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Abnormal Microarchitecture and Stiffness in Postmenopausal Women Using Chronic Inhaled Glucocorticoids

Yi Liu¹, Emily Dimango², Mariana Bucovsky³, Sanchita Agarwal³, Kyle Nishiyama³, X. Edward Guo⁴, Elizabeth Shane³, and Emily M. Stein¹

¹Division of Endocrinology and Metabolic Bone Disease, Hospital for Special Surgery, New York, NY

²Division of Pulmonology, Columbia University College of Physicians and Surgeons, New York, NY

³Division of Endocrinology, Columbia University College of Physicians and Surgeons, New York, NY

⁴Bone Bioengineering Laboratory, Department of Biomedical Engineering, Columbia University, New York, NY

Abstract

Purpose—While oral glucocorticoids are well recognized to have destructive skeletal effects, less is known about the effects of inhaled glucocorticoids (IGCs). The detrimental skeletal effects of IGCs may be greatest in postmenopausal (PM) women, in whom they compound negative effects of estrogen loss and aging. The goal of this study was to evaluate microarchitecture and stiffness in PM women using chronic IGCs.

Methods—This case-control study compared PM women using IGCs for ≥ 6 months (n=20) and controls matched for age and race/ethnicity (n=60). Skeletal parameters assessed included areal BMD (aBMD) by DXA, trabecular and cortical volumetric BMD (vBMD) and microarchitecture by high resolution peripheral computed tomography (HRpQCT) of the radius and tibia and whole bone stiffness by finite element analysis.

Results—By DXA, mean values in both groups were in the osteopenic range; hip aBMD was lower in IGC users ($P<0.04$). By HRpQCT, IGC users had lower total, cortical and trabecular vBMD at both radius and tibia (all $P<0.05$). IGC users had lower cortical thickness, lower trabecular number, greater trabecular separation and heterogeneity at the radius (all $P<0.03$) and greater heterogeneity at the tibia ($p<0.04$). Whole bone stiffness was lower in IGC users at radius ($P<0.03$) and tended to be lower at the tibia ($P=0.09$).

Corresponding Author: Emily M. Stein, Associate Research Scientist and Attending Physician, Hospital for Special Surgery, Associate Professor of Medicine, Weill Cornell Medical College, 535 East 70th Street, New York, NY 10021, Phone (646) 714-6558, Fax (212) 606-1967, steine@hss.edu, Please address reprint requests to Dr. Stein.

Disclosure

Yi Liu, Emily Dimango, Mariana Bucovsky, Sanchita Agarwal, Kyle Nishiyama, X. Edward Guo, Elizabeth Shane, Emily M. Stein declare that they have no conflict of interest.

Conclusions—PM women using IGCs had substantial abnormalities in vBMD, microarchitecture and stiffness compared to controls. These abnormalities were most severe at the radius. These preliminary results suggest that there may be major, heretofore unrecognized, skeletal deficits in PM women using IGCs.

Keywords

Osteoporosis; microarchitecture; bone quality; inhaled glucocorticoids

Introduction

There are approximately 40 million patients with asthma and chronic obstructive pulmonary disease (COPD) in the United States [1]. Inhaled glucocorticoids (IGCs) are widely used and effective in treating these patients [2]. IGC treatment in asthmatics is often chronic, and as many patients with asthma are diagnosed as children or young adults, cumulative lifetime exposure may be very high. Given the prevalence and chronic nature of IGC use, it is important to understand the adverse consequences of these medications.

Glucocorticoids decrease bone formation by inhibiting osteoblast differentiation and inducing osteoblast apoptosis. In addition, glucocorticoids promote the Receptor activator of nuclear factor kappa-B ligand (RANKL) system and increase osteoclast mediated bone resorption [3] and reduce osteocyte viability [4, 5]. Systemic glucocorticoids also exert negative skeletal effects by increasing urinary calcium excretion and decreasing intestinal calcium absorption [6]. While it is well established that oral and intravenous glucocorticoids are associated with osteoporosis and increased fracture risk [7], the skeletal effects of IGCs remain controversial [8]. Although systemic absorption of IGCs is less than with oral or intravenous administration, some does occur [9]. A dose-dependent relationship between IGCs and fracture risk has been demonstrated [10, 11].

The mechanisms by which IGCs may increase fracture risk are not well understood. Previous studies have demonstrated that fracture risk is higher in patients using both oral glucocorticoids and IGCs than in control patients with similar areal bone mineral density (BMD) [12, 13]. This discrepancy suggests that other factors, like bone microarchitecture, may contribute to the fracture risk among these individuals.

The detrimental skeletal impact of IGCs may be greatest in postmenopausal women, in whom these medications may compound the negative effects of estrogen loss and aging [14]. Therefore, we conducted this study to investigate skeletal microarchitecture and stiffness in postmenopausal women with a history of chronic IGC use and matched controls. We hypothesized that IGC users have microarchitectural abnormalities and lower stiffness compared controls and that differences would be most pronounced in trabecular bone, mirroring findings in patients treated with oral GCs [15].

Materials and Methods

Patients

Postmenopausal women, over age 60 or more than 5 years post menopause, were recruited at Columbia University Medical Center (New York, NY) by advertisement, self- or physician referral. Cases were women with asthma or COPD who were using IGCs currently and continuously for at least 6 months. Subjects who used oral GCs for a total of 6 weeks in the past 3 years were excluded. Exclusion criteria included endocrinopathies (e.g., untreated hyperthyroidism, Cushing's syndrome, prolactinoma), celiac or other gastrointestinal diseases, abnormal mineral metabolism (e.g., osteomalacia, primary hyperparathyroidism), or malignancy (except for skin cancer), current or prior use of teriparatide and current use, or prior use for > 1 year of bisphosphonates. Hormone replacement therapy (HRT) and raloxifene were permitted in both groups. Control subjects had no history of oral, intravenous or inhaled glucocorticoids. There were no BMD requirements for entry into IGC or control groups. Among IGC subjects, non-vertebral fractures were confirmed by review of radiographs or radiograph reports when possible. Vertebral fractures were identified by spine x-rays according to the semi-quantitative method of Genant *et al.*[16]. Control subjects had no history of low trauma fractures at any site and no vertebral deformity on lateral radiographs, as dictated by pre-specified exclusion criteria. At the study visit, medical history, reproductive history and medication use were assessed. A physical exam was performed including height by Harpenden stadiometer. Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) questionnaire, a tool validated for older populations [17]. All subjects provided written informed consent and the Institutional Review Board of Columbia University Medical Center approved this study.

Areal bone mineral density (aBMD)

Areal BMD was measured by DXA (QDR-4500, Hologic Inc., Walton, MA) at the lumbar spine (LS, L1-4), total hip (TH), femoral neck (FN), 1/3 radius (1/3R), and ultradistal radius (UDR). Lumbar vertebrae with significant deformity, osteosclerosis, osteophytes or degenerative disease were excluded from the analysis. T-scores compared subjects and controls with young-normal populations of the same race and sex, as provided by the manufacturer.

HRpQCT and Image-Based μ FEA of the distal radius and tibia

HRpQCT (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) was performed by immobilizing the non-dominant forearm and ipsilateral tibia in a carbon fiber shell and scanning as we have described in prior publications [18-20]. The European Forearm Phantom was scanned daily for quality control. All scans were acquired by the same highly experienced technician. The standard patient thresholding procedure was used to segment the mineralized phase. In addition to standard cortical and trabecular measurements of volumetric BMD, cortical thickness and trabecular microarchitecture, HRpQCT data were used to calculate whole bone stiffness by finite element analysis, a measure of bone's resistance to force.

Statistical Methods

Analyses were conducted with STATA version 11.0 (Stata Corp, College Station, Texas). Normality testing (Shapiro Wilk) was performed and variables that were not normally distributed were logarithmically transformed prior to group comparisons. Two-sided *p* values < 0.05 were considered to indicate statistical significance. Descriptive data are presented as mean $\pm$ standard deviation (SD) and group comparisons as mean $\pm$ standard error of the mean (SEM). Differences between IGC and control subjects were assessed by Student's *t* test or Chi-square. Relationships between dose and duration of IGC use with microarchitecture were assessed using Pearson correlations.

Results

Demographic characteristics

Twenty postmenopausal women using IGCs were matched one to three by age and race/ethnicity to a postmenopausal control group with no GC exposure. Demographic characteristics of the study subjects are shown in Table 1. The mean age of enrolled individuals was 69 ± 7 years. The majority of women were Caucasian (68%) and Latina (32%). There was no difference in years since menopause, family history of osteoporosis or fractures, calcium intake, tobacco use, alcohol use, HRT, or raloxifene use between the IGC users and controls. The average duration of IGC use was 9 years, average daily dose was 567 ± 260 mcg/d and cumulative dose was 1.3 ± 0.7 grams. Physical activity, assessed by the Physical Activity Scale for the Elderly questionnaire, was not significantly different between groups (96 ± 53 in IGC subjects and 113 ± 72 in controls; *P* = 0.44). Values in both groups were similar to the mean value of 103 reported in the general population [17].

Fractures

Fourteen of the IGC treated women had prevalent fractures, the most common sites were metatarsal (*n*=5) and forearm (*n*=4). Among IGC users, those with fractures had a significantly longer duration of IGC use (IGC fracture: 9 years vs IGC no fracture 5 years; *p*<0.02). As per protocol specifications, there were no fractures among the control group.

Areal BMD

By DXA, the prevalence of osteoporosis and osteopenia was similar in two groups. Mean values in both groups were in the osteopenic range; *T* scores tended to be lower in IGC users at the lumbar spine (-2.0 ± 1.7 in IGCs vs. -1.0 ± 1.4 in controls, *P*=0.07), and were lower at the total hip (-1.4 ± 1.0 in IGCs vs. -1.0 ± 1.1 in controls, *P*<0.04) but did not differ at the femoral neck or radius (Figure 1).

Volumetric BMD and Microarchitecture

Bone size, vBMD, and cortical and trabecular microarchitecture were assessed by HRpQCT, which demonstrated substantial differences between groups (Figure 2). At the radius, women using IGCs had lower total density (-25% ; *P*<0.001), lower cortical density (-9% ; *P*<0.001) and lower trabecular density (-26% ; *P*<0.002) compared to controls. IGC users had lower cortical thickness (-19% ; *P*<0.002) lower trabecular number (-15% ; *P*<0.03) and

greater trabecular separation (+42%; $P<0.01$) and trabecular heterogeneity (+111%; $P<0.02$). In contrast, trabecular thickness did not differ significantly. Among IGC treated women, we found an inverse relationship between years postmenopause and cortical density at the radius ($r = -0.76$; $p<0.001$) and a trend in the relationship between years post-menopause and cortical thickness ($r = -0.42$; $p=0.06$).

At the tibia, women using chronic IGCs had lower total density (−15%; $P<0.006$), lower cortical density (−6%; $P<0.006$) and lower trabecular density (−14%; $P=0.05$). There was no difference in cortical thickness between women using IGCs and controls. Trabecular number (−8%; $P=0.14$) and trabecular thickness (−7%; $P=0.14$) did not differ. IGC users tended to have higher trabecular separation (+12%; $P=0.10$) and had greater trabecular heterogeneity (+33%, $P=0.03$). We did not find a relationship between years postmenopause and any parameter at the tibia.

Biomechanical Properties

Biomechanical properties were measured by finite element analysis. Whole bone stiffness was lower in IGCs users compared to controls at the radius (−15%; $P<0.03$) and tended to be lower at the tibia as well (−6%; $P=0.09$). We did not find a relationship between microarchitectural abnormalities with dose or duration of IGC use.

Discussion

To our knowledge, this is the first study to investigate volumetric BMD, microarchitecture and biomechanical properties of bone by HRpQCT in individuals using IGCs. We found substantial abnormalities in women using chronic IGCs compared with age and race/ethnicity- matched controls. Specifically, postmenopausal women using IGCs had lower volumetric BMD in both cortical and trabecular compartments. They had thinner cortices, more widely and irregularly spaced trabeculae. Whole bone stiffness was lower in IGC users as well. These abnormalities were seen at both radius and tibia, but were most pronounced at the radius.

The vast majority of studies evaluating bone in IGC users have utilized only DXA measurements. These DXA-based studies have found conflicting results. While several have reported lower aBMD at the spine and femoral neck in asthmatic patients using IGCs compared to untreated controls, this finding is not uniform [8, 21-23]. In our study, although the prevalence of osteopenia and osteoporosis was similar between the two groups, aBMD T-scores were significantly lower in IGC users at TH and tended to be lower at LS. These results are similar to Ip et al., who found an inverse correlation between IGCs use and aBMD [24, 25]. The discrepancy between studies based solely on DXA may relate to the fact that IGCs may impact bone quality in ways independent from their effects on aBMD. Although to our knowledge there are no prior HRpQCT studies, a longitudinal pQCT study by Medici et al. did not detect any trabecular bone loss after 12 months follow up in asthmatic patients treated with inhaled fluticasone and budesonide [26]. However, this study did not include untreated controls and the pQCT technology used did not have the resolution necessary to evaluate microarchitecture. Further, their study population was premenopausal women and men age under 55 years old, in contrast to our focus on postmenopausal women.

Postmenopausal women may be more susceptible to the harmful effects of IGCs, as suggested by Fujita et al. who found that IGC use was associated with lower BMD, decreased bone turnover markers in early postmenopausal women, but not premenopausal women [27]. Our population of postmenopausal women may have been more severely impacted than some of the other groups, so that we were able to detect differences in both aBMD and in microarchitecture.

Patients who are treated with both oral and inhaled GCs have an increased risk of fracture independent of bone density [12, 13]. The microarchitectural abnormalities that we observed in both cortical and trabecular bone may be important contributors to this increased fragility. In addition to lower vBMD, we found that IGC-treated postmenopausal women had abnormal trabecular microarchitecture, with lower trabecular number and greater trabecular separation and heterogeneity, as well as cortical thinning. We found that trabecular bone tended to be more severely affected than cortical bone. This pattern is similar to the microarchitectural phenotype that we previously reported in postmenopausal women using oral GCs [15]. As trabecular bone is metabolically more active than cortical bone, it may be more susceptible to the effects of chronic glucocorticoid exposure. This finding is supported by previous histomorphometric studies of the iliac crest in patients on systemic glucocorticoids, characterized by a decrease in the wall thickness, trabecular number and degrees of connectivity [28, 29].

We found that microstructural abnormalities were more significant at the radius than tibia, consistent with our previous study in postmenopausal women treated with oral GCs as well as other studies on women with hyperparathyroidism or osteopenic women with fractures [15, 30, 31]. This difference is likely related to the protective effect on weight bearing at the tibia. Using FEA, we found that patients receiving IGCs had reduced whole bone stiffness. Stiffness, too, was more profoundly impacted at the radius. At the tibia, values tended to be lower in IGC users but differences did not reach significance. With a larger sample size, we may have detected significant differences at both sites.

Although several authors have found a dose-response relationship between IGC and skeletal outcomes, we failed to detect any correlation between cumulative IGC dose and bone microarchitectural abnormalities [25]. Our small sample size may have limited our ability to detect a relationship. Another potential explanation is that patients were unable to accurately recall their prior medication use in this case control study. Previous studies have suggested that daily IGC doses of less than 800 mcg may not have a negative impact on skeletal health [32]. However, in our study, we were able to detect deleterious skeletal effects of IGCs even though our subjects were receiving a median daily dose of 500 mcg of fluticasone or the equivalent. This finding may relate to the fact that all individuals involved in our study were postmenopausal women, who had a higher risk of bone loss. In addition, long-term use may have impacted our results, as the mean duration of use in our subjects was almost 8 years. Further prospective, controlled studies are needed to explore the dose response relationship between IGCs and microarchitectural damage.

This study has several limitations, primarily the small sample size and cross-sectional design. However, we were able to detect significant differences with a limited number of

patients, suggesting that the potential detrimental skeletal effects of chronic IGCs may be quite large. A further limitation of the study is that we included both patients with asthma and COPD, as COPD may have independent effects on bone [33]. Although our controls were patients seen in our institution for chronic medical conditions, they were not specifically matched for illness. While this would have been preferable, we were not able to identify sufficient numbers of women with asthma and COPD who were not using oral or IGCs. This is an important limitation as the impact of disease specific factors could not be distinguished. While smoking could also be a risk factor for bone loss [34], we found that tobacco use was similar in the two groups, suggesting that it did not play a substantial role in the structural differences that we observed. Some of our skeletal findings may reflect glucocorticoid exposure in the distant past, which was not captured by our histories. Another limitation is that some participants used HRT and raloxifene, which may have blunted the detrimental skeletal effects of IGCs. However, use of these medications was similar in IGC and control groups. Additionally, while we did detect a relationship between fracture and IGC duration, this study was not designed to evaluate fracture as an outcome. Fracture prevalence may also have been related to oral steroid exposure prior to the three year history that we were able to capture in our study. The inclusion of controls without fractures is another important limitation. While controls and cases were well matched on many factors, it is conceivable that controls had particularly strong bones which would have enhanced the observed differences between groups. The relationship between IGC use and fracture requires investigation in future studies.

In summary, this is the first study to investigate volumetric BMD and microarchitecture by HRpQCT in patients using chronic IGCs. We found substantial microarchitectural abnormalities and compromised biomechanical properties of bone in postmenopausal women using IGCs compared to age matched controls. Abnormalities were most pronounced at the radius. If confirmed in larger studies, these results would provide a rationale for recognition of chronic IGC use as a significant risk factor for osteoporosis among postmenopausal women, and consideration of IGC use in treatment decisions.

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Summary

PM women using IGCs had substantial abnormalities in vBMD, microarchitecture and stiffness using HRpQCT compared to age and race matched controls. Abnormalities were most severe at the radius. These preliminary results suggest that there may be major, heretofore unrecognized, skeletal deficits in PM women using IGCs.

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; LS, lumbar spine; TH, total hip; FN, femoral neck; 1/3 R, 1/3 distal radius; UDR, ultradistal radius; IGC, inhaled glucocorticoids group; C, control; *, $P < 0.05$.

Figure 1. Areal BMD by DXA

Comparison of T-Scores by DXA in postmenopausal women using chronic IGCs (dark grey bars) and matched controls (light grey bars). * $p < 0.05$, ** $p < 0.01$. Abbreviations: lumbar spine (LS), total hip (TH), femoral neck (FN), 1/3 radius (1/3R), ultradistal radius (UDR).

Figure 2. Bone microarchitecture by HRpQCT

Comparison of the percent difference in volumetric BMD and microarchitecture by HRpQCT in IGC and control subjects at the radius (striped) and tibia (black) * $p < 0.05$, ** $p < 0.01$. Figure 2A shows group differences in Total vBMD (total density), Tb. vBMD (trabecular density), Ct vBMD (cortical density), Ct Thickness (cortical thickness), Tb Number (trabecular number), Tb Thickness (trabecular thickness). Figure 2B shows group differences in Tb Separation (trabecular separation), Heterogeneity (trabecular network heterogeneity).

Table 1
Characteristics of the Study Population (mean± SD)

	IGC (n=20)	Control (n=60)	P value
Age, y	70 ± 7	68± 7	0.29
Race, % Caucasian	70%	67%	0.78
Height, cm	159±7	160±7	0.53
Weight, kg	69±16	70±16	0.81
BMI, kg/m ²	27±6	27±6	0.95
Year since menopause	19±9	19 ±10	0.99
Family history of osteoporosis by BMD, n (%)	5 (25)	25 (42)	0.13
Family history of fracture, n (%)	10 (50)	19 (32)	0.16
PASE score	96±53	113±72	0.44
Tobacco use			
Never, n (%)	11(55)	28 (47)	0.45
Former, n (%)	9 (45)	28 (47)	
Current, n (%)	0	0	
Alcohol use			0.19
Never, %	5 (25)	25 (42)	
Former, %	11(55)	21 (35)	
Current, %	4 (20)	6 (10)	
Calcium supplementation, total daily dose, mg	1330±617	1475±690	0.42
Vitamin D supplementation, total daily dose, IU	1141±903	1177±1689	0.25
HRT, %	10 (50)	22 (37)	0.44
Raloxifene, %	1 (5)	0 (0)	0.27
Thyroxine, %	4 (20)	15 (25)	0.77
Disease condition			
COPD, %	4 (20)	n/a	
Asthma, %	16 (80)	n/a	
Thiazide diuretics (%)	2 (10)	13 (22)	0.33
IGC use			
Duration, y	7.9±4.7	n/a	
Current dose, mg/d	567±290	n/a	
Cumulative dose, g	1.3±0.7	n/a	

BMI, body mass index; BMD, bone mineral density; COPD, chronic obstructive pulmonary disease; HRT, hormone replacement treatment; IGC, inhaled glucocorticoids; PASE, Physical Activity Scale for the Elderly.