Allergology International. 2011;60:459-465
DOI: 10.2332/allergolint.10-OA-0276

ORIGINAL ARTICLE

Assessment of Bone Status in Inhaled Corticosteroid User Asthmatic Patients with an Ultrasound Measurement Method

Mayumi Sasagawa[1], Takashi Hasegawa[2], Jun-ichiro J Kazama[3], Toshiyuki Koya[3], Takuro Sakagami[3], Kazuo Suzuki[4], Katsuhito Hara[5], Hideo Satoh[6], Katsuya Fujimori[7], Fumitoshi Yoshimine[8], Kazuhiro Satoh[9], Ichiei Narita[3], Masaaki Arakawa[3], Fumitake Gejyo[3] and Eiichi Suzuki[2]

ABSTRACT

Background: The effect of inhaled corticosteroid (ICS) on the bone status of asthmatic patients is still uncartain, becuase it can differ by race and because there have been few cases in Japan. In this study, the bone status of ICS users with asthma was evaluated in an actual clinical setting in Japan.

Methods: In 7 participating hospitals, ICS users with asthma and control subjects were age- and gender-matched and recruited into this study. To assess bone status, ultrasound measurements of each individual's calcaneus were made using an AOS-100. The ratio of the osteo sono-assessment index (OSI) to the average OSI corrected for age and gender was denoted as %OSI and used for quantitative assessment. The second %OSI measurement was performed 6 months after the first %OSI one. During the study period, individual treatment remained unchanged.

Results: There were no significant differences in the 1st and 2nd %OSI between the ICS users and control subjects. However, the 2nd %OSI significantly decreased compared with 1st %OSI in female ICS users, although there were no significant changes in the male and female control subjects and male ICS users.

Conclusions: The 6 month manegement of asthma in the actual clinical setting, including regular ICS use, might have a harmful influence on the bone status of female asthmatic patients. It may be necessary to manage and treat female patients for potent corticosteroid-induced osteoporosis, although further analyses of bone status in asthma patient ICS users will be required.

KEY WORDS

adult asthma, adverse drug reaction, asthma, bone status, inhaled corticosteroid

ABBREVIATIONS

BDP, hydrofluoroalkane-beclometasone; BMD, bone marrow density; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DEXA, dual-energy X-ray absorption-metry; FP, fluticasone; ICS, inhaled corticosteroid; LABA, inhaled long-acting beta agonist; LTRA, leukotriene receptor antagonist; OSI, osteo sono-assessment index; OSRT, oral sustained-released theophylline; SOS, speed of sound; TI, transmission index; YAM, bone marrow density of young adult meaning.

[1]Department of Respiratory Medicine, Nanbugo General Hospital, [2]Department of General Medicine, [3]Department of Medicine II, Niigata University Medical and Dental Hospital, [4]Department of Medicine, Prefectural Muikamachi Hospital, [5]Department of Medicine, Prefectural Yoshida Hospital, [6]Department of Respiratory Medicine, Nagaoka Chuo General Hospital, [7]Department of Medicine, Prefectural Kamo Hospital, [8]Department of Medicine, Prefectural Tsugawa Hospital and [9]Department of Respiratory Medicine, Nagaoka Red Cross Hospital, Niigata, Japan.
Correspondence: Takashi Hasegawa, Department of General Medicine, Niigata University Medical and Dental Hospital, 1–754 Asahimachi-dori, Niigata 951–8510, Japan.
Email: htaka@med.niigata–u.ac.jp
Received 4 October 2010. Accepted for publication 1 February 2011.

INTRODUCTION

Guidelines in various countries recommend inhaled corticosteroids (ICS) for the primary treatment of bronchial asthma in adults.[1-3] The spread of ICS use has led to dramatic improvements in the management of asthma in Japan.[4,5] However, several potential adverse effects of ICS have been reported,[6] which have been divided into systemic adverse effects[7] and local ones.[8] With wide and longitudinal use of ICS, the former is an important factor in the ICS treatment of asthma. Recently, an increasing body of literature suggests the adverse effects of ICS use on bone status are one of the most important problems in the management of asthma.[9-27]

It is known that impaired bone status can lead to osteoporosis, which may result in an unexpected pathological fracture of the femoral neck, have an impact on patients' quality of life, and frequently is a direct cause of death.[28-31] In this sense, it is essential, if any adverse effects of ICS use on bone status can exist. Moreover, it is now possible to adequately treat osteoporosis, whether idiopathic or secondary to corticosteroid use. In such management, the assessment of bone status is beneficial in the prediction of pathological fracture.[32,33]

The adverse effects of ICS on bone status have been frequently studied as mentioned above, and it has been reported in some major studies, including 4 double-blinded placebo controlled studies, that there were few effects on bone status with regular administration of ICS,[9-18] whereas others have reported that ICS use influenced on the bone status.[17-27] Therefore, the main stream of the relationship between ICS use and its effect on bone status is not likely to exist. However, we thought that the conclusion have not been established completely, because bone status can differ with several factors, such as race,[34,35] and because there have been a few studies on the effect of ICS on bone status in Japan. In one of these report in Japan,[18] there were no control group and case numbers were relatively small. It is necessary, therefore, to clarify the adverse effect on bone status in a Japanese clinical setting with large case and control numbers. To evaluate bone status, a new method, that of ultrasound measurement, has been developed and has been reported as easy to use.[36-40] In the present study, on the assessement of the bone status of asthmatic patients, we used this ultrasound measurement method, because a possible large case numbers could be recruited due to both the easeness to handle and no adverse effects of radiation.

METHODS

This study was performed with the approval of the Ethics Committees of the School of Medicine of Niigata University in Niigata Prefecture, Japan, as well as those of each participating institution, based on the Ethical Principles for Medical Research Involving Human Subjects (the Declaration of Helsinki). The subjects gave a written informed consent and patient anonymity were preserved using documents and method approved by the ethical review committee of the hospital. The study involved the following seven hospitals: Prefectural Muikamachi Hospital, Prefectural Yoshida Hospital, Nagaoka Chuo General Hospital, Prefectural Kamo Hospital, Prefectural Tsugawa Hospital, Nagaoka Red Cross Hospital and Nanbugo General Hospital. The study was performed over 22 months from September 2005 to June 2007. Subjects were ICS users (aged 16 years and over) with bronchial asthma who regularly visited the participating institutes for asthma management (typically once or twice per month) and controls were patients with other diseases or volunteers at the same institutes.

To assess bone status, ultrasound measurements of the right calcaneus were carried out using an AOS-100 (Aloka Co. Ltd, Tokyo, Japan). The AOS-100 measures the ultrasound properties of the calcaneus by a transmission technique using a pair of unfocused broadband ultrasound transducers, positioned on each side of the calcaneus. Three ultrasonic parameters are obtained using the AOS-100 system. These are the speed of sound (SOS), the transmission index (TI) and the osteo sono-assessment index (OSI). OSI, calculated as (SOS)2 x TI, which has been reported to be well-correlated to bone marrow density (BMD), as measured by dual-energy X-ray absorptionmetry,[32] is a commonly-used as an indicator of bone status.

In this study, a quantitative assessment of bone status with AOS-100 was performed twice in each subject. The second OSI was measured 6 months after the first one. The ratio of the OSI in the right individual calcaneus to the average OSI, corrected for age and gender was denoted as %OSI and used for quantitative assessment. Other clinical information, including patients' backgrounds, was recorded at the first assessment of bone status.

Results are expressed as arithmetic means (±SD) for continuous variables. A Mann-Whitney U-test was used to test the equality of distributions of the continuous variables. The differences between dichotomous variables were analyzed with a chi-square test. A pairwise comparison was performed using Wilcoxon's rank sum test for the significance level. All statistical analyses were performed with the statistical software StatView 5.0 PowerPC version (SAS Institute Inc., Cary, NC, USA). For all statistical analyses, a P-value < 0.05 was considered to be significant.

RESULTS

BACKGROUND IN CONTROL SUBJECTS AND ICS USERS WITH BRONCHIAL ASTHMA

The backgrounds of the ICS users with bronchial asthma and control subjects are summarized in Table

Table 1 Background in control and ICS users

	control	ICS users	*P* value
gender (male/female)	43/50	84/114	0.5409
age (year: mean +/- SD)	60.6 +/- 12.4	59.1 +/- 15.8	0.8796
age of male (year: mean +/- SD)	63.8 +/- 10.7	60.9 +/- 15.2	0.6882
age of female (year: mean +/- SD)	57.9 +/- 13.2	57.8 +/- 16.1	0.8709

ICS, inhaled corticosteroid.

Table 2 Complications in control cases

	male	female
COPD	13	0
mycobacterial infection	1	2
pneumoconiosis	3	0
sleep apnea syndrome	10	2
hypertension	5	10
sarcoidosis	0	1
bronchiectasis	0	4
neurosis	0	1
depression	0	1
diabetes mellitus	0	1

1. The control subjects and ICS users with asthma were composed of 43 males and 50 females, and 84 males and 114 females, respectively. The mean ages of control subjects and ICS users were 60.6 +/- 12.4 and 59.1 +/- 15.8 years. There were no significant differences in terms of gender or age in the two groups. The mean ages of male control subjects and ICS users, and female control subjects and ICS users were 63.8 +/- 10.7 and 60.9 +/- 15.2, 57.9 +/- 13.2 and 57.8 +/- 16.1, respectively. There were no significant differences in terms age between male control subjects and ICS users and between females in the two groups. As for the systemic corticosterod user, there were 2 male and 2 female users.

COMPLICATIONS IN CONTROL SUBJECTS

Table 2 shows a summary of complications in the 93 control subjects. Of the 43 male control subjects, 13 cases had chronic obstructive pulmonary disease (COPD), 10 cases had sleep apnea syndrome, 5 cases had hypertension, 3 cases had pneumoconiosis and 1 case had mycobacterial infection. There were 10 hypertension cases, 4 bronchiectasis cases, 2 mycobacterial infection cases, 2 sleep apnea syndrome cases, 1 sarcoidosis case, 1 neurosis case, 1 depression case and 1 diabetes mellitus case amongst the female controls. However, there were no potent medicines that can affect bone status, such as corticosteroid, administrated for these pathological conditions.

AGE, DISEASE DURATION, TYPE, SEVERITY AND TREATMENT IN ICS USERS WITH ASTHMA

Table 3 shows the age, disease duration, type, severity and treatment in male and female ICS users. The type of asthma was decided in accordance with the elevation in serum total IgE or detection of specific IgE for allergens. Age and duration of disease was 60.9 +/- 15.2 and 8.7 +/- 7.1, 57.8 +/- 16.1 and 8.9 +/- 8.1 years in male ICS users and in female ICS users, respectively. The proportion of patients by disease type and disease severity amongst male and female ICS users was 42.6%, 53.6% and 50.9%, 43.9% (atopic type, non-atopic type), and 1.2%, 39.3%, 31.0%, 9.5% and 4.4%, 35.1%, 41.2%, 3.5% (step 1, step 2, step 3, step 4), respectively. There were no significant differences in terms of age, disease duration, type of asthma, and disease severity between the male and female ICS users. Of the male ICS users, 78.6% used fluticasone (FP), 8.3% used budesonide (BUD) and 10.7% used hydrofluoroalkane-beclometasone (BDP), and the percentages of those using inhaled long-acting beta agonists (LABAs), leukotriene receptor antagonists (LTRAs) and oral sustained-released theophylline (OSRT) were 44.0%, 35.7% and 39.3%, respectively. Of the female ICS users, 72.8% used FP, 16.7% used BUD and 8.8% used BDP, and the use rate of LABAs, LTRAs and OSRT was 41.2%, 41.2% and 38.6%, respectively. The doses of administered ICS, which was calculated as FP (mean +/- SD) based on Japanese Society of Allergology in male and female ICS users, were 460 +/- 214 and 392 +/- 181 (μg/day), respectively, and the ICS doses administered to male users were significantly higher than those administered to females. There were no significant differences in the distribution of the types of ICS, or in the percentage of those using LABAs, LTRAs and OSRT.

COMPARISON OF %OSI BETWEEN THE CONTROL SUBJECTS AND ICS USERS WITH BRONCHIAL ASTHMA AND CHANGES FROM 1ST %OSI TO 2ND %OSI IN THE CONTROL SUBJECTS AND ICS USERS WITH BRONCHIAL ASTHMA

First-time measured OSI (1st %OSI) and second-time measured OSI (2nd %OSI) were 100.7 +/- 12.0 and 100.5 +/- 13.5% for all control subjects, and 102.8 +/- 12.0 and 102.1 +/- 11.0% for the ICS users, respectively (Table 4a). There were no significant differences in first-time measured OSI (1st %OSI) and second-time measured OSI (2nd %OSI) between the two groups (Table 4a). In the male subjects and the

Table 3 Age, disease duration, type, severity and treatment in ICS users with asthma

	male ICS users (84 cases)	female ICS users (114 cases)	*P* value
age (year: mean +/- SD)	60.9 +/- 15.2	57.8 +/- 16.1	*P* = 0.1975
duration (year: mean +/- SD)	8.7 +/- 7.1	8.9 +/- 8.1	*P* = 0.9288
type (%: atopic/nonatopic)	42.9/53.6	50.9/43.9	*P* = 0.2654
severity (%: step1/2/3/4)	1.2/39.3/31.0/9.5	4.4/35.1/41.2/3.5	*P* = 0.1064
used ICS (%: FP/BUD/BDP)	78.6/8.3/10.7	72.8/16.7/8.8	*P* = 0.2274
doses of ICS calculated as FP (μg/day)	460 +/- 214	392 +/- 181	*P* = 0.0308
% use of LABA	44.0	41.2	*P* = 0.8598
% use of LTRA	35.7	41.2	*P* = 0.5288
% use of OSRT	39.3	38.6	*P* = 0.9271

ICS, inhaled corticosteroid; FP, fluticasone propionate; BUD, budesonide; BDP, hydrofluoroalkane-beclometasone; LABA, inhaled long-acting beta agonist; LTRA, leukotrien receptor antagonist; OSRT, oral sustained-released theophylline.

Table 4a %OSI and its change in control and ICS users

	control	ICS users	*P* value (control v.s. ICS users)
1st %OSI	100.7 +/- 12.0	102.8 +/- 12.0	0.1264
2nd %OSI	100.5 +/- 13.5	102.1 +/- 11.0	0.1204
P value (1st v.s. 2nd %OSI)	0.3788	0.4009	

ICS, inhaled corticosteroid; OSI, osteo sono-assessment index.

Table 4b %OSI and its change in male control and male ICS users

	control	ICS users	*P* value (control v.s. ICS users)
1st %OSI	98.3 +/- 12.2	101.4 +/- 13.9	0.2602
2nd %OSI	97.7 +/- 13.4	101.8 +/- 12.4	0.0548
P value (1st v.s. 2nd %OSI)	0.2213	0.1669	

ICS, inhaled corticosteroid; OSI, osteo sono-assessment index.

Table 4c %OSI and its change in female control and female ICS users

	control	ICS users	*P* value (control v.s. ICS users)
1st %OSI	102.8 +/- 11.5	103.9 +/- 10.4	0.7710
2nd %OSI	102.8 +/- 13.4	102.3 +/- 9.9	0.8709
P value (1st v.s. 2nd %OSI)	0.9591	0.0145	

ICS, inhaled corticosteroid; OSI, osteo sono-assessment index.

male ICS users, 1st and 2nd %OSI were 98.3 +/- 12.2 and 97.7 +/- 13.4, and 101.4 +/- 13.9, 101.8 +/- 12.4%, respectively (Table 4b). Those in the female controls and ICS users were 102.8 +/- 11.5 and 102.8 +/- 13.4, and 103.9 +/- 10.4 and 102.3 +/- 9.9%, respectively (Table 4c). There were no significant differences in 1st %OSI and 2nd %OSI between the control subjects and the ICS users in a gender-segregated comparison. There were no significant changes from 1st %OSI to 2nd %OSI in both all the control subjects and all the ICS users (Table 4a). In the male controls and male ICS users, there were also no significant changes from 1st %OSI to 2nd %OSI (Table 4b). Although there were no significant changes in the female controls, 2nd %OSI decreased significantly compared with 1st %OSI in the female ICS users (Table 4c). When the systemic corticosteroid users were excluded, the results were same (data not shown). Theses findings indicate that bone status was impaired during 6 months of ICS use in females.

DISCUSSION

Recently, excellent pharmacotherapies, such as bisphosphonates, have been developed, and they have certain preventive effects against pathological fractures due to osteoporosis.[41,42] Therefore, it is very important and meaningful to evaluate bone status for adults while managing various diseases. To prevent pathological fractures in the femoral neck, which can be one of the causes of death in the elderly,[33] world-

wide guidelines have been proposed based on an evaluation of bone status.[43] In Japan, guidelines have also been made, indicating criteria for starting pharmacotherapy in order to prevent pathological fractures in idiopathic osteoporosis.[44] According to these Japanese guidelines, pharmacotherapy should principally begin for adults when they have a BMD of under 70% of the mean of BMDs of those aged from 20 to 44 years old (YAM) without pathological fractures. However, another kind of criterion has also been proposed for systematic corticosteroid-administrated cases, because systemic use of corticosteroids has been clearly proven to have a negative impact on bone status.[45] In such cases, pharmacotherapy is started whenever there is systemic use of corticosteroids at doses of more than 5 mg/day prednisolone (PSL) equivalent, and when a BMD of lower than 80% of YAM at doses of lower than 5 mg/day PSL equivalent.

In this study, we evaluated the right individual calcaneus, giving rise to the question of whether the occurrence of pathological femoral neck fractures can be estimated by the measurement of calcaneus bone status. However, the evaluation of calcaneus bone status using quantitative ultrasound as used in this study has been reported to be an excellent predictor of femoral neck fractures.[46,47] In the present study, a significant deterioration of bone status in female ICS users over a short duration of only 6 months indicated that the standard 6 month asthma management in the actual clinical setting could impaire the female patient's bone status and that the use of ICS might play an important role in this decrease of %OSI. As we did not examine both the ICS use history of asthmatic patients perior to this study and transient use of systemic corticosteroids due to asthma exacervation during the study period, it may be difficult to conclude that the ICS use of 6 months impare the bone status of female asthmatic patients. However, it is possible to show that a female asthmatic patient under at least 6 momths standard asthma management including ICS therapy may be as same as a systemic corticosteroid user at lower dose. Therefore, evaluation of bone status, especially BMD value comparison with that of YAM, should be considered for adult female asthma patients at or 6 months after initiation of asthma management including ICS therapy. However, there were no significant changes observed during the 6 months in males, indicating that early prevention of osteoporosis may be unnecessary soon after the start of ICS therapy in male asthma patients.

Although we also examined the relationship between the daily ICS dose and the changes of %OSI in each asthmatic patient, there was no significant relationship (data not shown). In female patients, it was thought that not daily ICS dose but the ICS use itself at the usual dose of ICS might play an essential role in the changes of %OSI. Regarding to the doses of ICS of the male and female patients, there was no significant changes of %OSI between 1st and 2nd %OSI in male patients despite of significantly more ICS dose (460 +/- 214 mg/day calculated as FP) than that in female (392 +/- mg/day calculated as FP), indicating that there was little impact on the male bone status within 6 months asthma management, including ICS therapy, in the actual clinical setting. There was no significant difference of 1st %OSI between female controls and patients. There was no suitable explanation for it, because the mean disease duration in female patients was 8.9 years and because a certain influence of ICS use prior to this study on only female patients was supposed. The compliance of ICS during the study period was not investigated in this study. However, because we reported that the ICS compliance of male and older patients was better than that of female and younger[48] in the actual clinical setting, there was nothing controversial as for ICS compliance. Other potent predictive factors for bone status, including smoking status, were not analyzed in this study. However, the incidence of smoking in female asthma patients has been reported to be 7.4%[49] and is obviously less than that reported for the general female population. This indicates that the results of the present study, namely that a management of asthma, incuding ICS use, can affect bone status in female asthma patients, is not likely to be greatly influenced by the exclusion of smoking status.

In summary, this study found there to be no significant changes between male ICS users and control subjects. However, the 6-month management of asthma in the actual clinical setting, including ICS use, might have a harmful influence on the bone status of female asthmatic patients, indicating that it may be necessary to manage and treat female patients for potent corticosteroid-induced osteoporosis, although further analyses of bone status in asthma patient ICS users will be required.

CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

REFERENCES

1. Hoshino T, Toda R, Aizawa H. Pharmacological treatment in asthma and COPD. *Allergol Int* 2009;**25**:341-6.
2. National Institutes of Health; National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3, 2007. Publication No. 07-4051. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed December 30, 2007.
3. Monge RM, Montaner AE, Benitez MF *et al*. Consensus statement on the management of paediatric asthma. *Allergol Immunopathol (Madr)* 2006;**34**:88-101.
4. Hasegawa T, Suzuki E, Terada M *et al*. Improvement of asthma management in actual practice consistent with prevalence of anti-inflammatory agents. —Based on questionnaire surveys in Niigata Prefecture, Japan from 1998

to 2002—. *Allergol Int* 2005;**54**:555-63.
5. Hasegawa T, Suzuki E, Muramatsu Y *et al*. Questionnaire-based analysis of the current level of asthma control and management in Niigata Prefecture, Japan: Changes from 1998 to 2000. *Allergol Int* 2004;**53**:135-44.
6. Irwin RS, Richardson ND. Side effects with inhaled corticosteroids: the physician's perception. *Chest* 2006;**130**: 41S-53.
7. Kelly HW, Nelson HS. Potential adverse effects of the inhaled corticosteroids. *J Allergy Clin Immunol* 2003;**112**: 469-78.
8. Buhl R. Local oropharyngeal side effects of inhaled corticosteroids in patients with asthma. *Allergy* 2006;**61**:518-26.
9. Kemp JP, Osur S, Shrewsbury SB *et al*. Potential effects of fluticasone propionate on bone mineral density in patients with asthma: a 2-year randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2004;**79**:458-66.
10. Li JT, Ford LB, Chervinsky P *et al*. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. *J Allergy Clin Immunol* 1999;**103**:1062-8.
11. Medici TC, Grebski E, Häcki M, Rüegsegger P, Maden C, Efthimiou J. Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. *Thorax* 2000;**55**: 375-82.
12. Harmanci E, Colak O, Metintas M, Alatas O, Yurdasiper A. Fluticasone propionate and budesonide do not influence bone metabolism in the long term treatment of asthma. *Allergol Immunopathol (Madr)* 2001;**29**:22-7.
13. Tattersfield AE, Town GI, Johnell O *et al*. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. *Thorax* 2001;**56**:272-8.
14. Luengo M, del Rio L, Pons F, Picado C. Bone mineral density in asthmatic patients treated with inhaled corticosteroids: a case-control study. *Eur Respir J* 1997;**10**: 2110-3.
15. Herrala J, Puolijoki H, Impivaara O, Liippo K, Tala E, Nieminen MM. Bone mineral density in asthmatic women on high-dose inhaled beclomethasone dipropionate. *Bone* 1994;**15**:621-3.
16. Nagasaka Y, Fujita E, Okawa K *et al*. [Effect of inhaled steroid on bone metabolism in the treatment of bronchial asthma]. *Arerugi* 1994;**43**:1398-404 (in Japanese).
17. Hughes JA, Conry BG, Male SM, Eastell R. One year prospective open study of the effect of high dose inhaled steroids, fluticasone propionate, and budesonide on bone markers and bone mineral density. *Thorax* 1999;**54**:223-9.
18. Matsumoto H, Ishihara K, Hasegawa T, Umeda B, Niimi A, Hino M. Effects of inhaled corticosteroid and short courses of oral corticosteroids on bone mineral density in asthmatic patients: a 4-year longitudinal study. *Chest* 2001; **120**:1468-73.
19. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med* 1999;**10**:941-55.
20. Sharma PK, Malhotra S, Pandhi P, Kumar N. Effect of inhaled steroids on bone mineral density: a meta-analysis. *J Clin Pharmacol* 2003;**43**:193-7.
21. Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med* 2001;**345**:941-7.
22. Wong CA, Walsh LJ, Smith CJ *et al*. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000;**355**:1399-403.
23. Sambrook PN. Inhaled corticosteroids, bone density, and risk of fracture. *Lancet* 2000;**355**:1385.
24. Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 1994;**105**:1722-7.
25. Toogood JH, Baskerville JC, Markov AE *et al*. Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma. *J Allergy Clin Immunol* 1995;**96**:157-66.
26. Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 1995;**96**:571-9.
27. Boulet LP, Milot J, Gagnon L, Poubelle PE, Brown J. Long-term influence of inhaled corticosteroids on bone metabolism and density. Are biological markers predictors of bone loss? *Am J Respir Crit Care Med* 1999;**159**: 838-44.
28. Liu H, Paige NM, Goldzweig CL *et al*. Screening for osteoporosis in men: a systematic review for an American College of Physicians guideline. *Ann Intern Med* 2008; **148**:685-701.
29. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet* 2002;**359**:1929-36.
30. Sweet MG, Sweet JM, Jeremiah MP, Galazka SS. Diagnosis and treatment of osteoporosis. *Am Fam Physician* 2009;**79**:193-200.
31. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. *Osteoporos Int* 2000;**11**:556-61.
32. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: scientific review. *JAMA* 2002;**288**:1889-97.
33. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996;**312**:1254-9.
34. Kalkwarf HJ, Zemel BS, Gilsanz V *et al*. The Bone Mineral Density in Childhood Study (BMDCS): Bone mineral content and density according to age, sex and race. *J Clin Endocrinol Metab* 2007;**92**:2087-99.
35. Wu XP, Liao EY, Huang G, Dai RC, Zhang H. A comparison study of the reference curves of bone mineral density at different skeletal sites in native Chinese, Japanese, and American Caucasian women. *Calcif Tissue Int* 2003;**73**: 122-32.
36. Gonnelli S, Cepollaro C, Gennari L *et al*. Quantitative ultrasound and dual-energy X-ray absorptiometry in the prediction of fragility fracture in men. *Osteoporos Int* 2005; **16**:963-8.
37. Karlsson MK, Duan Y, Ahlborg H, Obrant KJ, Johnell O, Seeman E. Age, gender, and fragility fractures are associated with differences in quantitative ultrasound independent of bone mineral density. *Bone* 2001;**28**:118-22.
38. He YQ, Fan B, Hans D *et al*. Assessment of a new quantitative ultrasound calcaneus measurement: precision and discrimination of hip fractures in elderly women compared with dual X-ray absorptiometry. *Osteoporos Int* 2000; **11**:354-60.
39. Tsuda-Futami E, Hans D, Njeh CF *et al*. An evaluation of a new gel-coupled ultrasound device for the quantitative assessment of bone. *Br J Radiol* 1999;**72**:691-700.
40. Sasaki M, Harata S, Kumazawa Y, Mita R, Kida K, Tsuge M. Bone mineral density and osteo sono assessment in-

dex in adolescents. *J Orthop Sci* 2000;**5**:185-91.
41. Papapoulos SE, Quandt SA, Liberman UA, Hochberg MC, Thompson DE. Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. *Osteoporos Int* 2005;**16**:468-74.
42. Cranney A, Wells G, Willan A *et al*; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev* 2002;**23**: 508-16.
43. Osteoporosis Prevention, Diagnosis, and Therapy. *NIH Consensus Statement* 2000; **17**: 1-45. Available from: http://consensus.nih.gov/2000/2000Osteoporosis111html.htm.
44. Orimo S. *[Osteoporosis Prevention and Management Guideline 2006]*. Tokyo: Life Science Publishing, 2006 (in Japanese).
45. Nawata H, Soen S, Takayanagi R *et al*, and Subcommittee to Study Diagnostic Criteria for Glucocorticoid-Induced Osteoporosis. Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research (2004). *J Bone Miner Metab* 2005;**23**:105-9.
46. Bauer DC, Gluer CC, Cauley JA *et al*. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 1997;**157**:629-34.
47. Schott AM, Hans D, Duboeuf F *et al*, and EPIDOS Study Group. Quantitative ultrasound parameters as well as bone mineral density are better predictors of trochanteric than cervical hip fractures in elderly women. Results from the EPIDOS study. *Bone* 2005;**37**:858-63.
48. Hasegawa T, Suzuki E, Koya T *et al*. Analysis of drug compliance in adult patients with bronchial asthma. Based on questionnaire surveys in Niigata Prefecture, Japan. *General Med* 2004;**5**:7-12.
49. Satoh H, Hasegawa T, Suzuki E *et al*. Gender differences in susceptibility of asthma to active smoking. Questionnaire based analysis in the Niigata Prefecture, Japan. *Allergol Int* 2005;**54**:401-10.