

Impact of treatment with inhaled corticosteroids on bone mineral density of patients with asthma: related with age

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Received: 5 January 2015 / Accepted: 25 February 2015
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Abstract

Summary The effect of inhaled corticosteroid on bone mineral density (BMD) was investigated in 44 asthmatic patients after median treatment duration of 6.5 years. Compared with controls, BMD decreased only in patients aged <50 years in both the spine (11.3 %, $p=0.013$) and hip (8.8 %, $p=0.044$), whereas in patients ≥ 50 years BMD did not decrease significantly.

Introduction The results of studies which addressed the impact of inhaled corticosteroid (ICS) therapy on BMD of patients with asthma are conflicting. This case-control study aimed to compare BMD status in ICS user with asthma with healthy controls according to age.

Methods BMD at the lumbar spine (LS), femoral neck (FN) was measured by dual energy X-ray absorptiometry (DEXA). Patients and controls were compared according to BMD gr/cm^2 , BMD T-score, BMD Z-score, frequency of osteoporosis (defined as BMD T-score ≤ -2.5), and frequency of patients with BMD Z-score < -1 at LS and FN with regard to age <50 and ≥ 50 years old.

Results Forty-four ICS user patients (females 63.6 %) with median treatment duration of 6.5 years and 50 controls (females, 69.4 %) with respective mean age of 49.2 ± 9.5 and

47.4 ± 10.5 years ($p=0.38$ and $p=0.35$) entered the study. Overall LS-BMD and FN-BMD gr/cm^2 in total patients were lower than in controls by 6 % ($p=0.065$) and 5.9 % ($p=0.09$), respectively. In patients <50 years, mean LS-BMD gr/cm^2 was lower than controls by 11.3 % ($p=0.013$) and FN-BMD by 8.8 % ($p=0.044$). Mean BMD T-score and BMD Z-score in both measurement sites were also lower than controls ($p=0.013$ and 0.01 , respectively). Frequency of osteoporosis did not differ but frequency of patients with BMD Z-score < -1 was significantly higher in patients (odds ratio (OR)=6.57 95 % CI, 1.8–23.9, $p=0.004$). In age group ≥ 50 years old, reduction of BMD in both measurement sites did not reach to a significant level.

Conclusion This study indicates that BMD reduction in ICS user with asthma is dependent on age and appears that younger patients are at greater risk of BMD loss. These findings suggest preventive measures particularly in patients <50 years.

Keywords Asthma · Bone mineral density · Inhaled corticosteroid · Treatment

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Introduction

Pulmonary airway diseases like asthma and chronic obstructive lung disease (COPD) are associated with systemic inflammation and increased levels of inflammatory markers as well as proinflammatory cytokines [1–3]. Administration of inhaled corticosteroids (ICS) is the mainstay of treatment which are usually used in combination with conventional inhaled bronchodilators [4–6].

In patients with asthma, in addition to conventional risk factors of osteoporosis, inflammatory process and treatment with corticosteroids may also predispose them for further bone loss [7, 8].

The impact of ICS on bone mineral density (BMD) of patients with asthma has been investigated in several previous studies but the results are conflicting [7, 9–14]. Many studies have found significant BMD changes by administration of ICS in patients with asthma [7, 13–15] but in several other studies treatment with ICS for asthma was not associated with BMD changes [9–11, 16].

In a longitudinal study, beclomethasone dipropionate (BDP) for an average period of 7.7 years did not result in BMD Z-score changes between patients taking high dose versus low doses of BDP [9]. The results of a meta-analysis revealed that ICS therapy in asthma was associated with BMD reduction by 4.1 % which did not differ with controls, and so the authors concluded that ICS treatment in asthma can be considered safe [17]. On the other hand, the results of a population-based study, the Nord-Trøndelag Health Study (the HUNT Study), found no dose response association between ICS and BMD, or difference in BMD by type of ICS [18].

Several factors such as study design, patients selection and characteristics of the study population, measures of BMD changes, age, sex, smoking status, reproductive and hormonal factors, lifestyle, duration of asthma as well as duration of treatment, and the dosages of medications vary across various studies and so may differently affect the outcomes and result in discrepancies.

To overcome these shortcomings, we performed the present case–control study in patients with asthma and healthy controls who have been recruited from a general population with similar characteristics and lifestyle which is expected to be associated with less confounding effect. Furthermore, we provided additional data regarding several associated factors of bone loss and used more sensitive measures of BMD changes and appropriate data analyses to minimize the confounding effects.

The aim of this study was to compare BMD status in ICS user asthmatic patients with age and sex-matched controls.

Patients and method

The patients of this case–control study were recruited among ICS user asthma patients presented to the Rouhani Teaching Hospital Outpatient Clinic for follow-up examination. This hospital is affiliated to the Babol University of Medical Sciences, Babol, Iran. All patients were under follow-up for treatment of asthma. The Diagnosis of asthma was confirmed by compatible clinical features and pulmonary function tests [19]. All patients of this study were treated with ICS according to the guideline suggested by the National Asthma Education and Prevention Program's Expert Panel Report III [19]. Patients who have received ICS therapy for at least 1 year or more were included to study consecutively.

Exclusion criteria were history of osteoporosis, treatment with anti-osteoporotic drugs, premature menopause, metabolic bone diseases, inflammatory musculoskeletal diseases, and chronic renal and gastrointestinal diseases.

Sample size was calculated to detect 0.1 g/cm² difference in BMD gr/cm² between the patients and controls with 95 % confidence and 80 % of power. Based on data from our earlier study of healthy controls [20], 36 patients for each group were required. However, we recruited 20 % greater participants to compensate for noncompliant patients or missed data.

Bone densitometry was performed using dual energy X-ray absorptiometry (DEXA). BMD at the lumbar spine (LS) and femoral neck (FN) was determined, and the results were expressed as BMD gr/cm², BMD T-score, and BMD Z-score. Osteoporosis was diagnosed according to the International Society for Clinical Densitometry criteria defined as BMD values of 2.5 SD or more below the mean value for young adults (T-score ≤ −2.5) at either FN or LS measurement sites (one diagnostic category) [21].

Data regarding, age, medications, duration of asthma, duration of treatment with ICS, oral corticosteroid, menopausal status, physical activity, duration of sunlight exposure, and adherence to medications were collected from medical records as well as by interview.

Age- and sex-matched healthy controls without pulmonary diseases were selected among subjects presented for bone densitometry to the same center. A similar exclusion criterion was also applied for the control group.

Since the World Health Organization (WHO) BMD classification according to T-score does not express similar significance in men younger than 50 years or premenopausal women as compared with ≥50 years [22], so the study population were classified as age group of <50 years old and ≥50 years and BMD Z-score which is more useful for this age group was added as a measures of BMD changes.

In statistical analyses, the patients and controls were compared with regard to BMD gr/cm², BMD T-score, BMD Z-score, and frequency of osteoporosis, frequency of low bone mass (defined as BMD Z-score < −1).

Student *t* test and Mann-Whitney *U* test was used for comparison of quantitative variables with and without normal distribution, respectively. Chi-square test with calculation of odds ratio (OR) and corresponding 95 % confidence interval (95 % CI) was employed to determine association. Informed consent obtained from all participants and the proposal of this study was approved by the Ethics Committee of the Babol University of Medical Sciences, Babol, Iran.

Results

A total of 44 ICS user patients (63.6 % females) with mean (±SD) age of 49.2±9.5 years and 50 healthy controls (females,

69.4 %) with mean age of 47.4 ± 10.5 years ($p=0.38$ and $p=0.35$, respectively, entered the study (Table 1).

Nineteen patients and 29 controls aged less than 50 years old (mean age 40.9 ± 8 and 40.4 ± 7.3 years, respectively). Characteristics of the study population are shown in Table 1. The patients <50 years age group were similar to patients ≥ 50 years old regarding FEV1% (67 vs 58 % $p=0.53$), duration of disease (median, 10 vs 10 years, $p=0.86$), and duration of treatment (median 7 vs 6 years, $p=0.33$), respectively. Overall, the whole number of patients and controls were comparable with regard to age, menopausal status, using oral contraceptive, calcium and vitamin D supplement, smoking, duration of physical activity, and sunlight exposure.

All patients received fluticasone with the median dosage of 650 mcg daily (500–1000), or BDP at median dosage of 600 mcg (400–1000) or budesonide at median dosage of 640 mcg (320–1280) for a median duration of 6.5 years. Eighteen patients received oral CS in addition to ICS for a total median period of 5 months. Analysis of these patients with remainder patients did not demonstrate a significant difference in BMD gr/cm^2 , BMD T-score, and BMD Z-score (data were not shown).

Table 1 Characteristics of patients with asthma treated with inhaled corticosteroids and age-matched healthy controls

	Controls	Patients	<i>P</i> values
No. of patients	50	44	—
Females, no. (%)	34 (69.4)	28 (63.6)	0.35
Age, years, mean $\pm$ SD	47.4 ± 10.5	49.2 ± 9.5	0.38
BMI, Kg/m^2	$28 (3.2), 27$	27 ± 4.6	0.58
Duration of asthma, mean ($\pm$ SD), year	—	12.7 ± 7.8	—
Median, years	—	10 (2–35)	—
Duration of treatment, mean ($\pm$ SD), year	—	7.3 ± 6.1	—
Median (range), years	—	6.5 (2–35)	—
Menopausal duration, years	3.6 ± 4	2.7 ± 4.6	0.10
Median (range)	4 (0–14)	1 (0–18)	—
Postmenopausal state no. (%)	12 (24)	15 (34)	0.40
FEV1 % ($\pm$ SD)	—	64.7 ± 18.4	—
OCP users no. (%)	1 (2)	3 (6.8)	0.56
Taking Calcium+vitamin D, no. (%)	13 (26)	5 (11.3)	0.45
Oral CS users no. (%)	—	18 (40.9)	—
Duration of taking oral CS, years	—	2.6 (4)	—
Physical activity score (0–400) ^a	69	60	0.90
Smoking, no. (%)	3 (6)	2 (4.5)	0.60
Duration of sunlight exposure median, hour/day	3 (1–4)	2.7 (1–4)	0.53

OCP oral contraceptive, Oral CS oral corticosteroid users, FEV1 force expiratory volume in 1 s

^a Determined using questionnaire for daily physical activity score

BMD in patients versus controls

Overall, LS-BMD and FN-BMD gr/cm^2 in patients were lower than controls by 6 % ($p=0.065$) and 5.9 % ($p=0.09$), respectively.

In the age group of <50 years old, the magnitude of LS-BMD gr/cm^2 in patients was lower than the controls by 11.3 % ($p=0.013$), and FN-BMD gr/cm^2 was lower by 8.8 % ($p=0.044$). In addition, the BMD T-score and BMD Z-score in patients were significantly lower than in controls (Table 2 a). Osteoporosis was found in three (15.8 %) patients versus none in the control group ($p=0.056$). Low bone mass was found in 12 (63.2 %) patients and 6 (20.7 %) controls, $p=0.004$. Treatment of asthma with ICS in this age group was associated with increased frequency of low bone mass by OR=6.5 (95 % CI, 1.8–23.9, $p=0.004$) (Table 3).

In age group ≥ 50 years old, LS-BMD gr/cm^2 was lower than control by 1.6 % ($p=0.18$) and FN-BMD gr/cm^2 by 0.18 % ($p=0.89$). The differences in BMD T-score and BMD Z-score between patients and controls did not reach to a statistically significant level (Table 2 b). In addition, the patients and the controls of this age group had no significant differences in frequency of osteoporosis as well as low bone mass (Table 3).

Discussion

The results of this study indicated that treatment of asthma with ICS for a median period of 6.5 years was associated with significant decrease in BMD at both BMD measurement sites particularly in the lumbar spine only in patients aged less than 50 years old but not ≥ 50 years old. Since patients and controls were similar regarding several associated factors of BMD loss (Table 1), so the observed changes between patients and controls should be attributed to ICS therapy. In this study, BMD outcome has been shown by several BMD parameters including BMD gr/cm^2 , BMD T-score, Z-score as well as frequency of osteoporosis and low bone mass at both BMD measurement sites. Concurrent changes in all BMD parameters at both measurement sites support validity of the BMD changes.

The results of this study showing particularly greater BMD reduction in the lumbar spine are in agreement with previous studies [13–15, 23]. In a cross-sectional study of perimenopausal women, Laatikainen et al. revealed a negative correlation between duration of treatment with ICS and LS-BMD changes [13]. In another study of premenopausal women, long-term treatment of asthma patients with ICS was associated with significant BMD changes in the lumbar spine and femoral neck in women as compared with age-matched controls without any BMD changes in men [14]. Similarly, in a cross-sectional study of patients 20–40 years taking ICS at mean current dose of 620 mcg daily; reduction of BMD was observed in the spine and in women [23].

Table 2 Bone mineral density (BMD) at lumbar spine and femoral neck in asthmatic patients treated with inhaled corticosteroids compared with age and sex-matched healthy controls according to age of <or ≥50 years old

A=participants aged <50 years old							
	Lumbar spine				Femoral neck		
	BMDgr/cm ²		T-score	Z-score	BMDgr/cm ²	T-score	Z-score
Controls	Mean (±SD)	1.0±0.18	-0.18±1	0.09±1	0.89±0.13	0.12±1.1	0.38±1.1
Patients	Mean (±SD)	0.94±0.13	-1.07±1.1	-0.81±1.1	0.81±0.12	-0.77 (0.85)	-0.38±0.9
<i>P</i> values ^α		0.016	0.013	0.01	0.048	0.016*	0.011
B=participants aged ≥50 years old							
	Lumbar spine mean (±SD)				Femoral neck mean (±SD)		
	BMDgr/cm ²	T-score	Z-score		BMDgr/cm ²	T-score	Z-score
Controls	0.91±0.16	-1.1±0.15	-0.16±0.13		0.77±0.15	-0.95±1.3	0.009±1.4
Patients	0.93±0.13	-1.1±1.3	-0.3±1.1		0.77±0.14	-0.83±1.1	0.15±1.2
<i>P</i> values	0.74	0.85	0.7		0.70*	0.80*	0.40*

^α Compared with Mann-Whitney *U* test (*) or Student *t* test

Jung et al., in a case-control study of airway hyperresponsiveness (AHR)-positive patients (indicating asthma) versus AHR-negative controls, have found significantly lower LS-BMD and FN-BMD in patients. After adjustment for age, sex, body mass index, smoking status, menopausal state, and previous history of hormone replacement therapy, osteoporosis or osteopenia in AHA-positive subjects was 1.71 times greater than that in AHA-negative patients [15].

In contrast, many studies have found no significant effect of ICS therapy on BMD in asthma [7, 9, 10, 17, 24–26].

In one cross-sectional study, asthmatic patients who were treated with ICS had lower BMD than controls but the difference was attributed to age and low BMI but not ICS [12]. Many case-control, longitudinal, and meta-analysis have found no significant BMD changes by ICS therapy in asthma and COPD, and so treatment with ICS has been considered safe [7, 9, 10, 17, 24–26].

In the present study, the safety of ICS therapy in asthma was observed in patients aged ≥50 years old, whereas in the younger age group, treatment of asthma with ICS was associated with significant BMD loss.

Data regarding contribution of age in the development of bone loss in ICS user patients with asthma are scarce.

Nonetheless, the study population of many previous studies which have shown a significant BMD loss were younger than 50 years [13–15, 23].

Women during menopausal transition have accelerated bone loss. Women of this age group, particularly during the ensuing 5 years, are at greater risk of BMD loss. Detection of BMD changes based on BMD T-scores alone is not sensitive and so patients with lower rates of BMD changes may be unrecognized by BMD T-score and so many high-risk patients may be missed by using the WHO criteria [27, 28]. In contrast, bone turnover in older patients is not as active as in younger patients. Moreover, osteoporosis or osteopenia is common in this age group, and thus they are less sensitive to BMD

changes during ICS therapy. Selection of an appropriate parameter of BMD changes is of particular importance.

We used BMD Z-score for comparison of BMD changes between patients and controls. BMD Z-score provides a direct comparison of an individual bone density with other individuals of the same age and so would not be affected by osteoarthritis which is common in the elderly subjects. This parameter has been considered for evaluation of BMD in women from age 20 years through menopause by the International Society of Clinical Densitometry guidelines recommendation [29] because the WHO BMD classification is not appropriate for men younger than 50 years as well as for premenopausal women [30]. In addition, the BMD Z-score <-1 which has been used as a parameter of BMD changes has a potential to predict fracture risk and necessity of treatment [22]. In older subjects, development of osteoarthritis increases BMD T-score falsely, and results in underestimation of BMD loss particularly in the spine [31]. Thus, application of BMD Z-score is more reliable and preferable than BMD T-score for estimation of BMD status in the older as well as in the younger age group.

Many factors unrelated to asthma or its treatment, like the level of physical activity, supplemental calcium, vitamin D, and reproductive factors in women, may differently affect BMD and confound the results [8, 15, 32–34]. Distribution and frequency of these factors as well as their contribution in the development of BMD loss varies among various populations and so may affect the results. Nonetheless, the results of this study are expected to be confounded minimally, because the patients and controls were comparable regarding many common responsible factors of BMD loss.

Based on the results of this study, age <50 years old is a risk factor for BMD loss in ICS user patients with asthma. This issue has not been investigated adequately and requires further studies.

Table 3 Frequency of osteoporosis (OP) and low bone mass (BMD Z-score<-1) at either lumbar spine and femoral neck in patients with asthma treated with inhaled corticosteroids compared with healthy controls according to age of less than 50 years old and ≥50 years old

	Age <50 years old			Age ≥50 years old		
	Total patients	Low bone mass n (%)	OP n (%)	Low bone mass n (%)	OP n (%)	Low bone mass n (%)
Controls	6 (12)	13 (26)	0 (0)	6 (20.7)	6 (28.6)	7 (33.30)
Patients	8 (18.2)	21 (47.7)	3 (15.8)	12 (63.2)	5 (20)	9 (36)
OR (95 % CI)	1.6 (0.51–5.1)	2.6 (1.09–6.1)	3.02 (0–0)	6.5 (1.8–23.9)	0.62 (0.16–2.4)	1.12 (0.33–3.8)
P values	0.29	0.024	0.056	0.004	0.39	0.54

Osteoporosis defined as BMD T-score ≤-2.5. Low bone mass defined as BMD Z-score <-1
OR (95 % CI) odds ratio (95 % confidence interval)

This study has a limitation regarding study design which is cross-sectional, and the association between BMD loss and ICS therapy does not indicate causality. On the other hand, using several measures of BMD changes can be considered as a strength.

In conclusion, the results of this study indicate that treatment of asthma with ICS for a median period of 6.5 years is associated with significant BMD reduction in patients aged less than 50 years old. Whereas, in older patients, BMD reduction was non-significant. These findings highlights preventive measures by performing bone densitometry at regular intervals in younger patients with asthma who receive ICS. This context requires further studies.

Acknowledgments We appreciate the collaboration of the Clinical Research and Development, Rouhani Hospital Babol University of Medical Sciences, Babol, Iran.

This study was funded by the Vice-Chancellor of Research and Technology, Babol University of Medical Sciences, Babol, Iran.

Conflicts of interest Mahmoud Monadi, Yahya Javadian, Mohaddesse Cheraghi, Behzad Heidari, and Mehrangiz Amiri declare no conflict of interest.

References

1. Yamagata Y, Taya S, Iwata T, Okada M, Ishiguchi T, Sato H, Itoh H (2008) Systemic inflammation in chronic obstructive pulmonary disease and asthma: similarities and differences. *Respirology* 13(1): 128–133. doi:10.1111/j.1440-1843.2007.01170.x
2. Heidari B (2012) The importance of C-reactive protein and other inflammatory markers in patients with chronic obstructive pulmonary disease. *Caspian J Intern Med* 3(2):428–435, Review
3. Firouzjahi A, Monadi M, Karimpoor F, Heidari B, Dankoob Y, Hajian-Tilaki K (2013) Serum C-reactive protein level and distribution in chronic obstructive pulmonary disease versus healthy controls: a case-control study from Iran. *Inflammation* 36(5):1122–1128. doi:10.1007/s10753-013-9646-7
4. van den Berge M, ten Hacken NH, van der Wiel E, Postma DS (2013) Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma. *Allergy* 68(1):16–26. doi:10.1111/all.12062
5. Usmani OS (2014) Small airways dysfunction in asthma: evaluation and management to improve asthma control. *Allergy Asthma Immunol Res* 6(5):376–388. doi:10.4168/aa.2014.6.5.376, Epub 2014 Jun 18
6. Bärnes CB, Ulrik CS (2014) Asthma and Adherence to Inhaled Corticosteroids: Current Status and Future Perspectives. *Respir Care*. Aug 12
7. Richy F, Bousquet J, Ehrlich GE, Meunier PJ, Israel E, Morii H, Devogelaer JP, Peel N, Haim M, Bruyere O, Reginster JY (2003) Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systematic review. *Osteoporos Int* 14(3):179–190, Epub 2003 Apr 23
8. Kling JM, Clarke BL, Sandhu NP (2014) Osteoporosis prevention, screening, and treatment: a review. *J Womens Health (Larchmt)* 23(7):563–572. doi:10.1089/jwh.2013.4611
9. Matsumoto H, Ishihara K, Hasegawa T, Umeda B, Niimi A, Hino M (2001) Effects of inhaled corticosteroid and short courses of oral

- corticosteroids on bone mineral density in asthmatic patients: a 4-year longitudinal study. *Chest* 120(5):1468–1473
10. Wheelock C, St Anna L (2012) Clinical Inquiry. Do inhaled steroids reduce bone mineral density and increase fracture risk? *J Fam Pract* 61(8):493–508
 11. Tattersfield AE, Town GI, Johnell O, Picado C, Aubier M, Brailon P, Karlström R (2001) Bone mineral density in subjects with mild asthma randomised to treatment inhaled corticosteroids or non-corticosteroid treatment for two years. *Thorax* 56(4):272–278
 12. How SH, Azian AA, Liam CK, Ng TH, Fauzi AR (2012) Bone mineral density in asthmatic patients on inhaled corticosteroids in a developing country. *Ann Thorac Med* 7(2):69–73. doi:10.4103/1817-1737.94522
 13. Laatikainen AK, Kröger HP, Tukiainen HO, Honkanen RJ, Saarikoski SV (1999) Bone mineral density in perimenopausal women with asthma: a population-based cross-sectional study. *Am J Respir Crit Care Med* 159(4 Pt 1):1179–1185
 14. Ip M, Lam K, Yam L, Kung A, Ng M (1994) Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 105(6):1722–1727
 15. Jung JW, Kang HR, Kim JY, Lee SH, Kim SS, Cho SH (2014) Are asthmatic patients prone to bone loss? *Ann Allergy Asthma Immunol* 112(5):426–431. doi:10.1016/j.anaai.2014.02.013
 16. Jones A, Fay JK, Burr M, Stone M, Hood K, Roberts G (2002) Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* (1):CD003537
 17. Sharma PK, Malhotra S, Pandhi P, Kumar N (2003) Effect of inhaled steroids on bone mineral density: a meta-analysis. *J Clin Pharmacol* 43(2):193–197
 18. Langhammer A, Norjavaara E, de Verdier MG, Johnsen R, Bjørner L (2004) Use of inhaled corticosteroids and bone mineral density in a population based study: the Nord-Trøndelag Health Study (the HUNT Study). *Pharmacoepidemiol Drug Saf* 13(8):569–579
 19. National Asthma education and Prevention Program (2007) Expert panel report III: Guideline for the diagnosis and management of asthma. Bethesda MD: National Heart, Lung and Blood Institute, (NIH publication no 08–4051)
 20. Heidari B, Jalali F (2005) Bone densitometry in rheumatoid arthritis. *Acta Med Iran* 43:99–104
 21. Hans D, Downs RW, Duboeuf F et al (2006) Skeletal site for osteoporosis diagnosis: the ISCD Official Positions. *J Clin Densitometry* 9:15–21
 22. National Osteoporosis Foundation (2010) Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation. 1–56
 23. Wisniewski AF, Lewis SA, Green DJ, Mslanka W, Burrell H, Tattersfield AE (1997) Cross sectional investigation of the effects of inhaled corticosteroids on bone density and bone metabolism in patients with asthma. *Thorax* 52:853–860
 24. Maspero J, Backer V, Yao R, Staudinger H, Teper A (2013) Effects of mometasone, fluticasone, and montelukast on bone mineral density in adults with asthma. *J Allergy Clin Immunol Pract* 1(6):649–55.e1. doi:10.1016/j.jaip.2013.07.011
 25. Luengo M, del Río L, Pons F, Picado C (1997) Bone mineral density in asthmatic patients treated with inhaled corticosteroids: a case-control study. *Eur Respir J* 10:2110–2113
 26. Schmier JK, Van Kerkhove MD, Watkins M, Kalberg CJ (2004) Impact of long-term inhaled corticosteroid therapy on bone mineral density: results of a meta-analysis. *Ann Allergy Asthma Immunol* 92(2):201–207, quiz 207–8, 267
 27. Lo JC, Burnett-Bowie SA, Finkelstein JS (2011) Bone and the perimenopause. *Obstet Gynecol Clin North Am* 38(3):503–517. doi:10.1016/j.ogc.2011.07.001
 28. Turner CH, Canalis E, Pacifici R, Sun L, Iqbal J, Guo XE, Silverman S, Epstein S, Rosen CJ (2009) Bone loss or lost bone: rationale and recommendations for the diagnosis and treatment of early postmenopausal bone loss. *Curr Osteoporos Rep* 7(4):118–126
 29. Lewiecki EM, Watts NB, McLund MR et al (2004) Official positions of the International Society for Clinical Densitometry. *JCEM* 89: 3651–3655
 30. Masud T, Miller PD (2000) Bone densitometry in the elderly. In: Fordham JN (ED). *Manual of bone densitometry measurement*. Springer, Verlag London
 31. Heidari B, Hoshmand S, Hajian K, Heidari P (2010) Comparing bone mineral density in postmenopausal women with and without vertebral fracture and its value in recognizing high-risk individuals. *East Mediterr Health J* 16(8):868–873
 32. Heidari B, Heidari P (2014) Bone mineral density loss in postmenopausal onset rheumatoid arthritis is not greater than premenopausal onset disease. *Caspian J Intern Med* 5(4):213–218
 33. Aljubran SA, Whelan GJ, Glaum MC, Lockey RF (2014) Osteoporosis in the at-risk asthmatic. *Allergy* 69(11):1429–1439. doi:10.1111/all.12438
 34. Heidari B, Heidari P, Nouroodini HG, Hajian-Tilaki KO (2013) Relationship between parity and bone mass in postmenopausal women according to number of parities and age. *J Reprod Med* 58(9–10): 389–394