Calcitropic Hormones and Markers of Bone Remodeling in Age-Related (Type II) Femoral Neck Osteoporosis: Alterations Consistent with Secondary Hyperparathyroidism-Induced Bone Resorption

Steven Boonen,1,2,3 Paul Broos,4 Geert Verbeke,3 Jeroen Aerssens,2 Eric Van Herck,2 Ivo Jans,2 Jan Dequeker,3 and Roger Bouillon2

1Department of Internal Medicine, Division of Geriatric Medicine, Laboratory for Experimental Medicine and Endocrinology, 2Arthritis and Metabolic Bone Disease Research Unit, 3Department of Traumatology and Emergency Surgery, and 4Department of Epidemiology, Biostatistical Centre, Katholieke Universiteit Leuven, Leuven, Belgium.

Background. Both a decrease in bone formation and the skeletal consequences of secondary hyperparathyroidism have been implied in the pathogenesis of age-related femoral neck osteoporosis. However, studies using biochemical indices of bone remodeling in hip fracture patients have yielded conflicting results. Similarly, secondary hyperparathyroidism has not been a consistent finding in this population. Some of these inconsistencies might reflect differences in the assays used as well as in the timing of the sampling. Moreover, measurements were mostly performed in a limited number of patients. In this regard, the aim of the present study was to analyze potential alterations in bone metabolism in a large population of elderly hip fracture patients.

Methods. Circulating concentrations of 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)2D3], intact parathyroid hormone (PTH), and calcitonin were measured in 117 elderly women (within a few hours after sustaining a fracture of the proximal femur) and in 117 healthy age-matched controls. In addition, serum osteocalcin and urinary excretion of (deoxy)pyridinoline were determined as markers of bone formation and resorption, respectively.

Results. Serum levels of 25(OH)D and 1,25(OH)2D3 were decreased in hip fracture patients. When correcting for differences in serum vitamin D binding protein, serum 25(OH)D was still significantly lower in patients than in controls, whereas serum 1,25(OH)2D3 was not. Moreover, 25(OH)D deficiency in hip fracture patients was associated with an increase in circulating PTH and urinary excretion of (deoxy)pyridinoline. Serum osteocalcin, on the other hand, was significantly decreased in fracture patients. There was no statistically significant difference in calcitonin.

Conclusion. These data suggest that there is reduced bone formation and increased bone resorption in patients with hip fracture. Although limited by its cross-sectional design, the present study emphasizes the role of secondary hyperparathyroidism-induced bone resorption in the pathogenesis of age-related osteoporosis, mainly due to a lack of 25(OH)D.

OSTEOPOROSIS is a systemic skeletal disease associated with low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (1). Bone loss implies an uncoupling of the phases of bone remodeling, with a relative or absolute increase in resorption over formation (2). Type I (postmenopausal) osteoporosis is characterized by a disproportionate postmenopausal trabecular bone loss in a subset of women and complicated by vertebral compression fractures. Type II (age-related) osteoporosis, on the other hand, is associated with a proportionate age-related loss of both cortical and trabecular bone, in men as well as in women, ultimately leading to hip fractures (3). Estrogen deficiency-induced bone resorption has been identified as the major determinant of bone loss in type I osteoporosis. In contrast, two other principal abnormalities in bone metabolism have been implied in the pathogenesis of bone loss in type II osteoporosis: impaired bone formation and the skeletal consequences of secondary hyperparathyroidism (3–6). First, at the level of individual remodeling foci, aging is associated with a decline in osteoblast function (4). Second, an age-related increase in parathyroid function may occur secondary to an age-related decrease in vitamin D status (5). As there is already a net loss of bone with each remodeling cycle in the elderly, and as the parathyroid hormone (PTH) induces bone resorption and increases the birth of new remodeling units, the effect of secondary hyperparathyroidism will be to amplify this uncoupling and to increase the amount of bone lost per unit time.

Bone histomorphometry of hip fracture patients has indeed provided evidence for a decrease in bone formation despite increased bone resorption (7). However, secondary hyperparathyroidism has not been a consistent finding in age-related osteoporosis (8–13). Similarly, studies using biochemical indices of bone remodeling in hip fracture patients have yielded conflicting results (10,12,14–20). As discussed below, some of these inconsistencies might
reflect differences in the assays used as well as in the timing of the sampling. In addition, measurements were mostly performed in a limited number of patients. In the present study, systemic hormones affecting bone metabolism and markers of bone remodeling were measured in 117 women after sustaining a hip fracture and compared to the values in 117 elderly nonfractured controls. Among the bone and mineral-regulating endocrine factors, intact PTH, calcitonin, and 1,25-dihydroxyvitamin D [1,25(OH)\(_2\)D] were measured. In view of the high prevalence of protein depletion in elderly hip fracture patients, serum concentrations of 1,25(OH)\(_2\)D, and its precursor 25-hydroxyvitamin D [25(OH)D] were adjusted for vitamin D binding protein (DBP). Formation and resorption of bone were assessed by serum osteocalcin and urinary (deoxy)pyridinoline, respectively. Serum osteocalcin, an osteoblast-specific protein (21), is the most abundant noncollagenous protein found in bone tissue, and circulating levels have been shown to reflect overall osteoblastic activity (22). Pyridinoline and deoxypyridinoline cross-links, on the other hand, are involved in connecting the collagen chains within the bone matrix. Urinary excretion of pyridinium cross-links has been identified as a specific marker of collagen degradation due to bone resorption (23). To minimize the potentially confounding effects of the trauma and the subsequent treatment, samples from hip fracture patients were obtained within 18 h after fracture, prior to surgery.

**Methods**

**Study design.** — The investigation was a cross-sectional study conducted in 117 Caucasian patients with hip fracture (mean age 79.2 years, range 60–95) and 117 Caucasian elderly controls (mean age 77.7 years, range 70–90). Both fracture cases and control subjects were sampled throughout the same period. Informed consent was obtained from all patients and controls, and all procedures were approved by the institutional ethical committee.

**Subject selection.** — Women admitted to the Department of Traumatology following a fracture of the proximal femur were recruited consecutively. To be eligible for participation, women had to be over 60 years of age, to be previously ambulatory, and to have suffered a fall resulting in a radiologically confirmed first hip fracture. Cervical and trochanteric fractures were defined from the surgical report. All patients were studied before surgery and within 18 h after fracture. Patients were excluded if they met any of the following criteria: (a) having been admitted with a pathologic fracture or fracture resulting from trauma other than a fall; (b) having sustained a previous hip fracture; (c) non-osteoporotic metabolic bone disease; (d) thyroid disease, whether controlled or uncontrolled; (e) calcium, fluoride, or vitamin D supplements; or (f) ever having used thiazides, glucocorticoids, estrogen, anabolic steroids, or calcitonins for more than 3 months. Details of the recruitment of the subjects have been described previously (24).

**Anthropometric measurements.** — Anthropometric measurements were made of height and body weight. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m\(^2\)).

**Biochemical measurements.** — Fasting blood and urine samples were collected in the morning from all subjects. In the osteoporotic patients, samples were obtained before surgical treatment and within 18 h after fracture. Total serum calcium, inorganic phosphate, albumin, and creatinine were determined by standard analytic methods. Creatinine clearance was estimated according to Cockcroft and Gault, relying on serum creatinine, weight, and age (25). Calcidiol (25-hydroxyvitamin D [25(OH)D]) was measured by competitive binding assay, calcitriol (1,25-dihydroxyvitamin D [1,25(OH)\(_2\)D]) by radioimmunoassay, and vitamin D binding protein (DBP) by single radial immunodiffusion. Prior to determination of 1,25(OH)\(_2\)D, serum samples were extracted in ethylacetate/cyclohexane and 1,25(OH)\(_2\)D isolated from the extract by means of Sephadex LH-20 and high-pressure chromatographic separation. While the competitive protein-binding assay for 25(OH)D did not discriminate between 25(OH)\(_2\)D and 25(OH)D\(_3\), the radioimmunoassay of 1,25(OH)\(_2\)D\(_2\) had only a low cross-reaction with 1,25(OH)\(_2\)D\(_3\). Details of methodology and validation have been previously reported from our laboratory (26–29). Both the free 25(OH)D index [based on the molar ratio of 25(OH)D to DBP] and the free 1,25(OH)\(_2\)D index [based on the molar ratio of 1,25(OH)\(_2\)D\(_2\) to DBP] were calculated. These molar ratios have been documented to be adequate estimations of the true free concentrations (30). Serum intact PTH was measured by a two-step immunochromatographic method involving an amino-terminal capture and a midregional detecting antibody, as described previously (31). Measurement of calcitonin was performed using a commercial radioimmunoassay system (Nichols Institute, San Juan Capistrano, CA), measuring native calcitonin[1-32]) (32). Human osteocalcin was determined by a previously reported radioimmunoassay as well (33). Pyridinium cross-links [pyridinoline and (deoxy)pyridinoline], corrected for creatinine, were measured on hydrolyzed urine extract by fluorescent detection after high-pressure liquid chromatography as previously described (34).
trochanteric area. Areal bone mineral density (BMD) was measured using the Lunar DPX-L scanner (Lunar Radiation, Madison, WI). Standard positioning was used with anterior–posterior scanning of the right proximal femur except in the event of hip replacement when the left femur was scanned. The precision of femoral BMD measurements in elderly women using our DXA equipment is 3.1% at the neck and 2.6% at the trochanter (24). According to World Health Organization (WHO) criteria (35), osteoporosis was defined as a BMD value more than 2.5 SD below the young adult average value.

Statistical analysis. — The relation between the biochemical variables was assessed by calculating Pearson’s product moment r, based on logarithmic transformation of creatinine clearance, 25(OH)D, PTH(1–84), osteocalcin, and (deoxy)pyridinoline. In view of the fact that no normalizing transformation was found for the parameters time (the interval elapsed after fracture) and age, Spearman rank correlation (p) was used to assess the effect of these parameters on the biochemical variables. Differences in clinical and biochemical data between patients and controls were evaluated with Student’s t-test. When comparing serum vitamin D metabolite levels in patients and controls, a correction for differences in DBP was made by adjusting differences in serum 25(OH)D and 1,25(OH)2D for differences in DBP as well as by calculating the free 25(OH)D index and the free 1,25(OH)D index. All statistical analyses were conducted with the use of SAS software (Statistical Analysis Systems, Cary, NC). All reported p-values are two-sided. The nominal significance level was set at .05.

RESULTS

Relationship between biochemical parameters of bone metabolism. — Both in elderly controls and fracture cases, age inversely correlated with calculated creatinine clearance \( r = - .33, p < .001 \) and \( r = - .48, p < .001 \), respectively. Circulating 25(OH)D \( r = - .20, p = .04 \) and \( r = - .24, p = .01 \), respectively) decreased as a function of age as well, whereas circulating levels of PTH \( r = .37, p < .001 \) and \( r = .18, p = .05 \), respectively) and osteocalcin \( r = .25, p = .006 \) and \( r = .24, p = .008 \) increased. Serum osteocalcin was related negatively to the calculated creatinine clearance \( r = -.20, p = .05 \) and \( r = -.29, p = .007 \), respectively) and positively to (deoxy)pyridinoline \( r = -.28–.37, p < .001 \) and \( r = -.21–.29, p = .03–.003 \), respectively). As expected, negative correlations were found between 25(OH)D and PTH, both in controls and patients \( r = -.23, p = .01 \) and \( r = -.18, p = .05 \), respectively. In the hip fracture group, 25(OH)D was inversely related to pyridinoline \( r = -.27, p = .006 \) and (deoxy)pyridinoline \( r = -.35, p < .001 \). In contrast, no statistically significant relationships were observed between 25(OH)D and urinary (deoxy)pyridinoline in the control group.

Effect of time elapsed since fracture. — According to the cross-sectional distribution of single values from all the patients, there was no significant correlation between the time elapsed after fracture and serum albumin \( r = .11, p = .28 \) or DBP \( r = .06, p = .47 \). Similarly, serum osteocalcin \( r = .09, p = .34 \) and urinary pyridinium cross-links \( r = .12, p = .22 \) and \( r = .14, p = .18 \), respectively did not correlate with the time elapsed between sustaining the fracture and the sampling.

Differences in clinical, biochemical, and densitometric parameters between patients and controls. — Clinical, biochemical, and densitometric data from the elderly controls and the hip fracture patients are indicated in Table 1. No significant differences were observed for mean age and weight between patients and controls. Osteoporotic patients, however, were taller and had a lower body mass index. Serum albumin was significantly lower in hip-fractured women as well. Phosphate levels, serum creatinine, and calculated creatinine clearance were not statistically different, whereas total calcium was lower in fracture patients. However, the decrease in serum calcium did not persist after adjustment for serum albumin (data not shown), indicating that the difference was due to the concomitant hypoalbuminaemia. Serum concentrations of the vitamin D metabolites [both 25(OH)D and 1,25(OH)2D] were lower in patients than in the control subjects. However, when correcting for differences in DBP, the difference in serum 1,25(OH)2D, was not significant anymore (data not shown). Similarly, the difference in the free 1,25(OH)2D index between patients and controls was not significant. Intact PTH concentrations were significantly greater in the fracture group than in the control group (Figure 2). Calcitonin levels, on the other hand, were not different in patients and controls. There was a decrease of osteocalcin in hip fracture patients compared with elderly controls, while the resorption markers pyridinoline and urinary (deoxy)pyridinoline correlate more strongly with clinical outcome variables in hip fracture patients than in elderly controls. As expected, osteocalcin was also significantly related to serum creatinine clearance in patients \( r = -.34, p < .001 \) and \( r = -.35, p < .001 \) and \( r = -.37, p < .001 \) and \( r = -.37, p < .001 \). In contrast, no statistically significant relationships were observed between 25(OH)D and urinary (deoxy)pyridinoline in the control group.
Table 1. Clinical, Biochemical, and Densitometric Data from Hip Fracture Patients and Elderly Controls

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n = 117)</th>
<th>Patients (n = 117)</th>
<th>Difference p-value, two-sided</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (years)</td>
<td>77.7</td>
<td>5.4</td>
<td>79.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.2</td>
<td>6.7</td>
<td>159.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.2</td>
<td>10.6</td>
<td>61.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.8</td>
<td>4.0</td>
<td>24.1</td>
</tr>
<tr>
<td>Total calcium (mg/100 mL)</td>
<td>9.9</td>
<td>0.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Phosphate (mg/100 mL)</td>
<td>2.9</td>
<td>0.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Albumin (g/100 mL)</td>
<td>4.3</td>
<td>0.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Creatinine (mg/100 mL)</td>
<td>1.1</td>
<td>0.2</td>
<td>1.0</td>
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<tr>
<td>Creatinine clearance (mL/min)</td>
<td>45.7</td>
<td>19.0</td>
<td>46.6</td>
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<tr>
<td>Total 25(OH)D (ng/mL)</td>
<td>21.5</td>
<td>13.3</td>
<td>10.1</td>
</tr>
<tr>
<td>Total 1,25(OH)₂D₃ (pg/mL)</td>
<td>50.6</td>
<td>13.1</td>
<td>35.6</td>
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<td>DBP (µg/mL)</td>
<td>342.8</td>
<td>45.0</td>
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<tr>
<td>Free 25(OH)D index</td>
<td>9.2</td>
<td>5.3</td>
<td>6.2</td>
</tr>
<tr>
<td>Free 1,25(OH)₂D₃ index</td>
<td>2.0</td>
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<td>1.9</td>
</tr>
<tr>
<td>PTH(1-84) (pg/mL)</td>
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<td>48.8</td>
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<tr>
<td>Calcitonin (pg/mL)</td>
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<tr>
<td>Osteocalcin (ng/mL)</td>
<td>36.5</td>
<td>9.7</td>
<td>25.6</td>
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<td>Pyridinoline (nmol/nmol creatinine)</td>
<td>70.4</td>
<td>25.7</td>
<td>112.4</td>
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<tr>
<td>(Deoxy)pyridinoline (nmol/nmol creatinine)</td>
<td>16.0</td>
<td>3.1</td>
<td>21.4</td>
</tr>
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<td>Femoral neck BMD (g/cm²)</td>
<td>0.781</td>
<td>0.111</td>
<td>0.561</td>
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<tr>
<td>Trochanteric BMD (g/cm²)</td>
<td>0.688</td>
<td>0.109</td>
<td>0.501</td>
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</table>

Notes: Significant p-values are indicated in bold type. 25(OH)D = 25-hydroxyvitamin D, 1,25(OH)₂D₃ = 1,25-dihydroxyvitamin D, DBP = vitamin D binding protein, PTH = parathyroid hormone, SD = standard deviation.

Figure 2. Comparison of serum-intact PTH, serum total 25(OH)D₃, and urinary pyridinoline in normal elderly women and in osteoporotic patients.

**p = .001.**

Deoxypyridinoline were significantly increased. Finally, a highly significant decline was observed in femoral neck and trochanteric BMD in (a subgroup of) hip fracture patients compared to the controls. According to the WHO criteria (35), 92% of the fracture patients were classified as osteoporotic at the femoral neck, compared to 11% of the elderly controls. Similar proportions were observed when based on trochanteric BMD (90% and 12%, respectively).

Comparison of both fracture types. — In 62% of the patients, the fracture was trochanteric. Patients with trochanteric fractures were older than women with cervical fractures, while no differences were found in anthropometry or any of the biochemical parameters between the two different types of fracture (Table 2).

**DISCUSSION**

As compared with the controls, the hip fracture patients had a lower BMI and lower serum albumin concentration. These findings are in line with previous reports (8,10,12, 20,36-43) and suggest nutritional deficiency. Poor nutrition and protein deficiency are indeed common findings in elderly people with hip fracture (8,40-43). On the other hand, circulating protein levels could be affected by acute


changes in extracellular fluid composition induced by the trauma. Both albumin (44) and DBP (45) have indeed been shown to decrease within 24 to 48 h after trauma. However, our patients were sampled within 18 h after fracture, and protein concentrations were unrelated to the time elapsed since trauma. Therefore, the low levels of albumin and DBP are likely to reflect preexistent deficiencies. Consistent with this assumption, previous studies including patients more than 48 h after trauma have observed decreases in serum albumin of a much greater magnitude (10,12,36,37). This may partially have been an effect of time elapsed from the fracture and thus be influenced both by the posttraumatic reaction and the surgical treatment.

Fracture patients showed an increase in bone resorption, as evidenced by increased urinary excretion of both pyridinium and deoxypyridinoline. Serum concentrations of osteocalcin, on the other hand, were lower in patients than in the control subjects. This level of osteocalcin in fractured patients agrees with a number of recent reports (10,12,20) and is consistent with a decreased bone formation, despite higher levels of PTH with a subsequent bone over remodeling. Bone histomorphometry of hip fracture patients has indeed provided evidence for decreased bone formation despite increased bone resorption (7,46,47), suggesting an imbalance (uncoupling) between formation and resorption in age-related osteoporosis. In contrast to our study, serum osteocalcin has been reported to be elevated (14,15,18) or normal (16,17,19) in hip fracture populations. However, the time passed between fracture and sampling in these studies ranged from 24-48 h to weeks. Therefore, the observed effects could be secondary. Recent prospective evidence has indeed shown that circulating proteins, including serum albumin and osteocalcin, remain unchanged within 18 h after fracture but then gradually decrease to reach a nadir after 48-72 h (20) and subsequently increase (16). These changes are probably only partially accounted for by changes in bone turnover but rather by a combination of the trauma and the subsequent surgery. In the present study, all samples from patients were collected within 18 h, and neither the serum osteocalcin nor the urinary excretion of (deoxy)pyridinoline correlated with the time elapsed after fracture; this suggests that the decline in bone formation and the increased resorptive activity were unrelated to short-term metabolic alterations induced by the trauma. In addition, the changes in bone markers could not be attributed to differences in renal function, as neither the serum creatinine nor the clearance rate was significantly different between both groups.

Lack of 25(OH)D has been implied in the induction of secondary hyperparathyroidism of the elderly and in turn to bone resorption and fracture risk (46,48,49). Consistent with this hypothesis, hip fracture patients in this study were found to have significantly lower levels of 25(OH)D, coupled with higher concentrations of serum PTH and urinary pyridinium cross-links. The difference in circulating 25(OH)D between patients and controls is in keeping with most previous reports (10,13,37,38,50) and cannot be explained by seasonal variation, as both groups were equally distributed over the year. However, deficiency of 25(OH)D has not been a consistent finding in fracture patients. The lack of evidence for vitamin D deficiency in some studies (12,17) may have been related to different inclusion criteria, in particular the selection of controls among institutionalized elderly women and geriatric patients.
Data on serum PTH in age-related osteoporosis have been conflicting as well. Compston et al. (11) were the first to report elevated serum-intact PTH levels in a large proportion of elderly patients with fracture of the proximal femur, but PTH values were compared to a young adult reference range. In view of the fact that PTH increases with age (51–53), their results are difficult to interpret. In a recent similar analysis using an immunoassay to measure intact PTH, serum levels of PTH were higher in femoral neck fracture patients than in controls of similar age (13). In contrast, a number of studies failed to show any increase in PTH in hip fracture patients (9,10,12). However, this could reflect the lack of specificity and sensitivity of the assays used, since intact hormone was not measured. In the present study, 25(OH)D deficiency in hip fracture patients was associated with a significant increase in circulating PTH and urinary (deoxy)pyridinoline, supporting the view that secondary hyperparathyroidism contributes to bone loss and the high incidence of osteoporosis in the elderly population. Although the relation between secondary hyperparathyroidism and fracture occurrence may be explained by the effect of PTH on bone loss during previous years, the increased urinary excretion of pyridinium cross-links in the fracture group reflects a currently increased bone resorption.

Bioavailability and bioactivity of 25(OH)D and 1,25(OH)₂D₃ are influenced by protein binding. In fact, vitamin D metabolites are more than 99% bound to serum proteins. At physiological concentrations, vitamin D binding globulin, an α₂-globulin, binds almost all 25(OH)D and 62% of 1,25(OH)₂D₃ (30,54), whereas the latter is bound to albumin for 23% (54,55). Therefore, part of the decrease in concentration of serum vitamin D metabolites in the patient group might be related to the low levels of circulating proteins. However, when correcting for DBP, serum 25(OH)D levels were still significantly lower in fracture cases. In contrast, differences in 1,25(OH)₂D₃ did not persist after adjustment for DBP. Similarly, estimates of the free 1,25(OH)₂D₃ concentrations showed no significant differences between patients and controls, suggesting that 1,25(OH)₂D₃ levels are maintained in the normal range in the hip fracture patients by an increase in serum PTH. The absence of a significant decrease of the active 1,25-dihydroxylated metabolite may explain the low incidence of osteomalacia in cases of hip fracture (46,56). However, the fact that the increase in PTH levels in fracture patients was not associated with a parallel increase in serum 1,25(OH)₂D₃ suggests renal 1α-hydroxylase resistance to PTH in this population.

Both in fracture patients and in elderly controls, serum concentrations of osteocalcin were found to increase as a function of age. Similar results were recently reported by Garnero et al. (57) and are considered to reflect the increasing overall skeletal rate of bone turnover with aging in women. Secondary hyperparathyroidism resulting from vitamin D deficiency is likely to be involved in this increase in bone turnover rate in the elderly. Consistent with this view, increased serum-intact PTH was associated with increased levels of circulating osteocalcin both in patients and controls. However, these findings do not preclude a decline in osteoblast function at the cellular level since biochemical markers of bone turnover (including osteocalcin) primarily reflect the overall net changes of formation or degradation of the bone matrix. As indicated, bone loss occurring in late menopause is attributed in part to an age-related decrease in bone formation, an assumption resulting from histological studies. Such a decrease in bone formation at the cellular level does not preclude an increase of the rate of bone formation (and resorption) at the skeletal level [i.e., an increase in the overall rate of bone turnover or activation frequency (57)]. Moreover, compared to the expected age-associated increase of serum osteocalcin as observed in the age-matched controls, the hip fracture patients had a decreased osteocalcin level despite higher concentrations of intact PTH. These differences further support the notion that this population of osteoporotic elderly women may have an impaired osteoblast function.

In concentrations near the physiologic range, human calcitonin abolishes osteoclast activity in vitro (58,59), suggesting that calcitonin may tonically inhibit bone resorption in vivo. However, it is uncertain whether physiological levels of calcitonin have any important role in regulating calcium homeostasis in humans (60), and the exact role of calcitonin in the pathogenesis of type II osteoporosis remains to be clarified. In fact, calcitonin metabolism in osteoporotic patients has not yet been exhaustively investigated, and data from the literature remain conflicting (61–63). Stevenson et al. (61) reported impaired calcitonin secretion in 10 women who had sustained a femoral neck fracture after minor trauma. The control group consisted of 10 osteoarthritic patients of similar age. Both basal values and peak levels following calcium infusion, 7–10 days after surgery, were lower in the osteoporotics compared to the controls, but there was considerable overlap between the two groups. In contrast, Reginster et al. (62) found that the basal level of calcitonin, the metabolic clearance rate, and its production rate did not appear to be different in 14 patients with hip fracture compared to 27 age-matched controls. However, femoral fractures occurred 6 months to 3 years before the determination of calcitonin levels. Similar results were obtained by Beringer et al. (63), analyzing 20 women within 24 h after femoral neck fracture and 10 nonosteoroporotic controls. In line with these reports, basal calcitonin levels in this study were not significantly depressed in a large population of elderly women shortly after hip fracture, suggesting that calcitonin deficiency is not involved in the pathogenesis of age-related osteoporosis.

Our conclusions need to be tempered by the limitations of the cross-sectional design used in this study. As indicated, the low levels of serum osteocalcin and the increase in urinary excretion of (deoxy)pyridinoline are likely to reflect preexistent alterations, independent of the trauma. However, we acknowledge that it is impossible to completely control for the effect of the moment of trauma in a cross-sectional analysis and that confirmation would require a longitudinal design. In addition, our control subjects were not selected as representative of the general elderly population but rather to allow us to study bone metabolic indices in the absence of confounding diseases and medications. Therefore, the results may not be generalizable to the overall elderly population at risk for hip fracture.
In summary, our data emphasize the role of secondary hyperparathyroidism-induced bone resorption in the pathogenesis of hip fractures, mainly due to low 25(OH)D levels. Age-related osteoporotic fracture occurrence is, on the other hand, not associated with 1,25(OH)2D deficiency. The efficacy of a preventive treatment with calcium and cholecalciferol in lowering the frequency of hip fractures among elderly institutionalized women (48) is consistent with the metabolic changes observed in the present study. However, the etiology of the decline in bone formation, as evidenced by low levels of circulating osteocalcin, deserves further investigation.

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Address correspondence to Dr. Steven Boonen, University Hospitals Leuven, Department of Internal Medicine, Division of Geriatric Medicine, Brusselsestraat 69, B-3000 Leuven, Belgium.

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