GYNECOLOGY

Physical characteristics and sex hormone levels in patients with osteoporotic hip fractures or endometrial cancer

LARRY R. LAUFER, M.D.
BERT J. DAVIDSON, M.D.
RONALD K. ROSS, M.D.
LEO D. LAGASSE, M.D.
PENTTI K. SIITERI, PH.D.
HOWARD L. JUDD, M.D.
Los Angeles and San Francisco, California

Comparisons were made of the physical characteristics and the sex hormone levels of 50 postmenopausal women, half of whom had sustained an osteoporotic hip fracture while the remainder had developed endometrial carcinoma. None of the patients had received estrogen replacement therapy for longer than 3 months during their lifetime. At the time of injury hip fracture patients were found to be lighter (121 ± 5 versus 167 ± 9 pounds) and older (73.4 ± 1.0 versus 62.6 ± 1.7 years) than the cancer patients at the time of diagnosis. Estrone, estradiol, percentage of free estradiol, and free estradiol levels were significantly lower in the hip fracture patients than in subjects with endometrial cancer, while sex hormone–binding globulin levels were significantly higher in the former group. Androstenedione and testosterone levels were similar. Previous studies have shown that the incidence of both lesions is influenced by body size. These data suggest that body size may exert this influence through alteration of endogenous estrogen metabolism with hip fracture patients having lower concentrations and endometrial cancer patients having higher concentrations of endogenous estrogens. (AM. J. OBSTET. GYNECOL. 145:585, 1983.)

From the Department of Obstetrics and Gynecology, University of California (Los Angeles), the Department of Family and Preventive Medicine, the University of Southern California, and the Department of Obstetrics, Gynecology and Reproductive Sciences, University of California (San Francisco).

This work was supported in part by United States Public Health Service Grants Ca-23093, Ca-27702, Ca-17054, and Ca-00652.

Received for publication June 3, 1982.

Revised July 29, 1982.

Accepted September 3, 1982.

Reprint requests: Howard L. Judd, M.D., UCLA School of Medicine, Department of Obstetrics and Gynecology, University of California, Los Angeles, California 90024.

OSTEOPOROTIC HIP FRACTURES and endometrial carcinoma are two illnesses that afflict women with increasing frequency after the menopause. The observations that exogenous estrogen administration retards the development of osteoporosis[1–3] while enhancing the risk of occurrence of endometrial carcinoma[4–6] have raised the possibility that endogenous estrogen metabolism may also influence the risk of both diseases.

This possibility becomes more attractive with the findings that the body size of the older woman has a positive correlation with circulating estrone and estradiol levels[7] and also influences the rate of occurrence of both conditions.[8, 9]

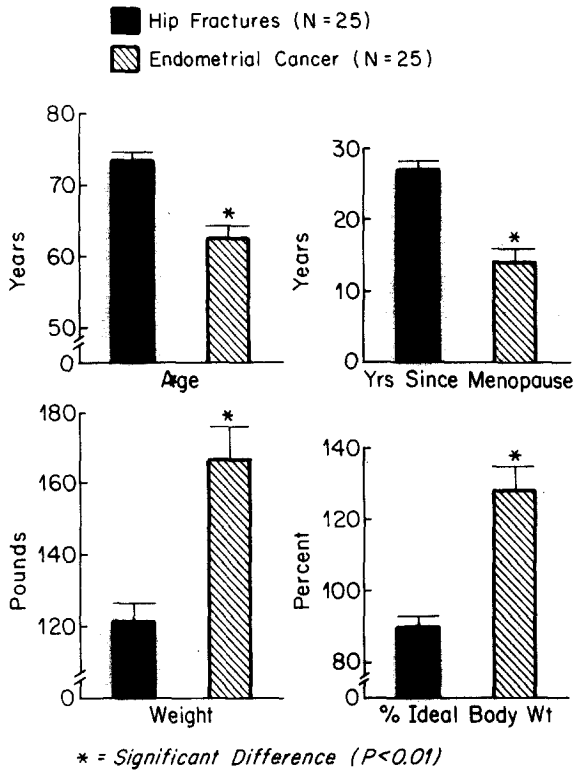

Fig. 1. Age, years since menopause, weight, and percentage of ideal body weight (mean ± SE) in 25 postmenopausal women with a history of hip fracture and a similar number of women with endometrial carcinoma.

The present study was undertaken to compare the physical characteristics and circulating sex steroid levels in 25 postmenopausal women who had sustained a hip fracture following minimal trauma and an equal number of older subjects who had developed endometrial cancer. The potential influence of exogenous estrogen administration on the occurrence of each disease was excluded by limiting the study to subjects who had not used the medication.

Material and methods

Osteoporotic hip fracture patients were selected from an upper socioeconomic class, retirement community in southern California. Cases eligible for study consisted of all women in the community who sustained a hip fracture involving minimal trauma between February, 1974, and September, 1979. The women chosen for study were postmenopausal, resided in the community at the time of the study, and consented to the study. The cases were ascertained by examination of the disease indices of the discharge records from the hospital adjacent to the community. This hospital is affiliated with the community and provides the nearest emergency care facility.

The patients were then interviewed by a trained medical interviewer regarding menstrual and reproductive histories, medical histories, certain physical characteristics, smoking and alcohol histories, and detailed usage histories of selected rugs, including estrogens. In addition, their medical histories were abstracted from the central medical record file of the community by a trained abstractor. On the basis of the information obtained, 25 subjects were chosen for study. All were Caucasian.

Endometrial cancer patients were postmenopausal women and were found to have endometrial adenocarcinoma at dilatation and curettage at UCLA or City of Hope Hospitals in Los Angeles from July 1, 1977, to June 30, 1981. Patients who consented to take part were studied at least 2 weeks after diagnostic dilatation and currettage but before definitive therapy for the tumor. Twenty-five patients were chosen for study, 23 of whom were Caucasian and two of whom were Mexican-American.

All patients selected for study were menopausal for at least 6 months, had used exogenous estrogen replacement for less than 3 months in their entire life, and had intact ovaries.

A single blood sample was obtained from the hip fracture patients by a nurse in the home between 0800 and 1000 hours. The interval between hip fracture and specimen collection ranged from 3 to 64 months. For the endometrial cancer patients, 10 ml blood samples were drawn at 15-minute intervals four times beginning at 0800 hours for 2 consecutive days.

Serum androstenedione, testosterone, estrone, and estradiol levels were measured on all samples by previously described radioimmunoassay techniques.[10, 11] Sex hormone–binding globulin levels were measured by a modification of the technique of Rosner.[12] Percentages of free estradiol were determined by a dialysis-ultracentrifugation method.[13] Free estradiol levels were calculated by multiplying the free percentage by the total estradiol level of each patient. Total hormone levels were measured on all samples drawn from the cancer patients and the mean measurement was used as the value for that subject. For all other parameters a single measurement was made for each subject. Values observed in the hip fracture patients have been reported previously. The data were analyzed by the double-tailed Student's t test.

Results

The physical characteristics of the subjects are depicted in Fig. 1. The mean values (±SE) of the hip fracture and cancer patients, respectively, were as follows: age, 73.4 ± 1.0 versus 62.6 ± 1.7 years; length of time since menopause, 26.9 ± 1.3 versus 14.2 ± 1.8

years; weight, 121.5 ± 5.3 versus 167.1 ± 8.8 pounds; and percentage of ideal weight, 89.4 ± 2.9 versus 128.3 ± 6.9. This last parameter was calculated by dividing a patient's actual weight by her ideal weight obtained from the Metropolitan Life Insurance tables and multiplying by 100. The differences in body size were highly significant at the $P < 0.001$ level.

Fig. 2 depicts the means and standard errors of the serum hormone levels. For androstenedione the levels were 401.6 ± 34.8 (hip fracture) and 481.4 ± 57.4 (cancer) pg/ml, while testosterone concentrations were 183.3 ± 24.4 (hip fracture) and 233.6 ± 24.0 (cancer) pg/ml. These concentrations were not different statistically.

Estrogen levels were as follows: estrone, 29.8 ± 2.3 (hip fracture) versus 42.9 ± 3.4 (cancer) pg/ml; estradiol, 10.6 ± 0.7 (hip fracture) versus 16.9 ± 1.7 (cancer) pg/ml. These were both highly significant differences ($P < 0.005$ and $P < 0.001$, respectively).

Fig. 3 shows the means and standard errors of the levels of total estradiol (picograms per milliliter), sex hormone–binding globulin (10^{-8}M), percentage of free estradiol, and free estradiol (picograms per milliliter). Total estradiol levels are listed above. Sex hormone–binding globulin levels were significantly higher ($P < 0.005$) in hip fracture (6.7 ± 0.4) than in cancer (4.6 ± 0.5) patients. The percentages of free estradiol were 1.5 ± 0.1 and 2.4 ± 0.1 in the same respective subjects. This difference was significant at the $P < 0.0001$ level. Free estradiol levels were 0.2 ± 0.01 (hip fracture) and 0.5 ± 0.1 (cancer) picograms per milliliter and this difference was also significant at the $P < 0.0001$ level.

The hip fracture patients were studied from 3 to 64 months after the occurrence of the fracture. All hormonal parameters were correlated with the time interval from injury to study, and no significant association was observed. Thus, it did not appear that the interval between fracture occurrence and the time of study influenced the results.

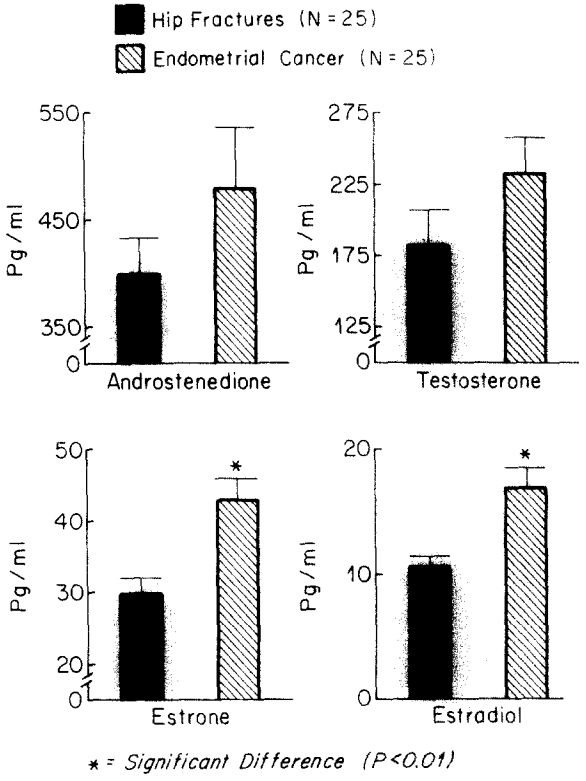

Fig. 2. Serum androstenedione, testosterone, estrone, and estradiol levels in postmenopausal women with a prior hip fracture or with endometrial carcinoma.

Comment

The women in this study provided a unique opportunity to view the physical characteristics and endogenous sex steroid levels of patients with two diseases that are apparently estrogen related. Since all the subjects had intact ovaries and none had used estrogen replacement therapy for more than 3 months, we were able to discount the extraneous effects of ovariectomy on hormone levels[14] and the influence of estrogen replacement on the occurrence of each disease.[1–6]

The hip fracture patients were found to be of advanced age (mean, 73.4 years) at the time of fracture, in keeping with results of previous series.[15–17] In contrast, the patients with endometrial cancer were younger (mean, 62.6 years). This mean age was similar to the average age of incidence of 56 to 60 years for previously reported series of endometrial cancer patients,[18, 19] which included some premenopausal individuals and patients receiving estrogen replacement. Although the difference of age between the two groups of subjects could potentially account for their differences in estrogen levels, this possibility is unlikely. Previous studies have shown conflicting findings in postmenopausal women of a lack of change of estradiol[20] or an increases[21] or a decrease of estradiol[22] but no change of estrone levels[20–22] with aging. The largest series to address this issue reported no change with age of either estradiol or estrone levels in 155 postmenopausal women or when the data were reexamined with exclusion of subjects with extremes of body size.[23] The exclusive source of estrone in postmenopausal women is from the peripheral conversion of androstenedione.[24, 25] In turn, estrone is converted peripherally to estradiol.[26] Hemsell and associates[27] reported a positive correlation of androstenedione to estrone conversion with age in 23 women aged 19 to 73 years. Although it has been difficult to identify this increase of peripheral aromatization with age by measuring circulating estrogen

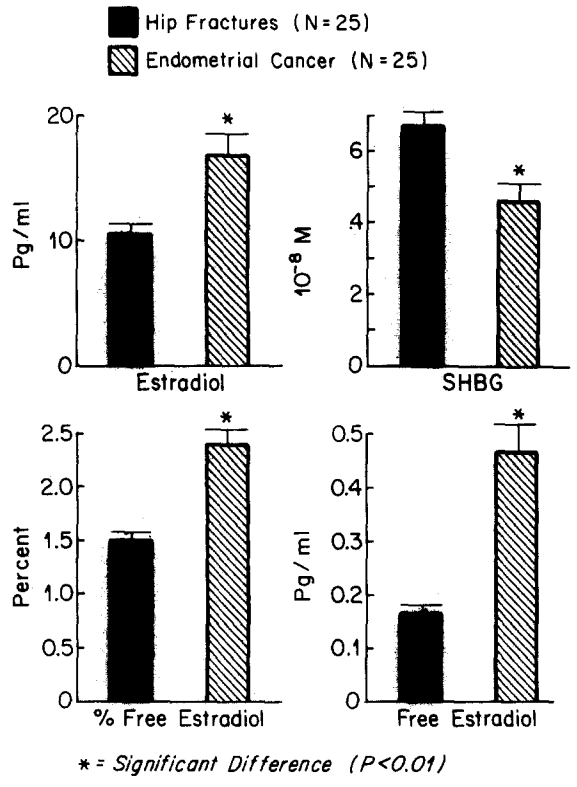

Fig. 3. Serum total estradiol, sex hormone–binding globulin, percentage of free estradiol, and free estradiol in postmenopausal women with hip fracture or endometrial carcinoma.

levels, it is unlikely that the higher conversion of androstenedione to estrone with age could have accounted for the differences of estrogen levels between the hip fracture and endometrial cancer patients since the older group (hip fracture) had the lower levels of circulating estrogens.

A more likely possibility to account for the estrogen difference was the body size of the two groups. The hip fracture patients were considerably lighter than the women with endometrial cancer. The slender body size (mean ideal body weight, 89.4%) of the former group was consistent with the previously reported increased vulnerability of thin women to symptomatic osteoporosis.[8] The relative obesity of the cancer patients (mean ideal body, 128%) also corresponded to the widely acknowledged increased risk of this disease in obese women.[9]

The issue of body size is of central importance in regard to the possible role that endogenous estrogens play in the development of these two diseases. In postmenopausal women estrone and estradiol levels show positive correlations with increasing body weight.[7] This results from enhanced peripheral aromatization of circulating androstenedione, a process that correlates positively with body size.[24, 25] Body size also correlates inversely with the level of sex hormone–binding globulin, a plasma protein that binds circulating estradiol.[28] Currently, it is believed that the fraction of estradiol bound to this plasma protein is not available for cellular actions of many tissues.[28]

In the hip fracture patients, the mean levels of total estrone and estradiol and free estradiol were significantly lower, while the average concentration of sex hormone–binding globulin was significantly higher than the value observed in the patients with endometrial cancer. Thus, the hip fracture patients were at a dual risk in regard to the possible protective effect of circulating estrogens on bone metabolism. They had lower total levels of estrone and estradiol and proportionally lower free estradiol levels because of increased sex hormone–binding globulin concentrations. Conversely, the patients with endometrial cancer were at a dual risk for the action of circulating estrogens on endometrial cells, having higher total estrone and estradiol concentrations and proportionately greater bioavailable estradiol because of reduced sex hormone–binding globulin levels. The high levels of estrone and estradiol in the cancer patients presumably reflected enhanced peripheral aromatization of circulating androstenedione since the mean levels of this androgen were similar in the two groups. The rate of peripheral aromatization can be estimated by calculating the ratio of circulating estrone to androstenedione, since this mechanism is the major source of circulating estrone in postmenopausal women and the metabolic clearance rates of these two hormones are similar.[29, 30] The higher mean ratio of estrone to androstenedione in the cancer patients $\left(\frac{42.9\ \text{pg/ml}}{481.4\ \text{pg/ml}} = 0.089\right)$ than in the hip fracture patients $\left(\frac{29.8\ \text{pg/ml}}{401.6\ \text{pg/ml}} = 0.074\right)$ supports the concept of a higher level of peripheral aromatization in the cancer patients.

The possible role of endogenous sex steroids in the development of osteoporotic fractures has been examined by several groups of investigators, and the findings of these studies have been inconsistent.[31, 32] A majority of these studies have been troubled by several limitations, including inadequate hormone assays to quantitate estrogen levels in the circulation of postmenopausal women, disregard of ovarian status of the subjects studied, and lack of attention to the issue of previous estrogen usage in case and control subjects.

The possible role of endogenous sex steroids in the development of endometrial cancer also has been examined and a consensus has developed. In studies in which the control subjects were not matched to the

cancer patients for body size, increased levels of estrone and estradiol and enhanced conversion rates of androstenedione to estrone have been reported in the cancer patients, presumably because of greater obesity.[25] In series in which the control subjects were matched to the cancer patients for body size, similar levels of circulating total and free estrogens and conversion rates of androstenedione to estrone have been reported.[7, 24] These latter findings indicate that there is nothing unique about circulating estrogens in patients with endometrial cancer in comparison to women not having cancer of the same body size.

Previous studies of patients with endometrial cancer have also ignored the issue of prior estrogen usage. This variable is of importance since several groups of investigators have observed estrogen usage to be more prevalent in slender women than in obese subjects with this disease.[4–7] Thus, inclusion into a study of patients with endometrial cancer who were prior estrogen users distorts the findings by underestimating the body size of patients with tumor who had not used the medication.

In summary, comparisons of the physical characteristics and sex steroid levels were made between postmenopausal women with osteoporotic hip fractures and those with endometrial cancer. The data obtained support the concept that body size may influence the occurrence of these diseases through its effect on endogenous sex steroid metabolism. Although these findings do not prove a relationship of causality, they do support such a hypothesis.

We thank Ms. M. Obnial and Ms. M. A. Lu for their expert technical assistance and Ms. M. Greenstein for her expertise.

REFERENCES

1. Lindsay, R., Hart, D. M., Aitken, J., MacDonald, E. B., Anderson, J. B., and Clarke, A. C.: Long-term prevention of postmenopausal osteoporosis by oestrogen, Lancet **1**:1038, 1976.
2. Recker, R. R., Saville, P. D., Heany, R. P.: Effect of estrogens and calcium carbonate on bone loss in postmenopausal women, Ann. Intern. Med. **87**:649, 1977.
3. Horsman, A., Gallagher, J. C., and Simpson, M.: Prospective trial of oestrogen and calcium in postmenopausal women, Br. Med. J. **2**:789, 1977.
4. Smith, D. C., Prentice, R., Thompson, D. J., Herrmann, W. L.: Association of exogenous estrogen and endometrial carcinoma, N. Engl. J. Med. **293**:1164, 1975.
5. Mack, T. M., Pike, M. C., and Henderson, B. E.: Estrogens and endometrial cancer in a retirement community, N. Engl. J. Med. **294**:1262, 1976.
6. McDonald, T. W., Annegers, J. F., and O'Fallon, W. M.: Exogenous estrogen and endometrial carcinoma: case-control and incidence study, Am. J. Obstet. Gynecol. **127**:572, 1977.
7. Judd, H. L., Davidson, B. J., Frumar, A. M., Shamonki, I. M., Lagasse, L. D., and Balloon, S. C.: Serum androgens and estrogens in postmenopausal women with and without endometrial cancer, Am. J. Obstet. Gynecol. **136**:859, 1980.
8. Daniell, H. W.: Osteoporosis of the slender smoker, Arch. Intern. Med. **136**:298, 1976.
9. Elwood, J. M., Cole, P., and Rothman, K.: Epidemiology of endometrial cancer, JNCI **59**:1055, 1977.
10. DeVane, G. W., Czekala, N., Judd, H. L., and Yen, S. S. C.: Circulating gonadotropins, estrogens, and androgens in polycystic ovarian disease, Am. J. Obstet. Gynecol. **121**: 496, 1975.
11. Anderson, D. C., Hopper, B. R., Lasley, B. L., and Yen, S. S. C.: A simple method for the assay of eight steroids in a small volume of plasma, Steroids **28**:179, 1976.
12. Rosner, W.: A simplified method for the quantitative determination of testosterone-estradiol-binding activity in human plasma, J. Clin. Endocrinol. Metab. **34**:983, 1972.
13. Hammond, G. L., Nisker, J. A., Jones, L. A., and Siiteri, P. K.: Estimation of percent free steroid in undiluted serum by centrifugal ultrafiltration-dialysis, J. Biol. Chem. **255**:502, 1980.
14. Judd, H. L., Lucas, W. E., and Yen, S. S. C.: The effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer, Am. J. Obstet. Gynecol. **118**:193, 1974.
15. Horowitz, B. G.: Retrospective analysis of hip fractures, Surg. Gynecol. Obstet. **123**:565, 1966.
16. Fitts, M. T., Lehr, H. B., and Schor, S.: Life expectancy after fracture of the hip, Surg. Gynecol. Obstet. **108**:7, 1959.
17. Murray, D. B., and Young, S.: Fractures of the femoral neck; review of management and results, Lancet **1**:597, 1957.
18. Malkasian, G. D., McDonald, T. W., and Pratt, J. H.: Carcinoma of the endometrium: the Mayo Clinic experience, Mayo Clin. Proc. **52**:175, 1977.
19. Schenker, J. G., and Tal, J.: Adenocarcinoma of the endometrium in Israel, 1960-1968, Cancer **46**:2752, 1980.
20. Longcope, C.: Steroid production in pre and postmenopausal women, *in* Greenblatt, R. B., Mahesh, V. B., and McDonough, P. G., editors: The Menopausal Syndrome, New York, 1974, Medcom Press, pp. 6-11.
21. Chakravarti, S., Collins, W. P., Forecast, T. D., Newton, J. R., Oram, D. H., and Studd, J. W. W.: Hormone profile after the menopause, Br. Med. J. **2**:784, 1976.
22. Vermeulen, A., and Verdonck, L.: Sex hormone concentrations in postmenopausal women, Clin. Endocrinol. **9**:59, 1978.
23. Meldrum, D. R., Davidson, B. J., Tataryn, I. V., and Judd, H. L.: Changes in circulating steroids with aging in postmenopausal women, Obstet. Gynecol. **57**:624, 1981.
24. MacDonald, P. C., Edman, C. D., Hemsell, D. L., Porter, J. C., and Siiteri, P. K.: Effect of obesity on conversion of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer, Am. J. Obstet. Gynecol. **130**:448, 1978.
25. Siiteri, P. K., and MacDonald, P. C.: Role of extraglandular estrogen in human endocrinology, *in* Greep, R. O., Astwood, E. B., editors: Handbook of Physiology, Washington, D. C., 1973, vol. 2, American Physiology Society, p. 615.
26. Judd, H. L., Shamonki, I. M., Frumar, A. M., and

Lagasse, L. D.: Origin of serum estradiol in postmenopausal women, Obstet. Gynecol. In press.
27. Hemsell, D. L., Grodin, J. M., Brenner, P. F., Siiteri, P. K., and MacDonald, P. C.: Plasma precursors of estrogen. II. Correlation of the extent of conversion of plasma androstenedione to estrone with age, J. Clin. Endocrinol. Metab. **38**:476. 1974.
28. Pardridge, W. *I.*: Transport of protein-bound hormones into tissue *in vivo,* Endocrinol. Rev. **2**:103, 1981.
29. Longcope, C., Layne, D. S., and Tait, J. F.: Metabolic clearance rate and interconversion of estrone and 17β-estradiol in normal males and females, J. Clin. Invest. **47**:93, 1968.
30. Horton, R., and Tait, J. F.: Androstenedione production and interconversion rates measured in peripheral blood and studies on the possible site of its conversion to testosterone, J. Clin. Invest. **45**:301, 1966.
31. Riggs, B. L., Ryan, R. J., Wahner, H. W., Jiang, N., and Mattox, V. R.: Serum concentrations of estrogen, testosterone, and gonadotropins in osteoporotic and nonosteporotic postmenopausal women, J. Clin. Endocrinol. Metab. **36**:1097, 1973.
32. Marshall, D. H., Crilly, R. B., and Nordin, B. E. C.: Plasma androstenedione and oestrone levels in normal and osteoporotic postmenopausal women, Br. Med. J. **2**:1177, 1977.