◎原 著

Cortical bone porosity in patients with asthma

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Abstract : In previous studies, we have demonstrated that chronic administration of systemic glucocorticoids decreases cortical bone mineral density (BMD), cortical bone volume, bone strength, and induces development of pathologic fractures in asthmatic patients. We have also demonstrated that glucocorticoid administration appears to be responsible for the process of cortical bone porosity at both endosteal and intracortical sites in postmenopausal asthmatic patients. There is a difference of gonadal hormones between male and female. To investigate the influence of hormonal difference on glucocorticoid-induced cortical bone porosity, we studied cortical bone volume and BMD in both male and female patients with asthma in this report.

A total of 99 asthmatic patients (male 26 cases, female 73 cases) were enrolled in the study. Peripheral quantitative computed tomography (pQCT) was used to measure cortical BMD and relative cortical volume.

The cortical volume-density relationship appeared to remain constant regardless of the level of systemic glucocorticoid administration, age or sex, suggesting cortical bone porosity causes similar and simultaneous decreases in cortical bone volume and density.

In conclusion, glucocorticoid administration appears to be responsible for the process of cortical bone porosity at both endosteal and intracortical sites despite the gonadal hormonal differences.

Key words : bronchial asthma, systemic glucocorticoid, cortical bone, cortical porosity, peripheral quantitative computed tomography

Introduction

Recently, techniques for measuring bone mineral density (BMD) have been developed. Peripheral quantitative computed tomography (pQCT) measures three-dimensional density, and separately determines both cortical bone density and trabecular bone density with a high level of precision[1-3]. pQCT on the radius is also known to provide an accurate assessment of the general condition of bone[4-6]. Other standard densitometric methods, such as dual energy X-ray densitometor (DXA) gave little or no information about bone quality or distribution[7].

Trabecular bone and cortical bone differ in their remodelling characteristics[8, 9], and structure[8]. Cortical bone is closely related to bone strength and stiffness[5, 10]. Both cortical bone density[7, 14] and cortical bone volume[5, 11-14] are known to influence bone strength.

Using pQCT, previous studies have reported that aging is associated with a reduction in cortical bone volume as well as a reduction in cortical bone density[8-10, 14-16]. Fujii et al.[13] demonstrated that a fixed ratio exists between the radius cortical volume and density in healthy adult humans regardless of either age or sex, suggesting that cortical bone porosity causes similar and simultaneous decreases in cortical bone volume and density during the aging processes. In secondary hyperparathyoidism, similar findings were observed in uremic patients on maintenance hemodialysis[17].

Chronic use of systemic glucocorticoids (GC) is known to lead to progressive bone loss and the development of pathologic fractures in a correlating manner with the cumulative dose of GC[18-21]. Recent our studies have demonstrated using pQCT that chronic administration of systemic glucocorticoids decreases cortical BMD, trabecular BMD, and induces development of pathologic fractures in asthmatic patients[6, 22]. We have also demonstrated that glucocor-ticoid administration appears to be responsible for the process of cortical bone porosity at both endosteal and intracortical sites in postmenopausal asthmatic patients[22].

In females, there is an irreversible and substantial loss of bone consequent to the lack of estrogen in the 10 year period following menopause[23]. Previous reports have detected perimenopausal bone loss in both trabecular and cortical bone using pQCT[15]. There is a difference of gonadal hormones between male and female, and this hormonal difference appear to influence bone metabolism. In GC-induced bone loss, however, the relationship between cortical volume and density concerning cortical bone porosity have to date never been studied in male patients. To investigate the influence of hormonal difference on glucocorticoid-induced cortical bone porosity, we studied changes in cortical bone volume and BMD using pQCT in both male and female patients with asthma undergoing systemic glucocorticoid therapy in the present study.

Methods

SUBJECTS

Ninety-nine outpatients with asthma (male 26 cases, female 73 cases) were enrolled in the study. Seventy-three patients were naturally postmenopausal females, and 59 out of 73 patients over 65 years of age had gone through menopause at least 10 years prior to the start of the study. Twenty-six patients were males, including 21 patients over 65 years of age were also included. All patients

had taken inhaled GC (range: 200 to 800 μg/day of beclomethasone dipropionate; mean: 318 μg/day) over a period of 2 to 8 years (mean: 4.7 years). All patients were devided to six groups by age and sex (Table 1, 2, 3). In aged male patients over 65 years, 6 patients without systemic GC therapy, GC(−) group, received less than a 0.5g cumulative dose of prednisolone, and 15 patients with systemic GC therapy, GC(+) group, received more than a 10g cumulative dose of prednisolone (mean: equivalent of 37.7g of prednisolone) over a prolonged period (mean: 9.7 years) (Table 1).

Table 1. Aged Male Patient Characteristics Divided by Cumulative Dose of Glucocorticoid Use.

	GC(−) group[a] (n=6)	GC(+) group[b] (n=15)	t test
Age (years)	72.4±3.4	72.3±4.1	N.S.
Height (cm)	158.9±6.7	163.2±6.1	N.S.
Weight (kg)	51.9±7.9	57.0±5.5	N.S.
BMI (kg/m^2)	20.5±2.5	21.4±1.7	N.S.
Cumulative dose of prednisolone (g)	0.03±0.07	37.7±20.1	p<0.01

Values are presented as the mean±SD.
GC: glucocorticoids; BMI: body mass index; BMD: bone mineral density; N.S.: not significant
a: patients without systemic GC therapy who received less than a 0.5g cumulative dose of prednisolone
b: patients with sytemic GC therapy who received more than a 10g cumulative dose of predonisolone

There were no significant differences in age, height, weight, or body mass index (BMI) between the two groups (Table 1). In aged female patients over 65 years, 22 patients without systemic GC therapy, GC(−) group, received less than a 0.5g cumulative dose of prednisolone, and 37 patients with systemic GC therapy, GC(+) group, received more than a 10g cumulative dose of prednisolone (mean: equivalent of 21.5g of prednisolone) over a prolonged period (mean: 7.7 years). There were no significant differences in age, age at menopause, years since menopause (YSM), height, weight, or BMI between groups (Table 2).

In patients under 65 years without systemic GC therapy, 5 male patients and 14 female patients were included (Table 3).

Table 2. Aged Female Patient Characteristics Divided by Cumulative Dose of Glucocorticoid Use.

	GC(−) group[a] (n=22)	GC(+) group[b] (n=37)	t test
Age (years)	71.9±3.6	71.9±4.7	N.S.
Age at menopause (years)	49.0±3.1	48.1±5.9	N.S.
Years since menopause (years)	22.9±5.0	23.6±5.1	N.S.
Height (cm)	148.0±5.3	148.0±6.0	N.S.
Weight (kg)	52.6±8.0	49.4±7.2	N.S.
BMI (kg/m^2)	24.0±3.2	22.6±2.9	N.S.
Cumulative dose of prednisolone (g)	0.08±0.18	21.5±24.0	p<0.01

Values are presented as the mean±SD.
GC: glucocorticoids; BMI: body mass index; BMD: bone mineral density; N.S.: not significant
a: patients without systemic GC therapy who received less than a 0.5g cumulative dose of prednisolone
b: patients with sytemic GC therapy who received more than a 10g cumulative dose of predonisolone

Table 3. Characteristics of Patient under 65 years without Systemic Glucocorticoid Use Divided by Gender.

	Male (n=5)	Female (n=14)
Age (years)	50.1±13.2	56.7±6.1
Height (cm)	164.1±9.1	154.4±7.6
Weight (kg)	63.9±13.3	58.0±11.1
BMI (kg/m^2)	23.6±4.0	24.3±4.1
Cumulative dose of prednisolone (g)	0.03±0.07	0.01±0.03

Values are presented as the mean±SD.
GC: glucocorticoids; BMI: body mass index; BMD: bone mineral density

Patients who had taken medication that affects bone metabolism or patients with medical conditions that affect bone metabolism were excluded from the study. No patient had undergone treatment for osteoporosis, such as hormone replacement therapy. No patient had alcohol dependency, and no patient was a smoker. A history was taken, and a physical examination was performed on all patients. Duration, daily dose, and lifetime cumulative dose of GC were calculated from medical records and a patient's personal records. The dose of GC is expressed in equivalent grams of prednisolone.

METHODS

pQCT was performed on the non-dominant radius using a Stratec XCT 960 (Nishimoto, Tokyo, Japan), as described previously[6, 24]. Briefly, the mid-radial 20% site was used to calculate cortical BMD. Constant threshold levels were used for all subjects (0.5mg/cm^3 for total bone and 0.93mg/cm^3 for cortical bone).

Total and cortical area were estimated based on voxel number at the mid-radial 20% site region, and relative cortical volume, defined as cortical volume divided by the total bone volume, was calculated by dividing cortical area with total area, as described previously[13, 22, 25].

Statistical analysis

Student's t test and other statistical analyses were performed using the software package, StatView (Abacus Concepts, Berkeley, CA, USA). A p value < 0.05 was considered to be significant.

Results

A significant correlation between relative cortical volume and cortical BMD showing a rectilinear relationship was observed in the aged (≧65years) male GC(−) group ($p< 0.05$, $r^2=0.373$) (Figure 1), the aged (≧65 years) male GC(+) group ($p<0.0001$, $r^2=0.919$) (Figure 2), the aged (≧65years) female GC(−) group ($p<0.0001$, $r^2=0.770$) (Figure 3), the aged (≧65years) male GC (+) group ($p<0.0001$, $r^2=0.767$) (Figure 4), the not aged (<65years) male GC(−) group ($p<0.0001$, $r^2=0.994$) (Figure 5), and the not aged (<65years) female GC(−) group ($p<0.0001$, $r^2=0.808$) (Figure 6).

No significant differences in the cortical volume-density slopes were observed among all groups of patients.

Discussion

Aging is reportedly associated with a reduction in cortical volume due to a widening of the marrow cavity as well as a reduction in cortical density[8, 13, 15, 16]. Using pQCT, Fujii et al. previously reported that the radius cortical volume and density are rectilinearly

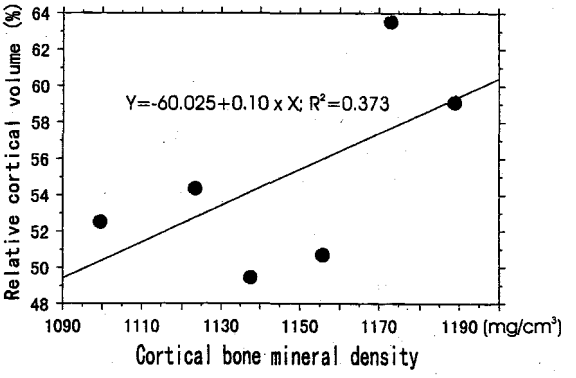

Fig. 1. Relationship between cortical density and relative cortical volume in 6 aged (≧65years) male asthmatic patients without systemic glucocorticoid therapy. A correlation ($p<0.05$) of $r^2=0.373$ was obtained.

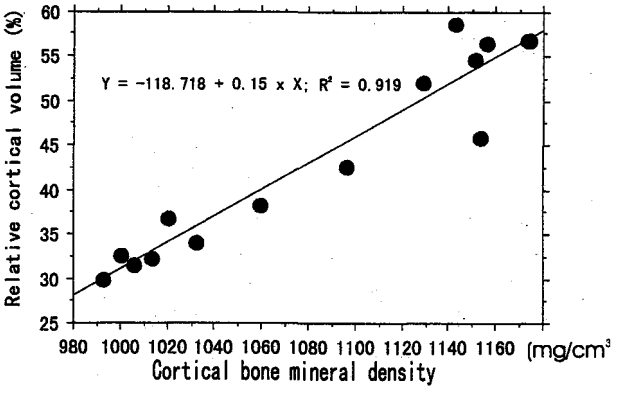

Fig. 2. Relationship between cortical density and relative cortical volume in 15 aged (≧65years) male asthmatic patients with systemic glucocorticoid therapy who received more than a 10g cumulative dose of predonisolone. A highly significant correlation ($p< 0.001$) of $r^2=0.919$ was obtained.

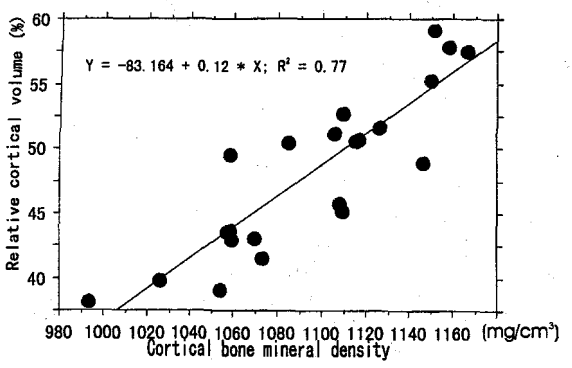

Fig. 3. Relationship between cortical density and relative cortical volume in 22 aged (≧65years) female asthmatic patients without systemic glucocorticoid therapy. A highly significant correlation ($p<0.001$) of $r^2 = 0.770$ was obtained.

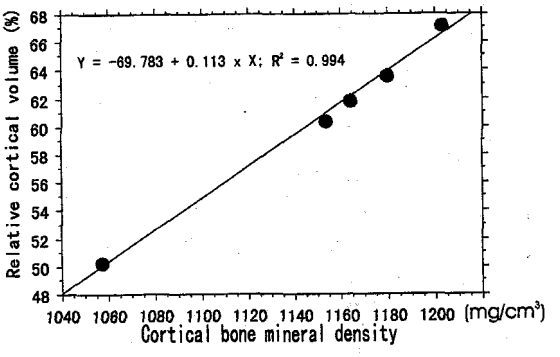

Fig. 5. Relationship between cortical density and relative cortical volume in 5 not aged (<65years) male asthmatic patients without systemic glucocorticoid therapy. A highly significant correlation ($p<0.001$) of $r^2 = 0.994$ was obtained.

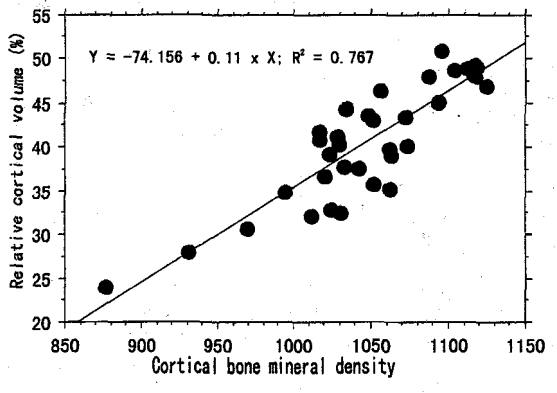

Fig. 4. Relationship between cortical density and relative cortical volume in 37 aged (≧65years) female asthmatic patients with systemic glucocorticoid therapy who received more than a 10g cumulative dose of predonisolone. A highly significant correlation ($p<0.001$) of $r^2 = 0.767$ was obtained.

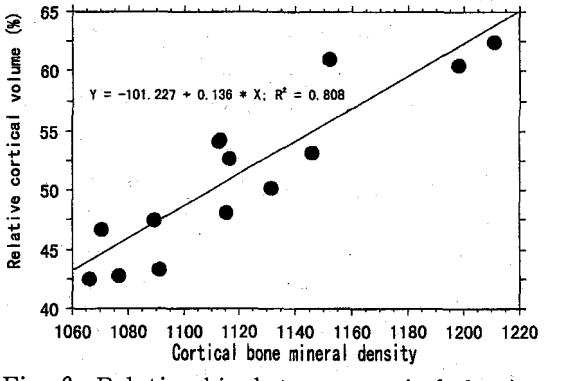

Fig. 6. Relationship between cortical density and relative cortical volume in 14 not aged (<65years) female asthmatic patients without systemic glucocorticoid therapy. A highly significant correlation ($p<0.001$) of $r^2 = 0.808$ was obtained.

correlated in the aging processes of healthy adult humans[13]. Similar findings have also been reported in secondary hyperparathyoidism in uremic patients on maintenance hemodialysis[17]. In the previous paper, we have also demonstrated that the radius cortical bone volume and density are rectilinearly correlated in postmenopasal asthmatic patients, regardless of the level of systemic GC therapy, and the two cortical volume-density slopes in patients with or without continuous systemic GC therapy appear largely identical[22].

In the present study, we confirmed these cortical volume-density relationships in postmenopausal patients regardless of the level of systemic GC therapy, and indicated similar relationships in male patients irrespective of the level of systemic GC therapy. These slopes were roughly identical to the slopes for not aged patients without systemic GC therapy in this study. These slopes were also roughly identical to the slopes for healthy adult humans in the previous report[13]. In view of the highly significant correlation between relative cortical volume and density in the radial cortex, a single process of GC-induced cortical bone resorption, or so-called cortical porosity, appears to be responsible at both the endosteal and intracortical sites for causing similar and simultaneous decreases in cortical bone volume and density despite the gonadal hormonal differences, as in the aging processes[13], or in secondary hyperparathyoidism in uremic patients on maintenance hemodialysis[17].

In conclusion, glucocorticoid administration appears to be responsible for the process of cortical bone porosity at both endosteal and intracortical sites despite the gonadal hormonal differences.

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気管支喘息症例における皮質骨海綿化

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【目的】これまでに我々は, 気管支喘息症例において経口ステロイドによる皮質骨骨密度, 容積の減少が骨折に関与する新知見を報告し, 閉経後女性では皮質骨骨密度-容積の減少はステロイド投与量にかかわらず一定であることを報告してきた。この皮質骨骨密度-容積の関係において性差による違いを検討するために, 男性, 女性患者の両方について検討を行った。【方法】対象はステロイド依存性喘息99例（男性26例, 女性73例)。性別, 年齢, 経口ステロイド積算総投与量により6群に分類した。椎体圧迫骨折はX線側面像にて評価し, 皮質骨容積比および皮質骨骨密度はpQCT (Stratec XCT960)を用いて測定した。それぞれの群の皮質骨骨密度-容積比の関係を算出し比較検定をおこなった。【結果】それぞれの群の皮質骨の骨密度と容積比は有意に相関した。それぞれの群の皮質骨骨密度-容積比の傾きは, いずれも有意差を認めなかった。【結論】気管支喘息症例におけるステロイド投与による皮質骨の骨密度と容積の減少は, 性別にかかわらずほぼ一定で, 皮質骨は内側と外側において同様に海綿化してゆくと考えられた。