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Total and Free Estrogens and Androgens in Postmenopausal Women with Hip Fractures*

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ABSTRACT. Hip fracture constitutes the most serious complication of postmenopausal osteoporosis. To examine the possible role of circulating estrogen or androgen levels in the development of this type of fracture, 25 patients with hip fractures after minimal trauma were compared to an equal number of controls, matched for age and years since menopause. All were from a retirement community, had intact ovaries, and had not taken estrogen replacement for longer than 3 months during their entire lifetime. Hip fracture patients were found to have a significantly lower ($P = 0.031$) mean (±SE) percent ideal weight (89.4 ± 2.9%) than controls (100.0 ± 2.5%). Sex hormone-binding globulin levels were significantly higher ($P = 0.004$) in patients ($6.7 \pm 0.4 \times 10^{-8}$ M) than in controls ($4.9 \pm 0.3 \times 10^{-8}$ M), resulting in lower concentrations of biologically available estradiol and testosterone. In a subgroup of 12 patients and controls matched for percent ideal weight, differences in sex hormone-binding globulin and free testosterone and estradiol levels were no longer statistically significant; however, the difference in the percentage of free testosterone persisted. These data suggest that endogenous sex steroids in their unbound form may play a role in the pathogenesis of postmenopausal hip fractures. The differences in free hormone levels appeared to be influenced by the differences in mean body size of the 2 groups. This factor is known to have an important negative effect on the concentration of sex hormone-binding globulin. (*J Clin Endocrinol Metab* **54:** 115, 1982)

THE INCREASED incidence of osteoporosis in older women compared to men of the same age (1) and the reduction of bone loss with estrogen (2-5) or androgen administration (6) suggest that sex steroids may play a role in the pathogenesis of this disorder. Attempts have been made to assess the possible role of endogenous estrogen and androgen metabolism in the development of osteoporosis, but results have been inconsistent and occasionally conflicting (7-10).

Hip fracture constitutes the most serious complication of osteoporosis, and its occurrence is associated with appreciable morbidity and mortality (11, 12). A comparison of sex steroid levels found in postmenopausal patients with hip fractures and unafflicted controls has not been reported previously. The present study examines the concentrations of serum androgens and estrogens and their free fractions in postmenopausal women from a retirement community who had or had not sustained a hip fracture. Patients and controls were carefully matched for age and years since menopause.

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Materials and Methods

The subjects in this study were drawn from a retirement community in the Los Angeles area with a population of 20,000 residents. Women in the community have a mean age of 72 yr and comprise 65% of the total population. Residents tend to be of a uniformly high economic status. Cases eligible for study consisted of all women in the community who fractured a hip between February 1974 and September 1979. For 2 women, this represented their second hip fracture. The women chosen for study were postmenopausal, sustained the fracture after minimal trauma, and were still residing in the community at the time the study was conducted. The cases were ascertained by searching the disease indices of the discharge records of the hospital adjacent to the community. This hospital is affiliated with the community and provides the nearest emergency care facility, the next closest facility being more than 15 miles away. Two controls drawn systematically from a complete roster of community residents were matched to each case by date of birth (±1 yr), date of entry into the community (±1 yr), and race. Controls, like cases, had to be postmenopausal, currently residing in the community, and without a previous hip fracture. The patients and controls were then interviewed by a trained medical interviewer regarding their menstrual and reproductive histories, medical histories, certain physical characteristics, smoking and alcohol histories, and detailed usage histories of selected drugs including estrogens, calcium, fluoride, and vi-

tamin supplements. In addition, their medical charts were abstracted from the central medical record file of the community by a trained abstractor.

Based on information obtained from chart abstraction and interview, the patients who had used estrogens for 3 months or less in their lifetime and who had not had their ovaries removed surgically were asked to provide a 10-cc venous blood sample. Twenty-five subjects consented to venipuncture. Blood specimens were collected by a nurse in the homes of the patients in the morning. The time between first hip fracture and specimen collection ranged from 2–85 months. From the interviewed controls, 1 was selected for each of the 25 cases, and was matched to the case for age and years since menopause. Each control also had not used estrogens for more than 3 months in her lifetime, and both of her ovaries were still present. Blood samples were collected from these women in a manner identical to that used for the patients.

The percent ideal weight was used as an index of the subjects' obesity. This was calculated by dividing the actual weight by the ideal weight and multiplying by 100. Ideal weights were obtained from the Metropolitan Life Insurance Tables.

Serum androstenedione (Δ), testosterone (T), estrone (E_1), and estradiol (E_2) levels were measured by previously described RIA techniques (13, 14). Sex hormone-binding globulin (SHBG) levels were measured by a modification of the method of Rosner (15). Percentages of free E_2 and free T were determined by a dialysis-ultracentrifugation method (16). Levels of free steroid were calculated by multiplying the percentages by the respective total levels. The data were analyzed by Wilcoxon signed rank testing. Vitamin, calcium, alcohol, and tobacco use were compared between the two groups by the χ^2 test.

Results

The physical characteristics of each subject as well as the mean (±SE) values observed in the hip fracture patients and their matched controls are summarized in Table 1. In hip fracture patients, values were oriented to the time of fracture. The mean ages in the patients and controls were 75.6 ± 0.8 and 75.8 ± 0.9 yr, respectively. The mean years since menopause were 29.1 ± 1.2 and 27.9 ± 1.3 yr for the same respective subjects. The patients' mean percent ideal weight was 89.4 ± 2.9 and the controls' was 100.0 ± 2.5. This was significantly

TABLE 1. Physical characteristics of 25 postmenopausal women with hip fracture and an equal number of matched controls

Patient no.	Hip fractures					Controls			
	Age (yrs)	yr since menopause	Wt (lbs)	% Ideal wt	Interval from fracture to study (months)	Age (yrs)	yr since menopause	Wt (lbs)	% Ideal wt
1	66	23	102	86	8	65	16	110	90
2	70	17	103	76	32	70	19	156	116
3	70	32	136	95	10	73	30	90	76
4	71	29	105	83	75	75	27	150	105
5	71	32	125	99	14	73	31	109	80
6	73	25	105	88	24	70	20	118	92
7	73	26	110	90	19	75	25	130	109
8	73	29	110	82	59	75	31	140	104
9	74	22	135	92	14	70	22	165	112
10	74	24	102	79	31	72	23	120	95
11	75	21	116	92	85	74	19	110	87
12	76	23	90	67	6	74	22	148	124
13	76	29	138	99	45	78	28	119	94
14	76	31	165	115	20	76	31	142	109
15	77	27	80	58	6	76	24	168	111
16	77	33	115	82	17	75	37	100	94
17	78	27	100	77	4	80	26	135	100
18	78	31	182	115	32	78	32	135	100
19	79	34	101	80	13	78	34	145	115
20	79	34	105	78	10	79	33	131	92
21	80	35	175	110	12	80	33	140	118
22	80	40	112	81	4	83	38	130	91
23	81	32	135	104	2	82	32	113	87
24	81	43	165	109	64	82	40	145	112
25	82	28	125	99	33	81	25	112	87
Mean	75.6	29.1	121.5	89.4	25.6	75.8	27.9	129.4	100.0
±SE	0.8	1.2	5.3	2.9	4.6	0.9	1.3	4.0	2.5

Age of fracture patients was at time of study.

different at the $P = 0.031$ level.

Of the hip fracture patients, 15 had taken or were taking multivitamin preparations, and 6 had used calcium supplements for at least 12 months consecutively. Since the menopause, 11 were current users of cigarettes and 16 used alcohol on a daily or almost daily basis. For the controls the figures were 15, 6, 7, and 13, respectively. No statistically significant differences were found between the 2 groups for these factors.

The mean serum levels of sex steroids are depicted in Fig. 1. For △, the levels (picograms per ml) were 402 ± 35 (hip fractures) and 427 ± 48 (controls), while the T concentrations (picograms per ml) were 183 ± 24 and 269 ± 38 for the same respective women. E_1 levels (picograms per ml) were 29.8 ± 2.3 for the patients and 29.0 ± 2.2 for the controls, while E_2 concentrations (picograms per ml) were 10.6 ± 0.7 and 11.6 ± 0.5, respectively. None of these hormonal differences was significant.

Figure 2 depicts the means and SEs of the levels of total E_2 (picograms per ml), SHBG (10^{-8} M), percent free E_1, and free E_2 (picograms per ml) for both groups. The total E_2 levels are listed above. For SHBG, the level was significantly higher ($P = 0.004$) in the hip fracture (6.7 ± 0.4) than in the control (4.9 ± 0.3) patients. The percent free E_2 levels were 1.54 ± 0.07 and 1.77 ± 0.07, respectively, and this difference was significant at the $P = 0.007$ level. Free E_2 levels were calculated for each subject by multiplying the level of total E_2 by the percentage of free E_2. Free E_2 levels were 0.17 ± 0.01 and

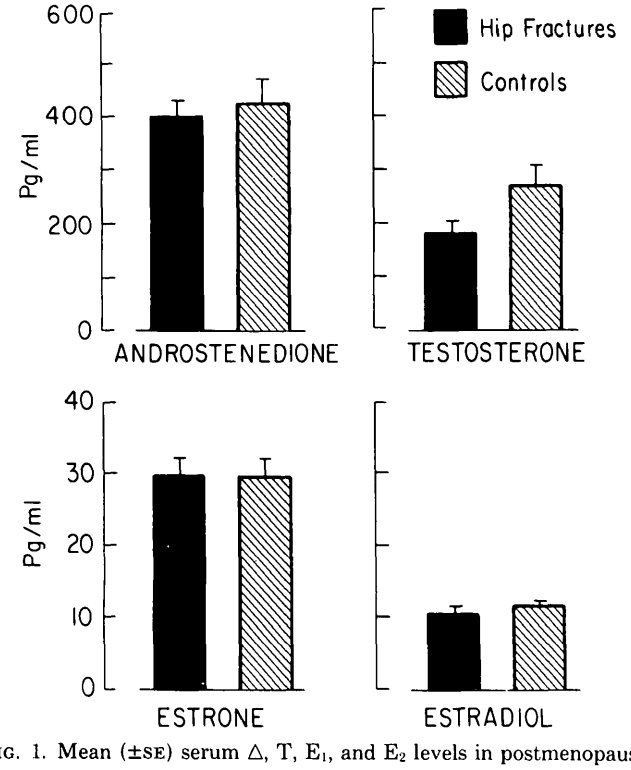

FIG. 1. Mean (±SE) serum △, T, E_1, and E_2 levels in postmenopausal women with a history of hip fracture and in their age-matched controls.

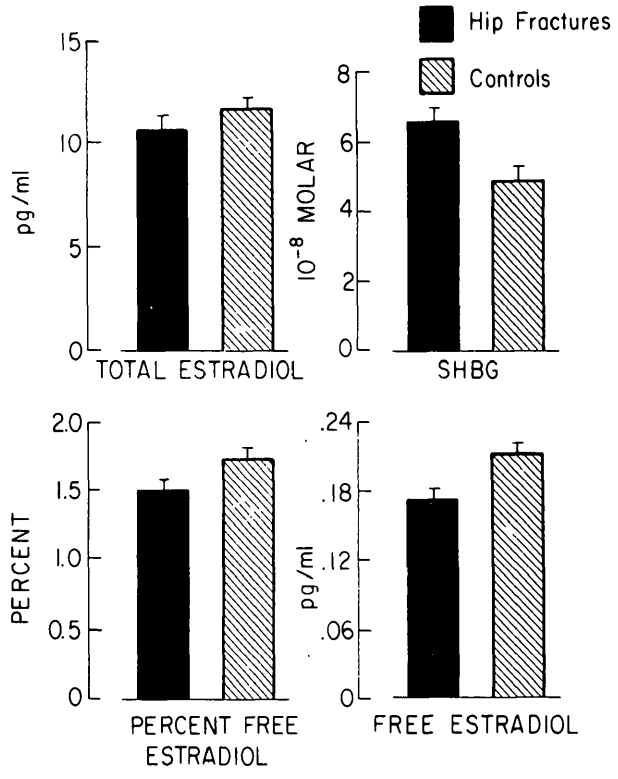

FIG. 2. Serum total, percent free, and free E_2 and SHBG levels in older women with and without a prior hip fracture.

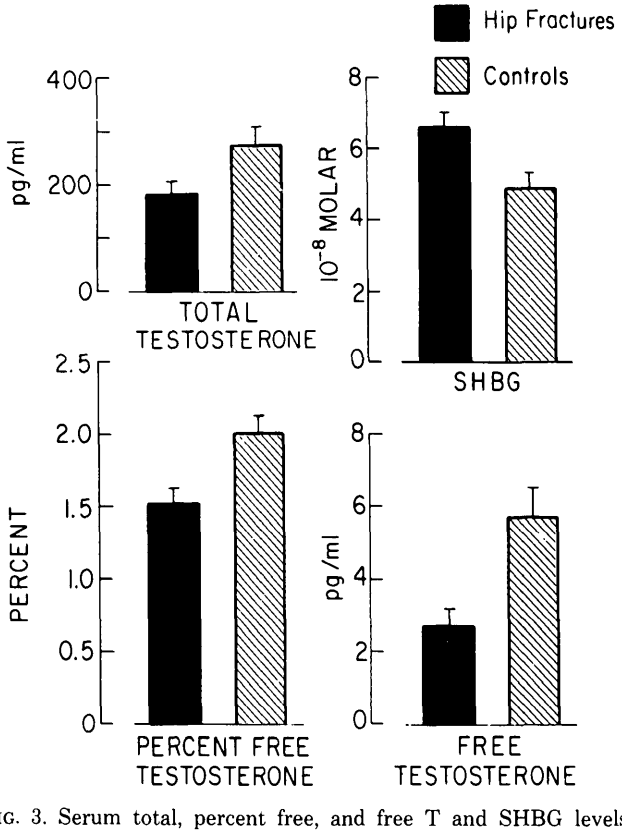

FIG. 3. Serum total, percent free, and free T and SHBG levels in women with and without a hip fracture.

TABLE 2. Mean (±SE) percent ideal weight and hormone levels in hip fracture patients and controls of similar body size

	Patients (n = 12)	Controls (n = 12)	*P*
Ideal wt (%)	96.2 ± 3.9	97.2 ± 3.0	NS
SHBG (10^{-8} M)	5.72 ± 0.54	4.73 ± 0.42	NS
E_2 (pg/ml)	11.4 ± 1.3	10.7 ± 0.6	NS
Dialyzable E_2 (%)	1.61 ± 0.08	1.72 ± 0.08	NS
Free E_2 (pg/ml)	0.19 ± 0.02	0.19 ± 0.02	NS
T (pg/ml)	145.3 ± 16.5	207.8 ± 45.9	NS
Dialyzable T (%)	1.66 ± 0.12	2.01 ± 0.13	0.05
Free T (pg/ml)	2.48 ± 0.34	4.14 ± 0.88	NS

0.21 ± 0.01, respectively, and this difference was also significant at the $P = 0.042$ level.

Figure 3 depicts the mean levels of total T, SHBG, percent free T, and free T (picograms per ml) found in both groups. The total T and SHBG levels are listed above. The percentages of free T were 1.54 ± 0.11 (hip fracture) and 2.02 ± 0.11 (controls), and this difference was significant at the $P = 0.001$ level. The free T levels were 2.67 ± 0.39 and 5.67 ± 0.87, respectively, and this difference was also significant at the $P = 0.019$ level.

The hip fracture patients were studied from 2-85 months after the occurrence of their initial fracture. Total and free levels and percent binding of T and E_2 as well as SHBG levels were correlated with the time interval from injury to study, but a significant association was not observed. Thus, it did not appear that the interval between fracture occurrence and time of study influenced the results.

A subgroup of 12 age-matched pairs of patients and controls whose percent ideal weights were within 15% of each other were then selected from the total group. The mean and SEs of the percent ideal weights of the hip fracture patients and controls were 96.2 ± 3.9 and 97.2 ± 3.0, respectively. The mean and SEs of the hormone and SHBG levels are listed in Table 2. No significant differences in SHBG, total and free E_2 and T, or percent dialyzable E_2 were noted.

In the fracture and control women, levels of total and free steroids and SHBG concentrations were compared between those who used vitamins, calcium, alcohol, or tobacco and those who did not. No differences were found.

Discussion

This study population provided a unique opportunity to examine the role of endogenous estrogens and androgens in the development of osteoporotic hip fractures. Both the cases and controls were identified from the same population pool. They were specially selected to discount the known effects of ovariectomy on hormone levels (17) and estrogen replacement on the occurrence of hip fractures (18). All subjects had both ovaries and had not taken estrogen replacement for longer than 3 months during their lifetimes. Each control was also carefully selected to match a fracture patient for age and years since menopause. The incidence of osteoporotic fractures is known to increase with both, necessitating control of these factors (11, 12, 19). The incidence of osteoporotic fractures also may be influenced by a woman's use of alcohol (20), tobacco (21), calcium (3, 22), fluoride (23), or vitamin supplements (24). The uses of these substances were similar in the patients and controls, and the levels of all hormones were similar in subjects who had or had not been exposed to these substances. Thus, their use did not appear to influence the results of the study. Although the interval from fracture to study varied from 2-85 months, this factor did not seem to influence the findings, since none of the hormonal results correlated with this time interval. Finally, measurements of bone density were not made to establish the degree of osteoporosis in the cases and controls. Studies were limited to those women who sustained the fracture after minimal trauma, such as a fall, and it is well established that bone density is reduced in women suffering from osteoporotic fractures (25).

In comparing the cases to the controls, the patients with fracture were found to be significantly more slender than the unafflicted controls. This result is consistent with earlier observations, in which a relationship of slender body habitus with vertebral crush fractures (21, 26) and the extent of cortical thinning of the radius (27) have been reported. However, not all studies have found an association (28).

Total levels of E_2, E_1, Δ, and T were similar in the hip fracture and control subjects. Previously, several groups of investigators have compared total levels of estrogens and androgens measured in postmenopausal women with or without osteoporotic fractures (7, 8) or in women who were found to be losing bone either at a rapid or slow rate (9, 10). The majority of these studies also have not observed differences in total sex steroid levels.

The women with hip fractures had higher levels of SHBG and lower concentrations of free E_1 and T than the age-matched controls. These differences were apparently influenced by the difference in the mean body size of the two groups, since the magnitude of the differences in SHBG and free E_1 and T levels were reduced in patients and controls of a comparable body size. The borderline significant differences ($P = 0.05$) of percent free T were probably incidental, since differences in SHBG and free T were not found. These findings are consistent with prior observations that in postmenopausal women, SHBG levels show negative correlations, and free E_2 and T show positive correlations with body weight and percent ideal weight (29-32).

There are several lines of evidence suggesting that endogenous estrogen can influence the rate of bone resorption and the occurrence of osteoporotic fractures. These include the demonstration of accelerated reduction of bone density after the menopause (19), the maintenance of bone density in older women taking estrogen replacement (2-5), and a lower incidence of estrogen usage in older women with hip fractures (18).

The mechanism by which estrogens affect bone metabolism is not understood. This action may not be direct, since estrogen receptors have not been identified in bone (33, 34). There are at least two possible indirect mechanisms that could explain the action of estrogen on bone. First, estrogen may act by regulating 25-hydroxycholecalciferol-1-hydroxylase activity in the kidney, thus modifying the endogenous synthesis of 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D (35). Second, estrogen may enhance calcitonin secretion, a potent inhibitor of bone resorption. Shamonki *et al.* (36) observed a lower response of circulating calcitonin to calcium challenge in older compared to younger women. MacIntyre (37) reported increased basal levels of calcitonin in women on birth control pills, and Morimoto *et al.* (38) observed increased secretion of calcitonin after a calcium infusion in postmenopausal women given estrogen. Further studies are needed to clearly define the action of estrogen on bone.

There are several lines of evidence that suggest that endogenous T may also influence the rate of occurrence of osteoporotic fractures. It is well recognized that men have a much lower incidence of osteoporotic fractures than women (1, 39) and fractures of this type are more common in hypogonadal males (40). T replacement has also been shown to improve bone metabolism in a hypogonadal man with osteoporosis (6).

T could influence bone metabolism through several possible mechanisms. It could have direct effects on bone metabolism through androgen receptors, but their presence in bone has not been evaluated. A direct action of T on bone is plausible, since Schweikert *et al.* (41) have shown conversion of T to dihydrotestosterone in ground spongiosa of bone. T could also influence bone metabolism through peripheral conversion to E_2. The recent demonstration of the aromatization of 19-hydroxyandrostenedione by human fatty marrow (42) suggests that this type of conversion occurs not only at sites which are at a distance from bone, *i.e.* adipose cells (43), liver (44), *etc.*, but actually within bone itself.

Finally, T could alter bone metabolism indirectly by altering factors which influence skeletal metabolism. Deftos *et al.* (45), reported that calcitonin responses to an iv calcium challenge were greater in men than women during all decades from age 20 to 80 yr. Hollo *et al.* (46) have also observed lowered sensitivity of bone to calcitonin in patients with androgen deficiency; this lowered sensitivity could be reversed with the administration of androgens.

In summary, the physical characteristics and total and free androgen and estrogen levels were compared between women who had sustained a hip fracture and age-matched controls. The fracture patients were found to have significantly higher levels of SHBG coupled with lower concentrations of free E_2 and T than the control subjects. These differences in SHBG and free hormone levels were apparently influenced by the difference in mean body size of the two groups. These results suggest that the levels of free or available estrogen and androgen may influence the occurrence of osteoporotic hip fractures in older women.

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