

ENDOGENOUS HORMONES AND THE RISK OF HIP AND VERTEBRAL FRACTURES AMONG OLDER WOMEN

STEVEN R. CUMMINGS, M.D., WARREN S. BROWNER, M.D., M.P.H., DOUGLAS BAUER, M.D., KATIE STONE, PH.D.,  
KRISTINE ENSRUD, M.D., M.P.H., SOPHIE JAMAL, M.D., AND BRUCE ETTINGER, M.D.,  
FOR THE STUDY OF OSTEOPOROTIC FRACTURES RESEARCH GROUP

**ABSTRACT**

**Background and Methods** In postmenopausal women, the serum concentrations of endogenous sex hormones and vitamin D might influence the risk of hip and vertebral fractures. In a study of a cohort of women 65 years of age or older, we compared the serum hormone concentrations at base line in 133 women who subsequently had hip fractures and 138 women who subsequently had vertebral fractures with those in randomly selected control women from the same cohort. Women who were taking estrogen were excluded. The results were adjusted for age and weight.

**Results** The women with undetectable serum estradiol concentrations (<5 pg per milliliter [18 pmol per liter]) had a relative risk of 2.5 for subsequent hip fracture (95 percent confidence interval, 1.4 to 4.6) and subsequent vertebral fracture (95 percent confidence interval, 1.4 to 4.2), as compared with the women with detectable serum estradiol concentrations. Serum concentrations of sex hormone-binding globulin that were 1.0 µg per deciliter (34.7 nmol per liter) or higher were associated with a relative risk of 2.0 for hip fracture (95 percent confidence interval, 1.1 to 3.9) and 2.3 for vertebral fracture (95 percent confidence interval, 1.2 to 4.4). Women with both undetectable serum estradiol concentrations and serum sex hormone-binding globulin concentrations of 1 µg per deciliter or more had a relative risk of 6.9 for hip fracture (95 percent confidence interval, 1.5 to 32.0) and 7.9 for vertebral fracture (95 percent confidence interval, 2.2 to 28.0). For those with low serum 1,25-dihydroxyvitamin D concentrations (≤23 pg per milliliter [55 pmol per liter]), the risk of hip fracture increased by a factor of 2.1 (95 percent confidence interval, 1.2 to 3.5).

**Conclusions** Postmenopausal women with undetectable serum estradiol concentrations and high serum concentrations of sex hormone-binding globulin have an increased risk of hip and vertebral fracture. (N Engl J Med 1998;339:733-8.)

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**I**N postmenopausal women, vertebral fractures are often attributed to low estrogen production, and hip fractures to secondary hyperparathyroidism due to age-related declines in calcium intake and in calcium absorption mediated by 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>vitamin D).<sup>1,2</sup> The results of retrospective case-control studies of the association between these hormones and the in-

cidence of hip or vertebral fracture are conflicting, because of the alterations in serum hormone or vitamin D concentrations that result from fracture, the selection of nonrepresentative case and control subjects, and the use of insensitive assays for serum estradiol.<sup>3-11</sup>

To determine the effects of endogenous hormones on the risk of hip and vertebral fractures, we prospectively studied a large cohort of women who were 65 years of age or older. We compared baseline serum concentrations of selected hormones in women who later had hip or vertebral fractures with those in randomly selected control women from the same cohort.

**METHODS**

From 1986 through 1988, we recruited women 65 years of age or older who lived in the community and who were identified from population-based listings in Baltimore, Minneapolis, Pittsburgh, and Portland, Oregon; 9704 of these women were enrolled in the Study of Osteoporotic Fractures.<sup>12</sup> We excluded black women (because of their low risk of hip fracture), women who had undergone bilateral hip replacement, and those who were unable to walk without help.

**Clinical Studies**

At base line, the women were asked whether they were taking estrogen, calcium supplements, or multivitamins containing vitamin D, about their cigarette-smoking habits, and about their dietary calcium intake (by means of a food-frequency questionnaire).<sup>13</sup> Lateral x-ray films of the thoracic and lumbar spine were obtained, and bone mineral density of the heel was measured by single-photon absorptiometry (OsteoAnalyzer, Siemens-Osteon, Wahiawa, Hawaii); the mean coefficient of variation between clinical centers for this measurement was 1.2 percent.<sup>14</sup> No recommendations about treatment were made. Blood was drawn between 8 a.m. and 2 p.m. after the women had followed a fat-free diet overnight, and serum was immediately frozen at -20°C. The samples were shipped to the Biomedical Research Institute (Rockville, Md.), where they were stored in aliquots in liquid nitrogen (at -190°C).

**Identification of Fractures**

The women were contacted by mail every four months to ascertain their vital status and to identify the occurrence of frac-

From the Departments of Medicine (S.R.C., W.S.B., D.B.) and Epidemiology and Biostatistics (S.R.C., W.S.B., D.B., K.S., S.J.), University of California, San Francisco; the Department of Medicine, Veterans Affairs Medical Center, and the Division of Epidemiology, School of Public Health, University of Minnesota — both in Minneapolis (K.E.); and the Division of Research, Kaiser Permanente Medical Care Program, Oakland, Calif. (B.E.). Address reprint requests to Dr. Cummings at Suite 600, 74 New Montgomery St., San Francisco, CA 94143.

tures; follow-up was more than 99 percent complete. Hip fractures were confirmed by a review of radiographs obtained at the time of hospitalization after the fracture. Follow-up lateral x-ray films of the thoracic and lumbar spine were obtained for 79 percent of the women who were still alive at 3.7 years. Fractures were identified by quantitative morphometry by study personnel who were unaware of the base-line assay results. A new fracture was considered to have occurred if there was a decrease of 20 percent and 4 mm in any vertical dimension of one or more thoracic or lumbar vertebrae.<sup>15,16</sup>

**Selection of Case Patients and Controls**

We excluded women who were taking estrogen therapy at base line. Using the case-cohort approach,<sup>17</sup> we randomly selected 133 of the 332 women in the cohort of 9704 who had a first hip fracture during a maximum of 5.9 years of follow-up after the base-line assessment. Similarly, we randomly selected 138 of the 389 women who had a new vertebral fracture. We also randomly selected 359 women from the original cohort to serve as controls. Four of these 359 women were excluded from the analyses of hip fractures because they had had a hip fracture before the base-line studies were conducted. Eighty-one of the 359 women were excluded from the analyses of vertebral fractures because spine films were unavailable at follow-up. This random sample included 12 of the 133 women selected from among those with hip fractures and 14 of the 138 women selected from among those with vertebral fractures; they were counted as case patients in the analyses of hip and vertebral fractures, respectively. We did not exclude control women who had a history of vertebral fractures at base line or who later took estrogen.

**Biochemical Analyses**

Estradiol and estrone were measured in serum by radioimmunoassay after extraction and separation by liquid chromatography; the interassay coefficient of variation for estradiol ranged from 8 percent to 12.5 percent and that for estrone from 6.2 percent to 7.0 percent. The limit of detection was 5 pg per milliliter (18 pmol per liter) for estradiol and 4 pg per milliliter (15 pmol per liter) for estrone. Serum testosterone was measured by radioimmunoassay after extraction and aluminum oxide column chromatography, with an interassay coefficient of variation of 6.1 to 13.4 percent. The testosterone-binding capacity of sex hormone-binding globulin in serum was measured by means of a displacement technique (interassay coefficient of variation, 4.1 to 14.4 percent). Serum free testosterone was measured with an ammonium sulfate precipitation procedure<sup>18,19</sup> (coefficient of variation,

10.7 to 15.5 percent). All these analyses were carried out at Endocrine Sciences (Calabasas Hills, Calif.).

Serum parathyroid hormone was measured by immunoradiometric assay, and serum 25-hydroxyvitamin D (25(OH)vitamin D) and 1,25(OH)<sub>2</sub>vitamin D by radioimmunoassay. The respective interassay coefficients of variation were 15.0 percent and 12.4 percent. Serum creatinine was measured with use of an automated analyzer. These analyses were carried out at the Calcitropic Hormone Reference Laboratory of the University of California, San Francisco.

All assays included coded samples of serum from case patients and controls and were performed in 1994 and 1995, seven to eight years after collection. After the selection of the case and control women, samples were sent directly to the analytic laboratory without thawing. Initial plans called for measurements of serum estrone but not estradiol; we therefore measured estradiol in only 247 of the 359 women randomly selected from the cohort as controls, 89 of the 133 women who had hip fractures, and 96 of the 138 women who had vertebral fractures.

We determined the stability of several hormones in serum from 51 postmenopausal women by analyzing serum samples both at base line and after 3.5 years of storage at -190°C. The correlations between the two measurements were as follows: 25(OH)vitamin D, r=0.88 (P<0.001); testosterone, r=0.99 (P<0.001); and estrone, r=0.98 (P<0.001).

**Statistical Analysis**

We used logistic-regression analysis (SAS Institute, Cary, N.C.) to analyze predictors of vertebral fractures and proportional-hazards analysis that took account of the case-cohort sampling design (Epicure, Hirosoft International, Seattle) to analyze predictors of hip fracture. Except where noted, the results of all analyses were adjusted for age and weight and are reported as relative risks. Population attributable risk was calculated by the following formula:  $p(RR-1)/[p \times (RR-1) + 1]$ , where p is the prevalence of a given risk factor and RR is the relative risk of fracture associated with it.<sup>20</sup>

**RESULTS**

As compared with the controls, the women who had hip or vertebral fractures during the study were older, were lighter, and had lower calcaneal bone density at base line (Table 1). The hip fractures occurred an average of 3.9 years (range, 0.2 to 5.9) after the base-line studies. The vertebral fractures were

**TABLE 1. CHARACTERISTICS OF THE WOMEN WITH FIRST HIP OR NEW VERTEBRAL FRACTURES AND THE CONTROLS.\***

CHARACTERISTIC	HIP FRACTURE			VERTEBRAL FRACTURE		
	WOMEN WITH FRACTURE (N=133)	CONTROLS (N=343)	P VALUE	WOMEN WITH FRACTURE (N=138)	CONTROLS (N=264)	P VALUE
Age (yr)	75±6	72±5	<0.001	73±6	72±5	0.004
Weight (kg)	61.9±10.9	68.2±12.5	<0.001	63.5±11.6	68.6±12.4	<0.001
Current cigarette smoking (%)	17	9	0.01	12	9	0.24
Calcium supplementation (%)	51	42	0.07	53	42	0.04
Vitamin D supplementation (%)	43	43	0.98	48	42	0.26
Dietary calcium intake (mg/day)	659±389	689±413	0.45	695±391	693±411	0.95
Calcaneal bone density (g/cm <sup>2</sup> )	0.34±0.10	0.41±0.41	<0.001	0.35±0.08	0.41±0.09	<0.001

\*Plus-minus values are means ±SD.

**TABLE 2.** ADJUSTED ASSOCIATIONS BETWEEN SERUM HORMONE CONCENTRATIONS AND VITAMIN LEVELS AND THE RISK OF HIP OR VERTEBRAL FRACTURE IN POSTMENOPAUSAL WOMEN.\*

VARIABLE	PREVALENCE†	RISK OF HIP FRACTURE		RISK OF VERTEBRAL FRACTURE	
		ADJUSTED FOR AGE	ADJUSTED FOR AGE AND WEIGHT	ADJUSTED FOR AGE	ADJUSTED FOR AGE AND WEIGHT
	%	relative risk (95% CI)			
Estradiol <5 pg/ml	33	3.3 (1.9–5.9)	2.5 (1.4–4.6)	2.9 (1.7–5.0)	2.5 (1.4–4.2)
Sex hormone-binding globulin ≥1.0 μg/dl	76	2.5 (1.4–4.7)	2.0 (1.1–3.9)	2.7 (1.4–5.1)	2.3 (1.2–4.4)
Serum sex hormone-binding globulin (each additional 1.0 μg/dl)	—	1.4 (1.2–1.8)	1.3 (1.0–1.6)	1.7 (1.3–2.1)	1.5 (1.2–2.0)
Estrone ≥15 pg/ml	77	1.1 (0.6–1.8)	1.3 (0.8–2.2)	1.5 (0.9–2.5)	1.7 (1.0–2.9)
Free testosterone ≤0.7 pg/ml	19	1.9 (1.2–3.1)	1.6 (1.0–2.7)	1.6 (1.0–2.6)	1.4 (0.8–2.4)
25(OH)vitamin D ≤19 ng/ml	22	1.1 (0.7–1.8)	1.2 (0.7–1.9)	1.1 (0.9–1.8)	1.1 (0.6–1.8)
1,25(OH) <sub>2</sub> vitamin D ≤23 pg/ml	15	1.9 (1.1–3.1)	2.1 (1.2–3.5)	1.6 (0.9–2.8)	1.6 (0.9–2.8)
Parathyroid hormone >50 pg/ml	11	0.8 (0.4–1.5)	1.1 (0.5–2.1)	0.5 (0.2–1.2)	0.4 (0.2–1.0)

\*To convert values for estradiol to picomoles per liter, multiply by 3.67; to convert values for sex hormone-binding globulin to nanomoles per liter, multiply by 34.7; to convert values for estrone to picomoles per liter, multiply by 3.7; to convert values for free testosterone to picomoles per liter, multiply by 3.467; to convert values for 25-hydroxyvitamin D (25(OH)vitamin D) to nanomoles per liter, multiply by 2.5; to convert values for 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>vitamin D) to picomoles per liter, multiply by 2.4; and to convert values for parathyroid hormone to picomoles per liter, multiply by 0.11. CI denotes confidence interval.

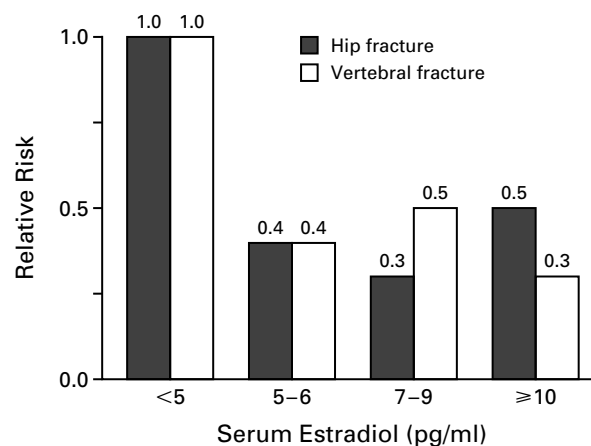
†Prevalence values are for the random sample of the cohort.

identified on x-ray films of the spine obtained an average of 3.7 years (range, 1.6 to 4.9) after the baseline studies.

**Serum Sex Hormones**

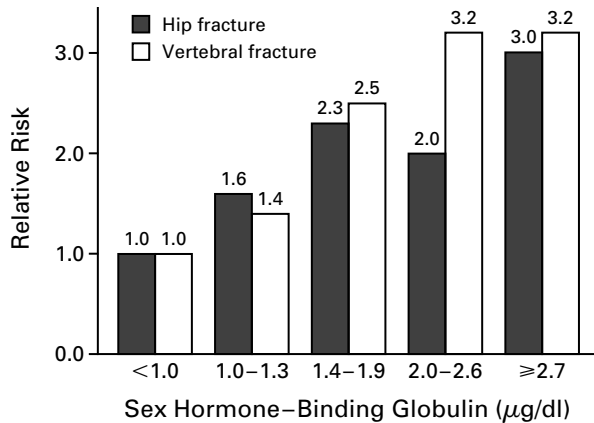
Among the 247 women randomly selected from the cohort as controls in whom serum estradiol was measured, 81 (33 percent) had undetectable concentrations (<5 pg per milliliter). After adjustment for weight and age, the women with undetectable serum estradiol concentrations had a greater risk of hip and vertebral fracture than the women who had detectable concentrations (Table 2 and Fig. 1). The women with serum estradiol concentrations from 5 to 9 pg per milliliter (18 to 33 pmol per liter) had approximately a 60 percent lower risk of hip fracture (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.7) and approximately a 60 percent lower risk of vertebral fracture (relative risk, 0.4; 95 percent confidence interval, 0.3 to 0.8) than the women whose serum estradiol concentrations were below 5 pg per milliliter. We estimated that an undetectable serum estradiol concentration was associated with an attributable risk of 33 percent for hip fractures and 32 percent for vertebral fractures.

The risk of hip fracture increased with increasing serum concentrations of sex hormone-binding globulin (Fig. 2). After adjustment for age, each increase of 1.0 μg per deciliter (34.7 nmol per liter) in the



**Figure 1.** Serum Estradiol Concentration at Base Line and Age-Adjusted Risk of Subsequent Hip or Vertebral Fracture in Postmenopausal Women.

There were 317 women in the hip-fracture analysis and 282 in the vertebral-fracture analysis. The reference group consisted of the women with serum estradiol concentrations below 5 pg per milliliter. To convert values for estradiol to picomoles per liter, multiply by 3.67. P for trend <0.01 for hip fracture and <0.005 for vertebral fracture.



**Figure 2.** Serum Concentrations of Sex Hormone-Binding Globulin at Base Line (in Quintiles) and Age-Adjusted Risk of Subsequent Hip or Vertebral Fracture in Postmenopausal Women.

There were 476 women in the hip-fracture analysis and 399 in the vertebral-fracture analysis. The reference group consisted of the women with values in the lowest quintile (<1.0 µg per deciliter). To convert values for sex hormone-binding globulin to nanomoles per liter, multiply by 34.7. P for trend <0.05 for hip fracture and <0.001 for vertebral fracture.

serum concentration of sex hormone-binding globulin was associated with a relative risk of 1.4 (95 percent confidence interval, 1.2 to 1.8) for hip fracture and 1.7 (95 percent confidence interval, 1.3 to 2.1) for vertebral fracture. For hip fracture, this effect appeared to be partly mediated by weight (Table 2).

Among the 244 women who were randomly selected from the cohort in whom both serum estradiol and serum sex hormone-binding globulin were measured, 63 (26 percent) had both an undetectable serum estradiol concentration and a serum sex hormone-binding globulin concentration of 1 µg per deciliter or higher. This combination was associated with an age-adjusted increase in risk by a factor of 14 for hip fracture (95 percent confidence interval, 3.0 to 62.0) and by a factor of 12 for vertebral fracture (95 percent confidence interval, 3.3 to 41.0). Adjustment for weight blunted these associations somewhat for both hip fracture (relative risk, 6.9; 95 percent confidence interval, 1.5 to 32.0) and vertebral fracture (relative risk, 7.9; 95 percent confidence interval, 2.2 to 28.0). The population attributable risks for this combination of factors were 60 percent for hip fracture and 64 percent for vertebral fracture.

Women with serum estrone values in the lowest quintile (≤14 pg per milliliter [52 pmol per liter]) had a lower risk of vertebral fracture than women with higher concentrations (Table 2). There was a moderate correlation between serum estrone and estradiol concentrations (r=0.6), and low serum estrone concentrations continued to be associated with

**TABLE 3.** HORMONAL PREDICTORS OF HIP AND VERTEBRAL FRACTURE IN POSTMENOPAUSAL WOMEN, ACCORDING TO MULTIVARIABLE MODELS.\*

VARIABLE†	MULTIVARIABLE-ADJUSTED	ALSO ADJUSTED FOR BONE DENSITY
	relative risk (95% CI)	
<b>Hip fracture</b>		
Serum estradiol <5 pg/ml	2.4 (1.3-4.5)	1.9 (1.0-3.6)
Serum sex hormone-binding globulin (each increase of 1µg/dl)	1.3 (0.9-2.0)	1.3 (0.9-1.8)
Serum 1,25(OH) <sub>2</sub> vitamin D ≤23 pg/ml	2.2 (1.0-4.8)	2.2 (0.9-5.0)
Calcaneal bone density (each decrease of 1 SD)	—	1.6 (1.0-2.6)
<b>Vertebral fracture</b>		
Serum estradiol <5 pg/ml	2.7 (1.5-4.7)	2.3 (1.3-4.2)
Serum sex hormone-binding globulin (each increase of 1 µg/dl)	1.6 (1.2-2.3)	1.5 (1.1-2.1)
Serum estrone ≥15 pg/ml	2.0 (1.0-4.2)	2.3 (1.1-4.8)
Calcaneal bone density (each decrease of 1 SD)	—	2.3 (1.5-3.3)

\*All results have been adjusted for age, weight, and the other variables shown in the table. The standard deviation of calcaneal bone density is 0.098 g per square centimeter. CI denotes confidence interval.

†To convert values for estradiol to picomoles per liter, multiply by 3.67; to convert values for sex hormone-binding globulin to nanomoles per liter, multiply by 34.7; to convert values for estrone to picomoles per liter, multiply by 3.7; and to convert values for 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>vitamin D) to picomoles per liter, multiply by 2.4.

a decreased risk of vertebral fracture after adjustment for estradiol concentrations (Table 3).

Women with serum free testosterone concentrations in the lowest quintile (≤0.7 pg per milliliter [2.4 pmol per liter]) had an increased risk of hip fracture (Table 2). However, this factor was no longer significant after adjustment for the serum estradiol concentration (relative risk, 1.2; 95 percent confidence interval, 0.7 to 2.4).

**Serum Vitamin D Concentrations**

Women whose serum concentration of 1,25(OH)<sub>2</sub>-vitamin D was in the lowest quintile (≤23 pg per milliliter [55 pmol per liter]) had a significant increase in the risk of hip fracture (relative risk, 2.1; 95 percent confidence interval, 1.2 to 3.5); there was no further decrease in the risk of hip fracture with higher serum 1,25(OH)<sub>2</sub>vitamin D concentrations. This association remained significant after adjustment for the serum concentrations of estradiol and sex hormone-binding globulin (Table 3); further adjustment for serum creatinine made no appreciable difference (relative risk, 2.3; 95 percent confidence interval, 1.0 to 5.2). There was no significant relation between serum 1,25(OH)<sub>2</sub>vitamin D concentrations and the risk of vertebral fracture (Table 2). There were no statistically significant associations

between serum 25(OH)vitamin D or parathyroid hormone concentrations and the risk of hip or vertebral fracture (Table 2) whether or not these associations were adjusted for the season or for the use or non-use of vitamin D supplements.

#### Adjustment for Bone Density

Adjustment for calcaneal bone density only slightly weakened the association between serum estradiol and sex hormone-binding globulin concentrations and the risk of hip and vertebral fracture (Table 3) and had no substantial effect on the association between serum 1,25(OH)<sub>2</sub>vitamin D concentrations and the risk of hip fracture or between serum estrone concentrations and the risk of vertebral fracture.

### DISCUSSION

We found that women 65 or older who had undetectable serum estradiol concentrations (<5 pg per milliliter) had an increased risk of subsequent hip or vertebral fracture. This association suggests that the risk of fractures in these women could be substantially reduced with even low-dose estrogen-replacement therapy. Standard doses of estrogen in postmenopausal women result in serum concentrations of estradiol that are greater than 40 pg per milliliter (147 pmol per liter).<sup>21</sup> In women treated shortly after menopause, such doses may prevent bone loss more effectively than lower doses,<sup>22,23</sup> but in one trial, low-dose estrogen alone prevented bone loss (without causing endometrial hyperplasia).<sup>24</sup> Less is known about the effects of low-dose estrogen in older women; very low doses of estradiol administered transvaginally significantly increase bone density.<sup>25</sup> There is also a dose-response relation between endogenous serum estradiol concentrations and the risk of breast cancer.<sup>26,27</sup> Thus, maintaining low, but detectable, serum estrogen concentrations might reduce the risk of fracture without increasing the risk of breast and endometrial cancer.

High rates of bone resorption indicate an increased risk of hip fracture that is independent of bone density at the hip,<sup>28</sup> perhaps because small cavities are created that decrease bone strength. The complete absence of estradiol substantially increases rates of resorption<sup>29</sup> and also causes osteocyte death.<sup>30</sup> Osteocytes modulate normal skeletal responses to microscopic bone damage and to strains imposed by weight bearing.<sup>31</sup> Osteocyte death also appears to be a common feature in elderly women who have hip fractures.<sup>32</sup> Thus, low but measurable serum estradiol concentrations may decrease the risk of fracture by decreasing bone resorption or maintaining the viability of osteocytes.

Higher serum concentrations of sex hormone-binding globulin, which binds estradiol and thereby decreases its bioavailability, increase the risk of hip and vertebral fracture. About one quarter of our

cohort had both an undetectable serum estradiol concentration and a serum sex hormone-binding concentration of 1 μg per deciliter or more; this combination indicated a very high risk of fracture.

The association between high serum estrone concentrations and an increased risk of vertebral fracture is surprising, because estrone has effects that are similar to, albeit weaker than, those of estradiol. This result might be a chance finding. However, high serum estrone concentrations also indicate high serum concentrations of 2-hydroxyestrone, an inactive metabolite that inhibits the actions of estradiol.<sup>33</sup> Our results are consistent with the view that vertebral and hip fractures are manifestations of estradiol deficiency<sup>1,2,6,9,34,35</sup> in older, as well as younger, postmenopausal women.<sup>36</sup>

Hip fractures, but not vertebral fractures, were more common among women with relatively low serum 1,25(OH)<sub>2</sub>vitamin D concentrations. We found no association between the serum concentration of parathyroid hormone or 25(OH)vitamin D and the risk of hip or vertebral fracture. The results of retrospective studies of the relation between vitamin D and hip fracture are conflicting.<sup>3,11,37-39</sup> In these studies, however, the serum measurements were made after fracture had occurred, and could have been influenced by trauma, hospitalization, or treatment.

Our study has several limitations. The women were elderly, were ambulatory, and almost all were white. The results are based on a single measurement and may underestimate the true associations between the markers we studied and the risk of fracture. We measured serum total estradiol, not bioavailable estradiol. Despite the large sample, our study had limited power to determine whether uncommon conditions, such as hyperparathyroidism, influenced the risk of fracture. Adjustment for bone density of the hip and spine, rather than the calcaneus, might account for more of the effects of hormones than we estimated.

We conclude that women with serum total estradiol concentrations below 5 pg per milliliter have an increased risk of hip and vertebral fractures. Higher serum concentrations of sex hormone-binding globulin are also associated with a greater risk of these types of fracture. Both effects are independent of bone density. If these associations are causal, they would account for a substantial proportion of the hip and vertebral fractures that occur in elderly white women.

Supported by grants (AG05407, AR35582, AG05394, AR35584, and AR35583) from the Public Health Service.

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