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The skeletal muscle cross sectional area in long-term bisphosphonate users is smaller than that of bone mineral density-matched controls with increased serum pentosidine concentrations

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ABSTRACT

Bisphosphonates are effective in increasing bone mineral density (BMD), but fragility fractures can still occur despite bisphosphonate treatment. The purpose of this study was to determine if long-term bisphosphonate users have characteristic findings in the musculoskeletal system, which could put them at risk of developing typical or atypical femoral fractures. We recruited 40 female patients who had taken bisphosphonates for more than 3 years. The control group included 60 volunteers who were matched by age, body mass index, and dual-energy X-ray absorptiometry-derived BMDs. We measured the skeletal muscle cross sectional area around the proximal thigh and buckling ratio of the femoral neck using quantitative computed tomography (qCT) and several biochemical markers of bone metabolism. Those parameters were compared between the groups. While no significant differences of buckling ratio derived from qCT were detected, the skeletal muscle cross sectional area was significantly smaller in the long-term bisphosphonate users than in the controls. Furthermore, the serum pentosidine level was significantly higher in the bisphosphonate users than in the controls. To determine if those differences were attributable to bisphosphonate treatment, we further compared those parameters between before and after 3 years of bisphosphonate treatment in 32 patients. After 3 years of bisphosphonate treatment, the BMD of the femoral neck and serum pentosidine level increased but not the skeletal muscle cross sectional area. In the present study, the skeletal muscle mass did not match the bone mass in long-term bisphosphonate users, thus suggesting that increases in BMD by bisphosphonates are unlikely to have secondary positive effects on the surrounding skeletal muscles. Also, serum pentosidine levels were greater in the long-term bisphosphonate users. Further study is necessary to test if such patients are prone to develop typical or atypical femoral fractures.

Introduction

Bisphosphonate (BP) is the most widely used drug for the treatment of osteoporosis. It has been known to reduce the rate of fragility fractures by approximately 50–90% [1]. Despite the increase in bone mineral density (BMD) after long-term BP treatment, typical fragility fractures or rarely, atypical femoral fractures (AFFs) can occur [2]. Although the pathophysiology of the development of AFFs is not well known, their characteristics are consistent with stress or insufficiency fractures and are accompanied by possible accumulation of advanced glycation end products [3–5]. The purpose of this study was to determine if long-term BP users have characteristic findings in the musculoskeletal system, which put them at risk for developing typical or AFFs.

Materials & methods

Study 1: Cross sectional comparison between the BP users and controls

We prospectively enrolled 40 postmenopausal women with idiopathic osteoporosis who were treated with oral BPs for more than 3 years (BP group). The average age of the participants was 74.9 years (range, 46–93 years). The bisphosphonates administered to the patients were alendronate, risedronate, or minodronate. The duration of bisphosphonate treatment ranged from 3 to 8 years with an average of 3.7 years. Total spinal plain radiographs were taken to confirm any

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morphological compression fractures. Previous fragility fractures were noted in a total of 16 patients, and of these, 10 had distal radius fractures, 2 had vertebral fractures, and 4 had both. Patients who received systemic glucocorticoids and those who had at least grade 3 chronic kidney disease, hyperparathyroidism, abnormalities of serum calcium and phosphorus, or diabetes were excluded.

The control group included 60 volunteers with an average age of 73.5 years (range, 54–93 years) who were matched by age, body mass index, and dual-energy X-ray absorptiometry (DXA)-derived BMDs of the left hip and lumbar spine (Table 1). All the volunteers had neither a history of fragility fracture nor intake of medication for systemic disease.

a. Physical measurements

Height and weight of all subjects were measured. Grip strength was measured 3 times in both hands using a Jamar® hydraulic hand dynamometer (Sammons Preston, Bolingbrook, IL, USA), and the average value of the stronger side was used.

b. DXA

DXA (PRODIGY; GE Medical Systems, Madison, WI, USA) was used to obtain the BMD of the left proximal femur (femoral neck) and lumbar spine (L2–L4). Using the manufacturer's internal standard, daily instrument calibration was performed before use. Coefficient variations (CV) for the lumbar spine and femoral neck were 0.7% and 1.1%, respectively.

c. Quantitative computed tomography (qCT) bone analysis

Acquired from the superior aspect of the acetabulum of the pelvis until approximately 5 cm distal to the lesser trochanter of the femur, spiral CT scans (LightSpeed VCT 64 Slice CT; GE Medical Systems, Waukesha, WI, USA) had a slice thickness of 2.5 mm. The qCT calibration phantom (Mindways Software Inc., Austin, TX, USA) was placed beneath the pelvis on the table. During the data acquisition period, quality assurance scans were performed monthly to verify the operational integrity of the qCT system. qCT data were then transferred to the QCT PRO PC (Mindways Software Inc., Austin, TX, USA), and all analyses were performed automatically using QCT PRO Bone Investigational Toolkit (BIT) software. The cortical bone segmentation threshold was subsequently set at 350 mg/cm^3 for all the subjects. Geometric parameters of the left hip were derived automatically using QCT PRO BIT software to obtain measurements of the cortical thickness of the femoral neck. For analysis of cross-sections of the femoral neck, 11 slices covering a 10-mm length of the femoral neck were obtained, and the middle 5 slices, which should include the minimum cross sectional area (CSA) of the femoral neck, were used for data analysis. The calculated biomechanical index was the cortical buckling ratio (CV = 7.6%).

d. qCT analysis of soft tissue

Using previously obtained CT data for proximal femoral geometric analysis, three 2.5-mm slices 2 cm distal to the inferior aspect of the lesser trochanter were selected. Tissue Composition Module software (Mindways Software, Inc., Austin, TX, USA) was used to perform cross-sectional analysis of the soft tissue in these slices. Initial segmentation was performed to fragment the phantom from the image and to apply a set of default tissue composition thresholds to the image. The left thigh image was subsequently isolated using a freehand tool. A semi-automated skin removal algorithm was used repeatedly until the epidermal layer was removed. To provide iterative refinement of the initial segmentation thresholds derived by the software, advanced segmentation was then performed. In this step, the default tissue segmentation thresholds were optimized using a Gaussian Mixture Model. An optional contour was defined around the selected group of thigh muscles. The location of the contour was constrained by a spline while a "snake" operation fit the contour precisely to the muscle group. This isolated muscle group consisted of fat, bone, and lean tissue (Fig. 1). Subcutaneous fat was excluded from the analysis. The average of the CSA of each structure in the 3 slices was used for data analysis. The skeletal muscles analyzed in these CSAs were the quadriceps femoris, sartorius, gluteus maximus, tensor fasciae latae, and adductors. CVs for the CSA of the skeletal muscle and fat were 1.7% and 11.3%, respectively.

Calibration data were utilized to derive a BMD estimate using standard methods as well as to estimate the expected pixel value for fat and skeletal muscle tissue using atomic compositions. Fat and skeletal muscle density was assumed to be 0.923 g/cm^3 and 1.055 g/cm^3, respectively. The details of the procedure were described elsewhere [6].

e. Biochemical markers associated with bone metabolism

The following parameters were measured for blood and urinary tests: bone-specific alkaline phosphatase (BAP) in μg/L by chemiluminescent enzyme immunoassay (CV = 6.8%), tartrate-resistant acid phosphatase 5b (TRACP-5b) in mU/dL by enzyme immunoassay (CV = 3.4%), serum homocysteine in nmol/mL by high performance liquid chromatography (CV = 8.9%), serum pentosidine in μg/mL by enzyme-linked immunosorbent assay (ELISA) (CV = 6.4%), urinary pentosidine in μg/mg creatinine by ELISA (CV = 14.5%), and 25(OH)D in ng/mL by radio-immuno assay (CV = 10.6%). All the measurements were performed by SRL Inc., Tokyo, Japan.

Table 1
Characteristics of the patients and volunteers.

	BP	Control	*p*-Value
N	40	60	
Age, years, mean (SD)	74.9 (9.6)	73.5 (7.8)	0.443
BMI, kg/m^2, mean (SD)	20.1 (2.7)	21.0 (2.4)	0.083
DXA-derived BMD, g/cm^2, mean (SD)			
Lumbar spine	0.909 (0.191)	0.897 (0.152)	0.740
Femoral neck	0.618 (0.103)	0.625 (0.092)	0.709
Previous fragility fracture	Distal radius 10 Vertebral 2 Both 4	None	

BMD, bone mineral density; BMI, body mass index; BP, bisphosphonate; DXA, dual-energy X-ray absorptiometry.

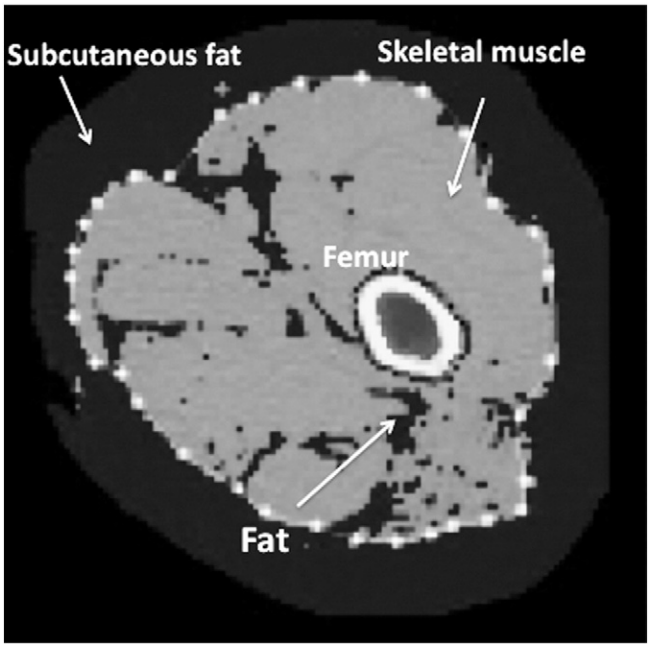

Fig. 1. Cross section of the left proximal thigh for analysis of the cross sectional area of skeletal muscle and fat. A spline is used to constrain the location of the contour, and a 'snake' operation is performed to fit the contour precisely to the muscle group. This isolated muscle group consists of fat, bone, and lean tissue. Subcutaneous fat was not included in the analysis.