ELSEVIER

Bone 36 (2005) 13–21

BONE

www.elsevier.com/locate/bone

Biochemical markers of bone formation reflect endosteal bone loss in elderly men—MINOS study

P. Szulc[a], P. Garnero[b], F. Marchand[c], F. Duboeuf[a], P.D. Delmas[a,*]

[a]*INSERM 403 Research Unit, Hôpital Edouard Herriot, Claude Bernard University, Lyon, France*
[b]*SYNARC, Lyon, France*
[c]*SSMB, Montceau les Mines, France*

Received 10 May 2004; revised 9 August 2004; accepted 10 September 2004
Available online 24 November 2004

Abstract

In the skeleton of elderly men, two opposite activities occur: bone loss at the endosteal envelope, which increases bone fragility, and periosteal apposition, which improves bending strength of bone. Both may contribute to serum bone formation markers although they have an opposite effect on bone fragility. The aim of this study was to determine if circulating bone formation markers reflect periosteal bone formation and endosteal bone remodelling in 640 men aged 55–85 years belonging to the MINOS cohort. We measured biochemical markers of bone formation (osteocalcin, bone alkaline phosphatase, N-terminal extension propeptide of type I collagen) and bone resorption (urinary and serum β-isomerised C-terminal telopeptide of collagen type I, total and free deoxypyridinoline). Parameters of bone size (cross-sectional surface of third lumbar vertebral body measured by X-ray, projected areas of total hip, femoral neck, radius and ulna measured by dual-energy X-ray absorptiometry) increased with age ($r = 0.20$–0.32, $P < 0.0001$). In contrast, parameters related to bone loss (areal bone mineral density [aBMD], volumetric bone mineral density [vBMD] and cortical thickness) and determined mainly by bone resorption, decreased with ageing ($r = -0.14$ to -0.23, $P < 0.005$–0.0001). Men in the highest quartile of bone resorption markers had lower aBMD (3.8–10.2%, $P < 0.05$–0.0001), lower vBMD (3.9–13.0%, $P < 0.05$–0.0001), and lower cortical thickness (1.5–9.6%, $P < 0.05$–0.0001) than men in the lowest quartile. Markers of bone resorption were not significantly associated with estimates of bone size at any skeletal site. Markers of bone formation were not associated with estimates of periosteal formation after adjustment for covariates. In contrast, men in the highest quartile of the bone formation markers had significantly lower aBMD (4.0–11.7%, $P < 0.05$–0.0001), lower vBMD (4.2–16.3, $P < 0.05$–0.0001) and lower cortical thickness (4.0–7.4%, $P < 0.05$–0.0001) than men in the lowest quartile.

In summary, serum levels of bone formation markers are negatively correlated with the estimates of endosteal bone loss. In contrast, they disclose no association with parameters reflecting periosteal apposition. Thus, in elderly men, bone formation markers reflect endosteal bone remodelling, probably because of the coupling between resorption and formation activities. In contrast, they do not reflect the periosteal bone formation, probably because the periosteal surface is smaller and has a slower remodelling rate than the endosteal surface.

Keywords: Bone formation; Endosteal bone loss; Elderly men

Introduction

In men, ageing of the skeleton is associated with two opposite cellular activities: periosteal apposition that tends to increase bone size and strength on one hand, and endosteal bone loss due to trabecular thinning, endosteal resorption and increase of cortical porosity that decrease bone strength on the other hand [1–4]. In men, bone resorption markers increase with age whereas bone formation markers levels remain stable or increase only slightly [5–7], suggesting that bone loss is due to increased bone resorption, which is not matched by a commensurate increased bone formation. This imbalance between bone resorption and bone formation as the mechanism of bone loss in elderly men is also supported by histological

* Corresponding author. INSERM 403 Research Unit, Hôpital Edouard Herriot, Claude Bernard University, 5 Place d' Arsonval, 69437 Lyon, France. Fax: +33 472 11 74 83.
E-mail address: delmas@lyon.inserm.fr (P.D. Delmas).

8756-3282/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.bone.2004.09.004

evidence of trabecular thinning and wall width decrease with ageing [8,9] as well as by the negative correlation between the levels of biochemical markers of bone remodelling and areal bone mineral density (aBMD) in elderly men [5,7,10].

Bone resorption is assessed by the serum level and urinary excretion of markers that originate from the catabolism of type I collagen, mainly derived from bone matrix [11]. In contrast, circulating bone formation markers can reflect two opposite activities. They are secreted by active osteoblasts on the endosteal surfaces, i.e., trabecular, endocortical and intracortical. Because of the coupling between resorption and formation, their increased concentrations reflect the acceleration of the endosteal bone remodelling, which, in elderly men, results in a decrease of trabecular bone density, cortical thinning and increased porosity leading to bone fragility. However, periosteal cells express also bone formation markers, i.e., osteocalcin, alkaline phosphatase and collagen type I [12,13]. Thus, the serum levels of these proteins might also reflect periosteal activity leading to increased bone size and improved bone strength [14]. The contribution of periosteal bone-forming cells to the circulating levels of bone formation markers may be limited because the endosteal surfaces are much larger and probably more active than the periosteal surface of ageing men. However, this dual source of bone formation markers could hamper the appropriate interpretation of their levels and create certain problems in their clinical use in men.

The aim of this study was to verify if serum bone formation markers reflect bone remodelling of the periosteal or of the endosteal envelope in elderly men belonging to the MINOS cohort. The analysis was limited to the men aged 55 and over because, in this age range, investigated variables disclosed homogenous age-related trends: decrease in aBMD, stable levels of bone formation markers, increase of the urinary excretion of deoxypyridinoline [7,15]. Other significant determinants of bone size such as body height, muscle mass, body weight and physical professional activity were also taken into account in the statistical analyses.

Subjects and methods

Description of the cohort

The MINOS study is a prospective study of osteoporosis and its determinants in men that was initiated in 1995 [15]. It is a collaboration between INSERM (National Institute of Health and Medical Research) and Société de Secours Minière de Bourgogne (SSMB) in Montceau les Mines. Montceau les Mines is a town situated 130 northwest of Lyon in the Department (District) of Saône et Loire. Its population is 21,000 inhabitants including 7150 men aged more than 19 years. SSMB is one of the largest health insurance companies in this district. We recruited 1040 men aged 19–85 years. All men responded to an epidemiological questionnaire covering demographic and behavioral information as well as detailed medical history (diseases, accidents, medications) of conditions that could influence bone mass and metabolism. A total of 106 men were excluded because of disease or treatment known to affect bone metabolism (Paget's disease, rheumatoid arthritis, primary hyperparathyroidism, Cushing's disease, haemochromatosis, cirrhosis, Klinefelter's syndrome, treatment with fluoride, bisphosphonate, thyroxin, oral corticosteroids) leaving 934 men. This study was performed in 640 men aged 55–85 years, because, in this age range, variables of interest disclosed homogenous age-related trends. In contrast, 294 men aged from 19 to 54 were not included in this analysis.

The intensity of the current and past professional physical activity was evaluated globally using a self-reported score based on the type of the daily activity as described previously [15]. Four levels of professional physical activity were included in the score: low (sitting position, little walking, no load carrying or lifting; e.g., clerk), medium (mainly standing position, extensive walking, lifting heavy objects rarely; e.g., physician, engineer, laboratory staff), high (walking upstairs and downstairs frequently, lifting heavy objects regularly; e.g., craftsman, electrician), very high (extensive lifting of heavy objects, exerting works necessitating permanent physical effort; e.g.; coal miner). Current leisure physical activity was evaluated by standardised questionnaire. Weekly individual activity was calculated on the basis of the overall amount of time spent on walking, gardening and leisure sport activity. An annual average assessment of seasonal activities (gardening, certain kinds of exercise) was also made. The leisure physical activity was expressed as hours per week regardless of the type of activity.

Bone mass measurement and estimates of structural geometry

Bone mineral content (BMC) and areal bone mineral density (aBMD) was measured at the right hip and at the third lumbar vertebra (L3) in the antero-posterior position using pencil-beam dual-energy X-ray absorptiometry (DEXA, QDR-1500, Hologic Inc., Waltham, MA) and at the distal nondominant forearm using single energy X-ray absorptiometry (Osteometer® DTX 100, Denmark) [15]. The OsteoDyne Hip Positioner System (HPS) [16] was used to minimize hip positioning error. The rectangle of femoral neck was positioned manually perpendicularly to the axe of femoral neck in order to cover its narrowest part. When necessary, the edges of femoral neck were adjusted manually. The lower limit of the total hip projected area was positioned manually 10 lines below small trochanter.

The Hologic QDR 1500 device was calibrated daily using a lumbar spine phantom yielding a coefficient of variation for aBMD of 0.33%. Twice a month, the Hologic hip phantom was measured yielding a long-term coefficient