ICS-treated asthmatics, ΔGH and GH-peak showed a significant correlation with UBPI. A significant difference was observed comparing asthmatics treated with ICSs to controls and asthmatics naive to ICSs in GH response to GHRH iv bolus. Serum osteocalcin was significantly reduced in asthmatic patients treated with ICSs.
Conclusions: In asthmatic patients, long-term ICSs treatment produces negative effects on bone quality assessed by QUBD, and such effects are associated to an impaired GH secretion.

Keywords: Quantitative bone ultrasound densitometry; Asthma inhaled corticosteroids; Growth hormone

Introduction

Quantitative ultrasound bone densitometry (QUBD) is a method to measure bone tissue in order to detect osteoporosis [1,2], it provides information about the bone structure and elasticity and not only about the bone mineral density (BMD) [3,4]. The human phalanx consists of both trabecular and cortical bone, a structure similar as vertebrae and hips. The ability of QUBD at the phalanxes to identify patients at risk of fragility fractures of the spine is accepted [5–7]. A recent study has demonstrated that QUBD at hand phalanxes predicts vertebral fractures as effectively as BMD [8]. In corticosteroid (CS)-treated patients, bone quality may be more affected than bone mineral density (BMD) as the frequency of vertebral fractures in these patients is reported higher than expected for their BMD [9,10]. Therefore, QUBD has been proposed as an effective method to evaluate and to monitor bone alterations during CS therapy [11,12].

Inhaled CSs (ICSs) are recommended as the first-line choice of anti-inflammatory drugs in the management of asthma, and, currently, they have a widespread use [13]. ICSs may cause dose-related systemic effects [14] affecting adrenal and growth hormone axis and bone metabolism [15–17].

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Osteoporosis is a potential but common side-effect of chronic treatment with CSs, however, the mechanisms by which CSs lead to a reduction in bone mass are complex, involving both direct and indirect effects on the remodeling cycle [18,19]. The reduction of growth hormone (GH) secretion observed during CS treatment seems to be relevant to induce bone loss [20–22]. Therefore, the aim of this study was to evaluate the effects of long-term therapy with ICSs on structural bone characteristics and their association with GH secretion and bone markers in asthmatic patients, in comparison with asthmatics who never used ICSs and control subjects.

Patients and methods

Patients

In a cross-sectional study, we enrolled 60 consecutive adult patients with mild to moderate persistent asthma, diagnosed according to National Institutes of Health (NIH) criteria [13], 22 on chronic (>1 year) ICS therapy (12 female, 10 male; age: 50.0 ± 7.0 years.; BMI: 26.5 ± 6.0 kg/m^2) and 10 naive to ICS treatment (6 female, 4 male; age 47.1 ± 5.2 years; BMI: 25.1 ± 4.0 kg/m^2), who were referred to our Pulmonary Function Laboratory in the Department of Internal Medicine (Brescia, Italy). We enrolled 28 healthy control subjects (15 female, 13 male; age 48.5 ± 8.8 years; BMI: 25.0 ± 4.0 kg/m^2).

Exclusion criteria were the following: age <18 years and >65 years, BMI >30 kg/m^2 and <20 kg/m^2, diseases potentially interfering with the study (i.e. endocrine disease, hepatic or renal failure, premature or surgical menopause without replacement hormonal therapy), treatment with other drugs known to influence either GH secretion or bone metabolism. Moreover, asthmatics with sedentary lifestyle, with excessive alcohol intake, with history of a course of systemic CSs in the past 6 months or more than two courses (no longer than 7 days) ever and more than 10 inhalers of a nasal CS or 10 prescriptions of dermal CS ever were excluded. At the time of inclusion, all the asthmatic patients were in a stable condition and free from respiratory exacerbations. The severity of asthma was classified in the groups studied by clinical features and pulmonary function tests before treatment [13]. The study protocol was approved by the local Ethics Board, and all subjects gave their written informed consent to participate, and the study was conducted in accordance with the Helsinki Declaration.

Demographic and functional characteristics of the asthmatic patients and controls are reported in Table 1.

Table 1
Characteristics of the population studied

	Asthmatics on ICS	Asthmatics ICS naive	Controls	*P*
Number	22	10	28	
Sex M/F	10/12	4/6	13/15	0.95 [a]
Age (years)				
Mean ± SD	50.8 ± 7.0	47.1 ± 5.2	48.5 ± 8.8	0.56
BMI (kg/m^2)				
Mean ± SD	26.5 ± 6.0	25.1 ± 4.0	25.0 ± 4.0	0.25
Smoking history				
Smoker	0	0	0	0.83 [a]
Ex-smoker	10	4	10	
Never smoker	12	6	18	
FEV1 (% pred)				
Mean ± SD	91.6 ± 5.5	89.3 ± 5.3	94.5 ± 3.5	0.07
UBPI				
Mean ± SD	49.8 ± 19.3 [b]	73.2 ± 9.6	77.0 ± 10.1	0.001
(CI95%)	(40.9/58.6)	(66.2/80.1)	(72.8/81.1)	
AdSos *Z* score				
Mean ± SD	−0.2 ± 1.4	0.09 ± 0.9	0.2 ± 1.2	0.364
(CI95%)	(−0.8/0.4)	(−0.5/0.7)	(−0.2/0.8)	
AdSos *T* score				
Mean ± SD	−1.1 ± 1.2	−0.1 ± 1.1	−0.7 ± 1.1	0.06
(CI95%)	(−1.7/−0.6)	(−1.2/0.9)	(−1.2/−0.3)	

BMI: body mass index.
FEV_1: forced expiratory volume in the first second.
UBPI: ultrasound bone profile index.
AdSos: amplitude-dependent speed of sound.
[a] Analysis performed by χ^2.
[b] Asthmatics on ICS vs. asthmatics naive ICS and controls (Bonferroni correction).

Study protocol

Clinical assessment

At the beginning, each subject completed a questionnaire and performed pulmonary function tests. The questionnaire asked about current and previous drug treatment, history of asthma, smoking and alcohol intake and physical activity. Exercise tolerance was not specifically assessed, however, no difference was found in the questionnaire concerning physical activity between asthmatics on ICSs and asthmatics ICS naive. Women were asked about menstrual history or premature or surgical menopause. All ICS-treated patients were on the lowest possible maintenance dose as a result of previous attempts of dose stepping down. The asthmatic patients taking ICSs who were included in the study used a standard dosage of either budesonide or fluticasone propionate. The mean daily dose of budesonide administered with a turbohaler was 780 ± 290 mcg in 13 patients, while the mean daily dose of fluticasone propionate administered with a metered dose inhaler was 695 ± 380 mcg in 9 patients. Given the relatively small number of asthmatics treated with ICSs and the almost equipotent mean dose of budesonide and fluticasone propionate they used, these patients were analyzed as a single group.

Quantitative ultrasound bone densitometry (QUBD)

QUBD measurements were taken at the fingers of the nondominant hand by the DBM sonic 1200 (Igea, Carpi, Mo, Italy). This instrument has an electronic caliper with arms that have transmitting and receiving probes that work at a frequency of 1.25 MHz. The device measures the amplitude-dependent speed of sound (AdSos) through the bone by

positioning the probes of the electronic caliper on the medial and lateral sites of the distal metaphysis of the proximal phalanx of the last four fingers. The averaged values of the four measurements are given as the examination result and expressed in m s^{-1}. The Sos is calculated by measuring the phalanx thickness (using a high-precision 10-μm electronic potentiometer contained in the positioning caliper) and dividing it by the flight time. The flight time is the time elapsed from the generation of the pulse to the instant when the signal received reaches a predetermined minimum amplitude value (2 mV) for the first time. The same device calculates the ultrasound bone profile index (UBPI), which is an index calculated from the ultrasound (US) graphic trace, giving a quantitative evaluation of the US signal characteristics carrying an important amount of information on bone quality. In detail, the following parameters on each graphic trace were considered: fast wave amplitude (FWA: mV), dynamics of the ultrasound signal (SDy: mV/mvs^2), time interval between the first received signal and the speed value of 1700 m/s (time frame [TF]: mcs), signal energy normalized (SE: mV^2 mcs), maximum signal amplitude in the TF (UPA: mV). As previously reported, calculation of UBPI was based on the following mathematical equation: UBPI = −(−0.0018 × SDy −0.0560 × FWA − 1.1467 × TF + 3.0300). Calibration of the device has been given using the dedicated Plexiglas phantom according to manufacturer's instructions. For QUBD measurement, in vivo coefficient of variation (CV) was estimated in twenty volunteers by three short-term QUBD repeated measurements taken by two operators over a period of 7 days. For UBPI, we found 3.1% CV intraoperator and 3.35% CV interoperator; for AdSos in the same data set, we found 0.85% CV intraoperator and 0.95% CV interoperator. These data are in line with what has been previously reported [6] Reference values for calculating *Z* score (SD decrease from age-matched normals) and T score (SD decrease below young normal value) were obtained from Italian population-based studies [23–25]. Measurements were performed using US contact gel.

Hormonal and bone markers

Hormonal and biochemical evaluations were performed as previously described [26]. Briefly, subjects underwent testing with IV bolus (1 μg/kg) injection of human GH-releasing hormone (GHRH) (Geref, Serono, Italy), and samples of GH (IRMA assay, Nichols Institute, USA, Allegro hGH, Nichols Institute, San Juan Capistrano, CA) were taken before and after GHRH administration to obtain values for peak GH (the highest GH value observed after stimulus with GHRH) and ΔGH [peak GH − (baseline GH + GH at time 0) / 2]. At baseline samples of serum, insulin-like growth factor 1 (IGF-1) (IRMA assay, Nichols Institute, USA, after acid–ethanol extraction) and blood–urine were collected for bone turnover markers and to measure serum and urine cortisol. Serum osteocalcin as marker of bone formation was assessed by radioimmunoassay (Nichols Institute, USA), and urinary deoxypyridinoline as marker of bone resorption was assessed by ELISA (corrected for urinary creatinine concentration).

Lung function measurements

Dynamic lung volumes were measured using a spirometer (CAD/Net system 1070, MCG, St. Paul, Minnesota USA) in accordance with the American Thoracic Society (ATS) standard procedure [27]. In subjects with forced expiratory volume in the first second (FEV_1) ≤70% of forced vital capacity (FVC), two puffs of bronchodilator (albuterol: 200 mcg) were administered with a metered dose inhaler (MDI), and FVC test was repeated after 20 min. A significant bronchodilator response was defined as an increase of 12% and 200 ml in respect to the baseline FEV_1.

Statistical analysis

Data are expressed as mean and standard deviation (SD) or 95% confidence intervals (CI95%). A normality of data distribution was established using Kolmogorov–Smirnov test. In case of normal data distribution, significant differences among groups were performed by one-way analysis of variance (ANOVA) with Bonferroni post-hoc analysis. Nonparametric test (Kruskal–Wallis test) was used when appropriate. Linear regression model was used to study the relationship between the considered variables. Chi-square analysis was used to test categorical variables. A P value of <0.05 was considered to be statistically significant.

Results

The data of subjects studied are reported in Table 1. No significant difference in anthropometric parameters was observed among the 3 groups studied. Median duration of treatment in the asthmatic patients taking ICSs was 38.5 months (range: 20–58 months).

Ultrasound bone profile index (UBPI) and correlations with hormonal and bone marker parameters

In ICS-treated asthmatic patients, UBPI was significantly lower ($P < 0.01$) compared to controls (49.8 ± 19.3 vs. 77.0 ± 10.1, respectively) and to asthmatic patients naive to ICSs (73.2 ± 9.6) (Fig. 1). No differences were observed in AdSos values among the groups studied. A significant correlation between structural characteristics of bone microarchitecture measured by UBPI, ΔGH and GH peak was observed ($R = 0.4$; $P < 0.05$) in ICS-treated asthmatic patients (Fig. 2). UBPI or AdSos values did not show a significant correlation with serum osteocalcin ($P = 0.069$) in the group of asthmatics taking ICSs.

GH secretion

Mean GH peak and ΔGH in asthmatic patients treated with ICSs were lower (4.0 ± 2.1 ng/ml; 1.9 ± 3.0 ng/ml,

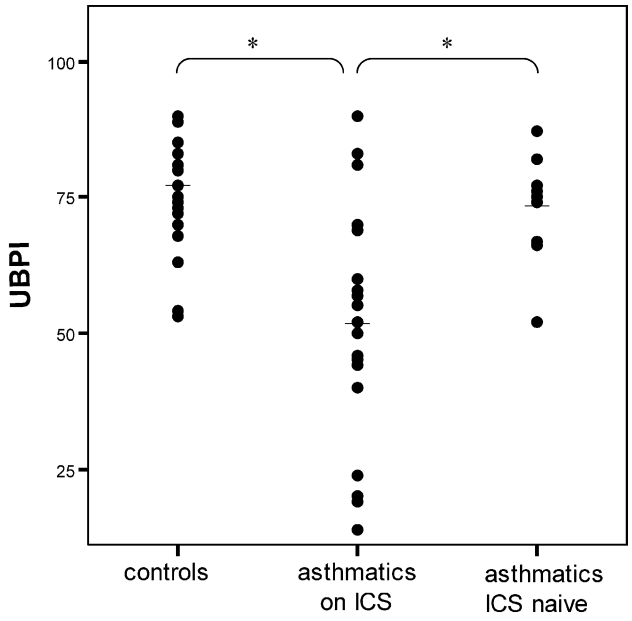

Fig. 1. Individual values of ultrasound bone profile index (UBPI) in the three groups studied. *$P < 0.1$.

respectively) as compared to mean GH peak and ΔGH both in controls (19.0 ± 12.7 ng/ml: $P < 0.01$; 13.2 ± 7.5 ng/ml: $P < 0.01$ respectively) and in asthmatics naive to ICSs (16.9 ± 15.1 ng/ml; $P = 0.04$; 12.4 ± 7.6 ng/ml; $P = 0.033$ respectively).

Biochemical data

Serum osteocalcin levels were significantly reduced in the group of asthmatic patients on chronic ICS treatment (6.4 ± 2.5 ng/ml) when compared with controls (17.6 ± 5.5 ng/ml; $P < 0.01$), and with asthmatics who never used ICS treatment (17.4 ± 4.5 ng/ml; $P < 0.01$), showing a significant correlation with values of GH peak ($r^2 = 0.34$, $P = 0.007$). Baseline IGF1 values were similar in all groups. ICS treatment had no significant effects on serum calcium, serum phosphorus, urinary calcium, urinary levels of deoxypyridinoline and urinary and serum levels of cortisol. No statistical difference in any variable considered was found between asthmatics naive to ICSs and the control group.

Discussion

The present study shows that, in asthmatic patients receiving long-term treatment with ICSs, the bone quality and osteocalcin levels are significantly reduced in comparison with asthmatic patients who have never been treated with ICSs and with control subjects. Moreover, these negative bone effects are associated with an impairment of GH secretion after GHRH stimuli. Our data demonstrate that, in asthmatics during long-term ICS treatment, the UBPI values are reduced compared to asthmatics not taking ICSs and control subjects, while AdSos values do not change among three groups. This latter finding can be explained by the fact that UBPI is a parameter correlated to bone quality and giving information about bone microarchitecture (density and disposition of trabeculae) [3], while AdSos is a more direct index of BMD. Bone loss due to ICSs differs from that of postmenopausal osteoporosis in terms of bone structure. In fact, CSs affect horizontal and vertical trabeculae, while, in postmenopausal osteoporosis, only horizontal structures are damaged [12]. According with this observation, Soballa showed that AdSos and UBPI significantly discriminated healthy subjects from patients with

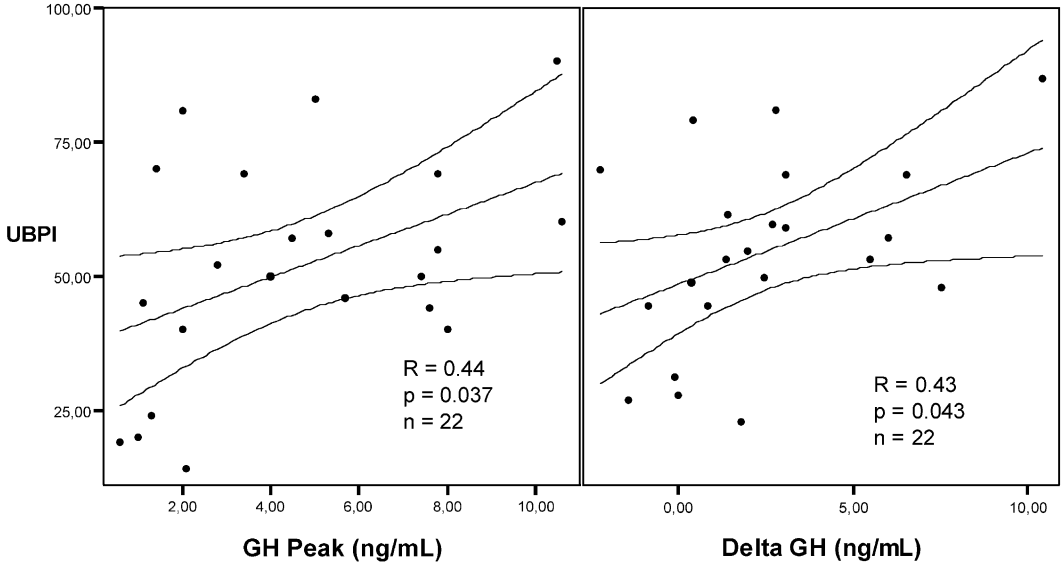

Fig. 2. Correlation between ultrasound bone profile index (UBPI) values, growth hormone (GH) peak and ΔGH in asthmatic patients treated with long-term inhaled corticosteroid therapy.

osteoporosis and from patients receiving CS treatment [28]. Finally, our data may explain the results of previous studies that fail to find a difference of BMD by dual photon X-ray absorptiometry (DEXA) in healthy people and asthmatics under ICS treatment [29,30], suggesting that in these patients the bone quality is more affected than bone mass, as demonstrated in patients during long-term CS systemic treatment [11].

A significant inhibition in GH secretion after GHRH in asthmatic patients under ICSs compared to asthmatics ICS naive and controls has been reported in our recent study [26], suggesting that long-term ICS treatment is able to influence GH axis in asthmatic patients as previously demonstrated in oral CS-treated patients [31]. GH is important in the regulation of bone metabolism by direct interaction with GH receptors on osteoblasts [32] Therefore, the correlation found between UBPI values and alteration of GH secretion after GHRH stimuli might partly explain the bone loss observed during long-term ICS treatment. Such hypothesis is supported by the observation that in asthmatic patients taking ICS the inhibition of GH secretion is significantly correlated with a reduction of osteocalcin levels, a marker of bone formation. A recent systematic review [33] showed a reduction of osteocalcin serum levels in the asthmatic patients taking ICSs. In the present study this reduction was associated with the decrease (not statistically significant) of UBPI values, suggesting a bone loss mechanism acting mainly by reducing bone formation. Our observation may be consistent also with other mechanisms recently described for glucocorticoid-induced reduction of bone formation. In fact, glucocorticoids promote the apoptosis of osteoblasts and osteocytes, and this contributes to decreased number of mature osteoblasts [34]. Moreover, it has been recently reported that glucocorticoids may be involved in a shift of cellular differentiation away from osteoblasts and toward adipocytes [35,36].

Limitations of the study are the relative small number of subjects studied and the lack of BMD measurements by DEXA. Comparisons of our results with those reported by other authors are difficult because of different methodology used in other studies and the lack of studies in asthmatics treated with ICSs evaluated by QUBD. A recent paper [37] has assessed the bone status by QUBD in asthmatic male patients under long-term oral CS treatment, showing that QUBD is able to discriminate between control subjects and male asthmatics under CSs and also the presence of a bone loss in these patients. It is noteworthy that present study shows similar findings in asthmatic patients taking CSs only by the inhaled route indicating the potential risk of osteoporosis following a chronic treatment with ICSs.

Therefore, despite the limitations abovementioned, our study can have practical implications since UBPI abnormalities should lead clinicians to the suspect of an increased risk of fracture to initiate an anti-osteoporotic treatment or eventually to modify the anti-asthmatic therapy (lower dose, change the treatment).

In conclusion, the results of our study indicate that the long-term administration of ICSs significantly reduces bone quality as assessed by QUBD at phalanxes and marker of bone formation in adult asthmatic patients, and such effects are associated with inhibited secretion of GH after GHRH stimuli. These data suggest that both the evaluation of bone microarchitectural structure by QUBD and the hypothalamic–pituitary–GH axis may be useful in the follow-up of asthmatic patients who are receiving long-term treatment with ICSs. However, further prospective studies are needed to confirm these results and also to evaluate whether in some patients is reasonable to discontinue chronic treatment with ICSs and/or to prescribe treatment to prevent bone loss.

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