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The hormonal profile of hip fracture female patients differs from community-dwelling peers over a 1-year follow-up period

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Abstract

Summary—Hormone levels were compared over a 1-year period between elderly women who had sustained a hip fracture and women of similar age and functional ability. Our study suggests progressive hormonal changes that may contribute to severe bone loss during the year following hip fracture.

Introduction—Alterations in hormones affecting the musculoskeletal system may increase risk of hip fracture or poor post-fracture recovery in postmenopausal women. Most studies lack appropriate reference groups, and thus cannot assess the extent to which these alterations are attributable to hip fracture.

Methods—Women aged ≥ 65 years hospitalized for an acute hip fracture (Baltimore Hip Studies, BHS-3; $n = 162$) were age-matched to 324 women enrolled in the Women's Health and Aging Study I, a Baltimore-based cohort with similar functional status to the pre-fracture status of BHS-3 women. Both studies enrolled participants from 1992 to 1995. Insulin-like growth hormone-1 (IGF-1), parathyroid hormone (PTH), 1,25 dihydroxyvitamin D [1,25(OH)2D], and osteocalcin were evaluated at baseline and 2, 6, and 12 months post-fracture, and at baseline and 12 months in the comparison group. Between-group differences in trajectories of each hormone were examined.

Results—Baseline mean IGF-1 levels were significantly lower in hip fracture patients than the comparison group (75.0 vs. 110.5 $\mu\text{g/dL}$; $p < 0.001$). Levels increased by 2 months post-fracture, but remained significantly lower than those in the comparison group throughout the 12-month follow-up ($p < 0.01$). Levels of PTH and osteocalcin were similar between groups at baseline, but rose during the year post-fracture to significantly differ from the comparison women ($p < 0.001$). 1,25(OH)2D levels did not differ between the hip fracture and comparison women at any time.

Conclusions—Older women who have sustained a hip fracture have progressive changes in hormonal milieu that exceed those of women of similar health status during the year following fracture.

Keywords

1,25, Dihydroxyvitamin D; Elderly; Hip fracture; Hormones; IGF-1; Osteocalcin; PTH; Women

Hip fractures are a common occurrence in older women, and they lead to progressive functional impairment, dependence and mortality [1,2]. Alterations in several hormones that affect the musculoskeletal system have been identified as potential risk factors for fractures in postmenopausal women, most notably the vitamin D/parathyroid hormone (PTH) and insulin-like growth factor-1 (IGF-1)/growth hormone axes. These hormones may be important determinants not only of risk for hip fracture but also for post-fracture recovery.

For a hormone to be a contributing factor of hip fracture, its pre-fracture levels should differ from those of women who have not sustained a fracture. Data on pre-fracture levels are difficult to obtain in large numbers of women, due to the requirement for pre-fracture phlebotomy. Furthermore, the choice of comparison group is critical. Ideally, this group should be comparable to the fracture group on age, functional status, and other risk factors for fracture, but have not sustained a fracture. Similarly, to affect post-fracture recovery, the pattern of post-fracture hormone levels should differ between these two groups over the same time frame. Because many hip fracture patients were frail and functionally impaired prior to the fracture, if “healthy” controls are used instead, it is not clear whether the alterations that are seen in women who have sustained hip fractures specifically predispose them to hip fracture, or if these alterations would be expected to occur in any population of women of similar health and functional status.

We previously published data from the third cohort of the Baltimore Hip Studies (BHS-3) on the longitudinal patterns of change in hormones from the vitamin D/PTH axis [3,4] and markers of bone turnover [4] during the year after an acute hip fracture. The current study compared trajectories of these hormones, plus IGF-1, to “expected” changes in older women over 1 year by comparing BHS-3 participants to a sample of Baltimore area women with similar health status and age who were enrolled in the Women's Health and Aging Study I (WHAS I). We included IGF-1 because lower levels may impair osteoblastic function in old age [5]. We hypothesized that levels of IGF-1 and 1,25 dihydroxyvitamin D [1,25(OH)2D] would be lower, and levels of PTH and osteocalcin would be higher over 1 year following the fracture in women with acute hip fractures than a comparison group.

Methods

Study population

Hip fracture patients were women enrolled in the third cohort of BHS-3, as previously described [1]. This cohort included 205 community-dwelling Caucasian women, aged at least 65 years, who were admitted to one of two hospitals in Baltimore between 1992 and 1995 with a new fracture of the proximal femur. Women with pathologic fractures were excluded. Subjects were evaluated at 3 to 10 days following hospitalization (baseline) and at 2, 6, and 12 months post-fracture (follow-up). The study was approved by the Institutional Review Boards of the University of Maryland, Baltimore, and of each participating hospital. All participants gave informed consent, or a proxy provided it for them if they could not provide consent for themselves due to cognitive limitations. The study sample included 162 participants with baseline phlebotomy.

Comparison subjects were obtained from a cohort of women who participated in WHAS I, as previously described [6]. Women were recruited from a random sample of community-dwelling women ≥ 65 years old selected from the Health Care Financing Administration's (HCFA) Medicare Eligibility list for Baltimore. Physical disability was identified through self-reported difficulty in four domains: (1) mobility tasks, (2) upper extremity tasks, (3) household management tasks, and (4) basic self-care tasks. Women who reported difficulty in two, three, or four domains represented the one third most disabled community-dwelling older women, and were eligible for inclusion into WHAS I. In 1992–1995, 1,002 women enrolled. Subjects were evaluated every 6 months for 3 years, with phlebotomy every 12 months. The Johns Hopkins University Institutional Review Board approved the study, and all participants gave informed consent.

The comparison group was formed by matching two white women enrolled in WHAS I who were aged within 5 years of a hip fracture patient and had phlebotomy performed. Women in WHAS I who had previously sustained a hip fracture were not excluded because some BHS-3 participants had had a previous fracture. This method resulted in 324 comparison subjects.

Biochemical measurements

In BHS-3, serum samples were collected between 12:00 noon and 3:00 p.m. at each interview point. They were processed and stored at -70°C . Samples from a single individual were assayed together once samples from all time points were collected. Total serum IGF-1 was measured by competitive binding radioimmunoassay after ethanol extraction (Endocrine Sciences Laboratories, San Juan Capistrano, CA, USA). Intact PTH was measured by immunoradiometric assay (IncStar Corporation, Stillwater, MN, USA). 1,25(OH) $_2$ D was measured by a competitive radioimmunoassay kit involving lyophilization and purification by column extraction (IncStar Corporation, Stillwater, MN, USA). Serum osteocalcin was measured by radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).

In WHAS I, serum samples were collected between 9 a.m. and 2 p.m. at baseline and 1 and 2 years. Samples were processed, frozen, and sent the same day to Quest Diagnostic Laboratories (Teeterboro, NJ, USA). The serum IGF-1 and osteocalcin levels were measured using the same assays as in BHS-3. The PTH assay changed during the course of the WHAS I study; only intact PTH levels, measured by chemiluminescence, are included in this analysis ($n = 156$). 1,25(OH) $_2$ D was measured by extraction, chromatography, and radioreceptor analysis.

Covariates

Baseline medical conditions for BHS-3 were obtained from medical charts during the initial hospitalization for hip fracture, abstracted by a research nurse. In WHAS I, participants were asked about specific medical conditions. Additional information was collected from the primary care physician and medical records, and adjudicated by a study physician according to a prespecified algorithm [6]. We included seven comorbid conditions collected in both studies: diabetes, hypertension, congestive heart failure (CHF), myocardial infarction (MI), cancer, stroke, and lung disease. Self-reported ability to walk 10 ft or across a room was obtained in both studies (1 week prior to the fracture in BHS-3), and walking impairment was defined as not being able to walk or using any help to walk at home, including a cane, walker, holding onto a person, or wheelchair [7].

Statistical analysis

Baseline characteristics were compared between groups using *t* tests or chi-square tests as appropriate. Longitudinal analyses were performed using mixed models in SAS v 9.1 with an independent covariance matrix. Robust standard errors were used. The longitudinal model was estimated with and without adjustment for age, education, body mass index (BMI), presence of baseline walking impairment, CHF, MI, hypertension, lung disease, and stroke. Imputed 2- and 6-month timepoints based on the slope over 1 year are displayed for WHAS I to allow illustration of time-specific comparisons. Additional analyses were performed after exclusion of those taking estrogen or corticosteroids at baseline. Results did not differ from the model including these participants and thus are not presented.

Results

Hip fracture patients were slightly more educated, had a lower BMI, and were less likely to have had a history of MI, pre-fracture walking impairment, or estrogen use than comparison group women (Table 1). Both groups had a high prevalence of comorbidities and a low prevalence of corticosteroid and estrogen use.

At baseline, IGF-1 and osteocalcin levels were significantly lower in hip fracture patients than in comparison women (75.0 vs. 110.5 µg/L, $p < 0.001$; 0.98 vs. 1.12 nmol/L, $p = 0.04$, respectively), whereas there was no difference in levels of PTH or 1,25(OH)2D (5.27 vs. 5.07 pmol/L, $p = 0.61$; 85.8 vs. 88.7 pmol/L, $p = 0.59$, respectively). Among hip fracture patients, levels of IGF-1 rose from 75.0 to 95.0 µg/L by 2 months post-fracture and remained stable throughout the follow-up period (92.6 µg/L at 6 months and 96.6 µg/L at 12 months), while remaining significantly lower than those of the comparison group ($p < 0.01$). Osteocalcin levels increased (from 0.98 to 1.50 nmol/L) by 2 months post-fracture, and they remained consistently and significantly higher than those in the comparison group ($p < 0.001$). By contrast, mean PTH levels rose steadily from a baseline of 5.27 pmol/L to a maximum of 6.90 pmol/L over the year of follow-up and were significantly higher than those of the comparison group at 12 months ($p < 0.001$). 1,25 (OH)2D levels remained stable over the follow-up period for hip fracture patients and did not significantly differ from comparison group levels at any timepoint. With the exception of baseline osteocalcin levels, adjustment for age, education, BMI, presence of baseline walking impairment, CHF, MI, hypertension, lung disease, and stroke did not change these relationships (Fig. 1).

Discussion

This study found that following a hip fracture, elderly women had significantly lower levels of IGF-1 and osteocalcin, but not PTH or 1,25(OH)2D than women of similar age and health status. Furthermore, hip fracture patients' levels of IGF-1, osteocalcin, and PTH differed

from the comparison group's over the ensuing year, whereas 1,25(OH)2D levels did not differ at all. These findings suggest a progressive change in hormonal milieu during the year following fracture that may contribute to severe bone loss noted in women who have sustained a hip fracture [8].

These results are consistent with several small, cross-sectional studies that found lower IGF-1 [9,10] and osteocalcin [11–13] and higher PTH [14,15] levels in elderly women hip fracture patients compared to healthy controls. Our comparison group of community-dwelling older women with similar health status to the pre-fracture status of hip fracture patients overcomes concerns about the results being confounded by a healthier comparison, and provides a more valid estimate of the degree to which these hormonal trajectories exceed expected aging effects in older women with functional limitations.

As the peripheral mediator of growth hormone, IGF-1 has anabolic properties and increases bone formation. IGF-1 levels are known to be slightly lower in women with decreased physical function compared to healthy, age-matched women without a recent hip fracture [16]. Our data demonstrate even lower IGF-1 levels in women over the year following a hip fracture. Depressed IGF-1 levels have been found in other settings of trauma or stress, suggesting down-regulation of the growth hormone axis. For example, IGF-1 levels decreased by 60% immediately following elective cardiac surgery, but returned to baseline levels 1 to 3 months later [17]. The stress of hip fracture may result in a similar reactive decrease and subsequent return to baseline of IGF-1 levels. If so, in the absence of pre-fracture IGF-1 levels in our hip fracture patients, our observation of sustained low IGF-1 levels from 2 to 12 months post-fracture imply a pre-fracture IGF-1 deficit even when compared to disabled controls.

A recurrent theme in osteoporosis research is the contribution of secondary hyperparathyroidism caused by hypovitaminosis D to the risk of hip fracture. In contrast to studies that used healthier controls [14,15], we found no difference in baseline PTH levels, suggesting that higher PTH is a generalized phenomenon in older women of poor functional status. This finding is consistent with data from the WHAS I and II studies showing higher PTH levels with increasing degree of disability [18]. Furthermore, it extends our previous findings of increased PTH levels in the year following hip fracture [3,4] by contrasting these to stable levels seen in the WHAS I women over a 1-year period. Our results on 1,25(OH)2D concur with previous studies, which failed to find a difference between hip fracture and healthy women [12,13,15]. This suggests that the elevated PTH from secondary hyperparathyroidism is sufficient to maintain 1,25(OH)2D, the activated form of vitamin D, despite low vitamin D stores [15].

Osteocalcin is a protein synthesized by osteoblasts and is found in extracellular bone matrix and an established marker of bone formation. Our finding of lower initial osteocalcin levels in hip fracture patients is consistent with previous studies on healthy controls [11–13], suggesting a lower baseline rate of bone formation, though this difference disappeared after adjustment. Low levels may also be a reflection of the initial response to trauma, which has been reported previously in patients undergoing total hip replacement [19]. We and others have reported an increase during recovery, consistent with increased bone formation during the healing process [4,20,21]. Our study extends these reports by providing appropriate reference data using the same assay to illustrate the timing and magnitude of the change from low to elevated osteocalcin levels post-fracture.

Prospective cohort studies provide inconsistent associations between pre-fracture levels of IGF-1, vitamin D/PTH status, and/or osteocalcin on risk of fracture in elderly women. In the Study of Osteoporotic Fractures (SOF), women with the lowest quintile of 1,25(OH)2D

level had a greater than twofold increased risk of hip fracture [22]. There was no association between 25(OH)D or PTH concentration and subsequent hip fracture. In the Os des Femmes de Lyon (OFELY) study, IGF-1 levels below the median were associated with a threefold increase in fracture risk, whereas neither low 25(OH)D nor high PTH was associated with an increase in fracture risk [23,24]. Post-fracture changes in hormone levels in hip fracture women were not described in these two studies. In the Malmö Osteoporosis Prospective Risk Assessment (OPRA) cohort, pre-fracture serum osteocalcin levels were not significantly different from those of women who did not sustain a hip fracture [25]. A subset of 30 women enrolled in this study was evaluated within a day after a hip fracture and 4 months later. Immediate post-fracture levels of osteocalcin were lower than pre-fracture levels, increasing to significantly above baseline by a 4-month evaluation [26].

A major strength of our study is the use of two large, established, concurrent cohorts of older Caucasian women living in the same urban area, one with recent hip fracture and the other without, who had hormone data assayed over a 1-year period. However, due to the composition of BHS-3, only white women were included in our comparisons, and each study used different methods to collect data on comorbid conditions. Furthermore, although the assays for PTH and 1,25(OH)₂D were performed by qualitatively similar methods, the same assay was not used in both studies. Thus, our results may reflect between-study differences in these measures. However, our findings of no difference in baseline PTH and 1,25(OH)₂D levels between the hip fracture and comparison groups suggest that assay differences play a negligible role. They also provide credibility for the subsequent between-group differences found in PTH levels over time. Moreover, although both BHS-3 and WHAS I measured levels of 25(OH)D differently by too great an extent to permit valid between-study comparisons, each study has previously published evidence of a high prevalence of vitamin D deficiency [18,27], suggesting that vitamin D deficiency may be a contributing factor, but is not sufficient to produce a hip fracture. Another inherent limitation is that we are unable to make direct comparisons using pre-fracture measures in BHS-3, as this cohort was enrolled after the fracture occurred.

A multitude of factors contribute to ongoing bone loss and declining physical function after hip fracture [28]. Our findings suggest a potential contribution of multiple hormonal alterations that are specific to women who have fractured a hip and the need for ongoing surveillance and intervention, such as vitamin D supplementation and improved nutritional status, months after the fracture itself.

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Fig. 1.

Longitudinal data for **a** IGF-1, **b** PTH, **c** 1,25(OH)₂D, and **d** osteocalcin for hip fracture and WHAS I (control) women. Mean values with SDs are presented for models adjusted for age, education body mass index, presence of baseline walking impairment, congestive heart failure, myocardial infarction, hypertension, lung disease, and stroke. Imputed 2- and 6-month timepoints are displayed for the WHAS I women to illustrate time-specific comparisons. *p* values are for time-specific comparisons: **p*<0.01, ***p*<0.001. *IGF-1* insulin-like growth factor-1, *PTH* parathyroid hormone, *1,25(OH)₂D* 1,25 dihydroxyvitamin D

Table 1

Baseline characteristics of the matched samples of women hip fracture patients and comparison subjects

Characteristics	Hip fracture (<i>n</i> = 162)	WHAS (<i>n</i> = 324)
Demographics		
Age, years	79.9 (7.5)	80 (7.6)
Education, years	12.0 (3.2) *	10.2 (3.7)
Race (% white)	100	100
Health status		
BMI, kg/m ²	23.1 (4.3) *	27.3 (6.1)
Diabetes (%)	13.6	12.7
Hypertension (%)	45.7	52.6
CHF (%)	13.0	9.9
MI (%)	13.6 *	24.1
Cancer (%)	16.7	17.3
Stroke (%)	8.6	13.9
Lung disease (%)	21.6	18.3
Walking impairment (%)	25.0 *	38.9
Medication		
Corticosteroid in the past 6 months (%)	5.2	8.6
Estrogen in the past 6 months (%)	2.9 *	11.4

Data are presented as mean (SD) unless otherwise indicated

*
p < 0.05*BMI* body mass index, *CHF* congestive heart failure, *MI* myocardial infarction