◎原 著

Determinants of trabecular bone mineral density of the lumber spines and vertebral fracture in patients with bronchial asthma

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Abstract : Clinical risk factors associated with the development of osteoporosis and vertebral fractures were evaluated in patients with asthma in relation to sex, age, and dose of glucocorticoids (GC). In 75 asthmatic patients including 44 steroid-dependent asthma, the bone mineral density (BMD) of the lumber spines was measured by quantitative computed tomography (QCT). Thirty five patients of them were followed up with radiographs over a period of 0.5 to 4 years (average : 2.6±1.3 years) The BMD was significantly lower in older ($p<0.01$) or female ($p<0.05$) patients. All the five patients developing vertebral compression fractures were female and more than 64 y.o., and received systemic glucocorticoid (GC) therapy for more than 3 years with a lot of cumulative gramdosage of GC. No significant correlation was demonstrated between the BMD and the dose of systemic GC per day, but multiple regression analysis demonstrated a significant relationship ($p<0.01$) between the BMD and lifetime cumulative gramdosage of GC. Multiple regression analysis also demonstrated significant relationships ($p<0.01$) between the BMD and clinical factors such as age and sex. These results indicates that the bone loss and vertebral fractures of patients with asthma are influenced by the patient's age, sex, and the lifetime cumulative GC dose.

Key words : bronchial asthma, osteoporosis, vertebral fracture, glucocorticoid therapy

Introduction

The pathogenesis of asthma is not related to bone metabolism and bone mineral density (BMD), but some patients with severe asthma who had prolonged oral systemic glucocorticoid (GC) therapy, and were difficult to wean off GC, have at high risk of developing bony complications due to glucocorticoids[1-7]. Other clinical risk factors such as age, sex and the other underlying diseases may also affect bone metabolism in patients with

asthma.

Numerous studies have reported that reduced BMD and progressive bone loss occur in patients receiving long-term systemic GC therapy[1, 3, 8].

The effects of GC on the skeleton are most markedly observed in the trabecular bone[1], and it is assumed that 30%−50% of patients treated for more than 1 year with 7.5−10 mg/day of prednisolone-equivalent will develop atraumatic vertebral fracture[1].

To identify clinical characteristics associated with the development of bone loss and fractures, we investigated the trabecular bone mineral density (BMD) of the lumber spines in 75 asthmatic patients, including 44 steroid-dependent asthma, using quantitative computed tomography (QCT)[9, 10]. We also studied a correlation between the BMD and daily and lifetime cumulative gramdosages of GC in patients with steroid-dependent asthma.

Subjects

The subjects in this study were 75 patients with bronchial asthma (60 females and 15 males). The characteristics of the study subjects are summarized in Table 1. Forty four patients with steroid-dependent asthma had received continuous oral systemic GC for at least 6 months preceding the study. Fourteen patients had medical conditions affecting bone metabolism ; such as diabetes mellitus (n= 7), hyperthyroidism (n= 2), pituitary insufficiency (n= 1), post total gastrectomy (n= 2), post bilateral ovarian resection (n= 3) and rheumatoid arthritis (n= 1). None of the patients was alcoholic, and none was smoker. History and physical examination were performed in all the patients. Duration, daily and cumulative lifetime gramdosages of GC were calculated from the medical records. The dose of GC was expressed in equivalent grams of prednisolone. Thirty two patients had received continuous inhaled GC (BDI≦800μg/day) for at least 6 months. Eight patients had been treated with vitamin D therapy, and 35 patients were followed up with radiographs over a period of 0.5 to 4 years (average : 2.6±1.3 years).

Table 1. Clinical details of 75 patients with bronchial asthma

Sex (M/F)	15/60
Age (Year)	64.8±10.7
Height(cm)	152±7.5
Weight(kg)	52.5±9.6
BMI (kg/m^2)	22.7±3.7
BMD(mg/cm^3)	99.4±50.4
With another disease	14 cases
Systemic prednisolone-equivalent :	
≧5mg/day	35 cases
5mg/day> >0mg/day	9 cases
Cumulative dose of prednisolone(g)	7.60±13.7
Inhaled steroid	32 cases

Methods

The following clinical parameters were evaluated in these subjects : 1) Lateral spine radiographs for compression fractures (defined as ≧ 20% loss of vertebral body height), 2) Trabecular bone mineral density (BMD) of the lumber spines measured by quantitative computed tomography (QCT)[9, 10] with a Toshiba X peed (Tokyo, Japan). The average BMD of L2−L4 was calculated. Alternate spine (above or below) was measured if vertebral compression fracture was suspected. The BMD was expressed as mg/cm³ $CaCO_3$ equivalent by means of a simultaneously scanned calibration phantom (Kyoto−Kagaku B−MAS, Kyoto, Japan).

Statistical analysis

Student's t-test, multiple regression analysis and other statistical analysis were performed using a software package, StatView 4.5 (Abacus Concepts).

Results

Using Student's t-test, a correlation was evaluated between BMD and the following clinical parameters : (1) body mass index (BMI)(≧23.0kg/㎡, <23.0kg/㎡), (2) age (≧65y.o., <65y.o.), (3) sex (male, female), (4) present daily systemic GC does (≧5㎎/day, 0㎎/day), (5) inhaled GC therapy, and (6) the other underlying diseases affecting bone metabolism. (Table 2).

Table 2. Comparison of BMD in sub-groups of patients

Index		BMD(mg/cm³)	t-test
BMI (kg/m²)	≧23.0(n=36)	98.1±44.9	
	<23.0(n=39)	100.6±55.6	N.S.
Age(year)	≧65(n=40)	79.3±41.3	
	<65(n=35)	122.3±50.6	p<0.01
Sex	M(n=15)	125.5±45.0	
	F(n=60)	92.9±49.9	p<0.05
Systemic steroid	≧5mg/day (n=35)	101.8±53.0	
(prednisolone)	non (n=31)	95.2±50.4	N.S.
Inhaled steroid	use (n=32)	99.8±46.7	
	non-use(n=43)	96.3±51.0	N.S.
Other disease	yes (n=14)	90.6±60.8	
	no (n=61)	102.1±47.8	N.S.

There was significant difference in the BMD between older (≧65 y.o.) and younger patients (<65 y.o.)($p<0.01$). There was also significant difference BMD between females and males ($p<0.05$). There was no significant difference in the other parameters assessed in this study, including daily systemic GC equivalent dose and the other underlying diseases affecting bone metabolism.

Multiple regression analysis was also performed (Table 3) to evaluate relationships between the BMD as a dependent variable and the following clinical parameters as independent variables : (1) age, (2) lifetime cumulative gramdosage of GC, (3) sex (male, female), and (4) BMI (Table 3). Significant relationship was demonstrated between the dependent variable and the independent variables ($R=0.651$, $p<0.001$). Multiple regression analysis showed that the BMD was oppositely proportional to age ($p<0.001$), female ($p=0.0044$) and lifetime cumulative gramdosage of GC ($p=0.0056$).

Table 3. Multiple regression analysis between BMD and clinical parameters in patients with asthma

Independent variable	Partial Regression Coefficient	Standard Error	Standard Partial Regression Coefficient	t-value	p-value
Constant	258.85	42.75	258.85	6.05	<0.0001
Age	-2.44	0.46	-0.52	-5.34	<0.0001
Total dose of PSL	-1.02	0.36	-0.28	-2.86	0.0059
Sex	-38.32	12.98	-0.30	-2.95	0.0044
BMI	1.63	1.33	0.12	1.23	0.2227

PSL: prednisolone

R= 0.651
R^2= 0.424
p<0.0001

Sex: Female = 1, Male = 0

(BMD)= -2.44(Age) - 1.02(PSL dose)-38.32(Sex)+1.63(BMI)+258.85

Five of the 35 patients followed up with radiographs developed vertebral compression fractures (Table 4). All the five patients with fractures were female, and more than 64 y.o., and received systemic GC therapy for more than three years. The average cumulative gramdosage of GC was 10.9 g. The average age was 71.2 y.o. The average BMD was 49.9㎎/㎠. Their postmenopausal periods were 15−25 years, and they had 1 − 3 children. The incidence of vertebral fracture of the asthmatic patients in this study was 0.055/year/case.

Table 4. Clinical details of 35 followed patients

Periods for observation (year)	2.6±1.3
Sex (M/F)	6/29
Age (y.o.)	64.9±10.0
BMI (kg/m^2)	22.7±3.7
BMD (mg/cm^3)	104.7±51.1
Systemic prednisolone-equivalent :	
≧5mg/day	16 cases
5mg/day> >0mg/day	9 cases
Cumulative dose of prednisolone(g)	3.71±3.49
Inhaled steroid	12 cases
With other disease	5 cases
With vitamin D therapy	5 cases

Discussion

The BMD in the present study was significantly lower in older or female patients with bronchial asthma, just like with primary osteoporosis. Numerous studies have reported that reduced BMD and progressive bone loss occur in patients receiving long-term GC therapy[1, 3, 8]. Side effects of GC on the skeleton are most markedly found in the trabecular bone[1], and this bone loss is closely related to fractures in the lumber spines[8]. It is assumed that 30% − 50% of patients treated for more than 1 year with 7.5−10 mg/day of prednisolone-equivalent will develop atraumatic vertebral fracture[1]. It is also suggested that the bone loss occurs predominantly within the first 6 months of long-term GC therapy[3].

In this study, no significant relationship was demonstrated between the BMD and the daily systemic GC equivalent dose, but multiple regression analysis demonstrated a significant relationship between the BMD and the lifetime cumulative gramdosage of GC. These results indicated that the lifetime cumulative GC dose was more important than the daily GC dose for the pathogenesis of GC-induced bone loss. According to this, GC-induced bone loss could develop even in patients with not exceeding 5.0 mg/day of prednisolone-equivalent if they had taken a lot of GC for a long time. These findings emphasized the need to consider prophylaxis against the bone loss from the outset.

All the patients who developed vertebral compression fractures (Table 4) were female, and more than 64 y.o., and had systemic GC therapy for a long time with a high cumulative GC dose, and had reduced BMD. These findings suggested the bone loss and vertebral fractures of patients with asthma were influenced by the patient's age and sex, just like primary osteoporosis, and by the cumulative GC dose.

Table 5. Clinical details of patients with compression fracture of spine

Case	Sex	Position	Age(Y)	BMD(mg/cm^3)	another disease	Systemic prednisolone	Periods (year)	Cumulative dose(g)
N.M.	F	L4	73.9	36.2	RA	5mg/day	12.0	21.90
Y.K.	F	L2	71.1	57.0	-	2.5mg/day	3.0	2.74
Y.Y.	F	L1	64.7	89.2	-	5mg/day	8.2	14.90
Y.T.	F	L2	68.0	48.7	-	5mg/day	4.6	8.35
S.J.	F	L3	78.1	18.2	-	5mg/day	3.6	6.53
Mean			71.2	49.9			6.3	10.88

In the present study, the incidence of vertebral fracture of asthmatic patients including those treated with GC was 0.055/year/case. This finding might suggest that vertebral fracture unusually developed in patients with asthma except those treated with a high cumulative GC dose. It has been reported the daily much dose of inhaled GC may adversely affect bone density[11, 12], but inhaled GC at daily doses lower than 1600 μg/day does not cause bone loss[13]. In the present study, all the patients receiving continuous inhaled GC was treated with not exceeding 800 μg/day of beclomethasone (BDI), and no significant

relationship was demonstrated between BMD and inhaled GC treatment.

Spinal QCT measurements have been reported to be sensitive for detecting cancellous bone mineral loss, such as GC-induced bone loss[5] and postmenopausal bone loss. This measurement instrument, however, is not extremely accurate. In further study, we want to measure with a more accurate measuring instrument such as peripheral QCT (pQCT). In the present study, a correlations was evaluated between the BMD and risk factors associated with the development of osteoporosis and vertebral fractures in patients with asthma. Further studies with more subjects are needed to clarify the risk factors and pathogenesis which associate with the development of osteoporosis and vertebral fractures in patients with asthma.

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気管支喘息患者における腰椎海綿骨骨塩量と脊椎圧迫骨折の臨床的特徴

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要　旨

対象は気管支喘息75症例。このうち44例はステロイド依存性難治症例であった。35症例については，0.5年から4年間(平均：2.6±1.3年間)の経時的観察もおこなわれた。これらの症例の骨塩量に影響を及ぼす因子について検討をおこなった。高齢者，女性に有意な低骨塩量を認めた。重回帰分析にて年齢，性別，経口副腎ステロイド投与総量などの項目に骨塩量と有意な関連が認められた。また，35症例中5例に脊椎圧迫骨折が発生し，いずれも骨塩量が低く，高齢者，女性，長期ステロイド内服例であった。これらのことから気管支喘息患者においては，女性，高齢者，長期ステロイド内服例に骨塩量減少や脊椎圧迫骨折のリスクが高いと考えられた。また，ステロイド続発性骨粗鬆症の発生には，ステロイドの現在の一日内服量よりもこれまでの総積算内服量が重要と考えられた。

索引用語：気管支喘息，骨粗鬆症，椎体骨折，ステロイド療法