Hormonal status in normal, osteoporotic and corticosteroid-treated postmenopausal women[1]

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In previous publications (Gallagher, Aaron, Horsman, Marshall *et al.* 1973, Nordin *et al.* 1975) we have reported a low vaginal smear maturation value in osteoporotic postmenopausal women, and have suggested that these patients are more 'oestrogen deficient' than the normal postmenopausal population. In this paper we report low plasma androstenedione and oestrone levels in osteoporotic women. Even lower values are found in postmenopausal women on corticosteroid therapy and we suggest that this may be a factor in the genesis of corticosteroid osteoporosis.

Methodology

Morning blood samples from fasting subjects were taken into heparinized tubes and the plasma separated and deep-frozen for subsequent assay. The androstenedione and oestrone assays were performed on ether extracts of 0.1 ml of plasma for the androstenedione assay and 0.5 ml of plasma for the oestrone assay using standard radioimmunoassay techniques with antisera supplied by Miles Laboratories. Details of the procedure have been described elsewhere (Pelc *et al.* 1978). For the testosterone assay, 0.1 ml of plasma was extracted in ether and the radioimmunoassay performed with locally-produced antisera raised to the bovine serum albumin conjugate of testosterone, 3-Oxine.

Hydroxyproline excretion was assessed by the hydroxyproline/creatinine ratio in the fasting urine as described by Nordin *et al.* (1976). Hydroxyproline and creatinine were measured in the urine by standard Auto-Analyzer techniques (Hodgkinson & Knowles 1976).

The normal and osteoporotic subjects were postmenopausal women presenting with backache in whom lateral thoracic and lumbar spine X-rays had been obtained and subjected to vertebral morphometry as described by Horsman (1976). In this procedure a wedged vertebra scores one point and a crushed vertebra 2 points, and patients are regarded as osteoporotic if the vertebral 'score' is 5 or more. The data presented in the present paper are based on observations from 18 normal subjects and 18 osteoporotic patients defined in this way and matched for years since menopause.

The 18 corticosteroid-treated subjects were postmenopausal women, all but 4 of them with vertebral fractures. The mean ages of the three groups of women and the mean years elapsed since menopause are given in Table 1.

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Table 1. Mean ages and years since menopause in normal osteoporotic and corticosteroid-treated women

Group	No.	Mean age (years)	Mean years since menopause
Normal	18	55.3 (42–69)	9.2 (2–20)
Osteoporotic	18	58.1 (52–68)	9.2 (2–20)
Corticosteroid-treated	18	64.9 (53–74)	16.1 (4–28)

Results

The plasma androstenedione levels in the normal, osteoporotic and corticosteroid-treated cases are shown in Figure 1. The mean value in the osteoporotics is significantly lower than in the controls and the mean value in the corticosteroid-treated cases is significantly lower than the osteoporotics.

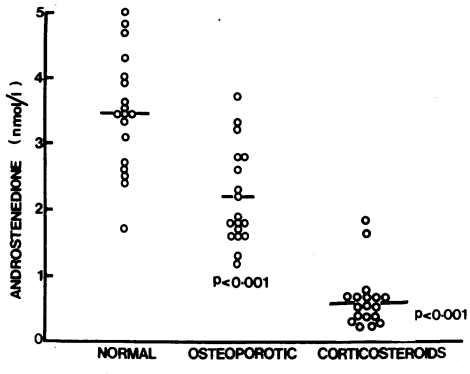

Figure 1. Plasma androstenedione levels in normal and osteoporotic postmenopausal women matched for years since menopause, and in a group of corticosteroid-treated postmenopausal women. The significance values refer to the difference between each patient group and the normal controls

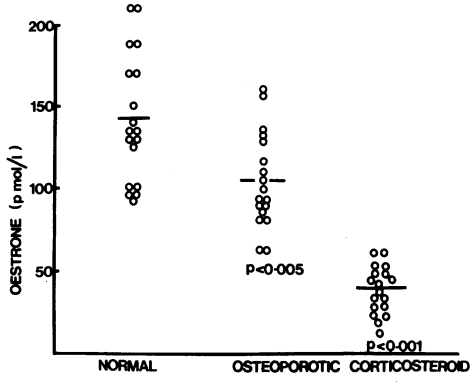

Figure 2. Plasma oestrone levels in the same subjects as Figure 1

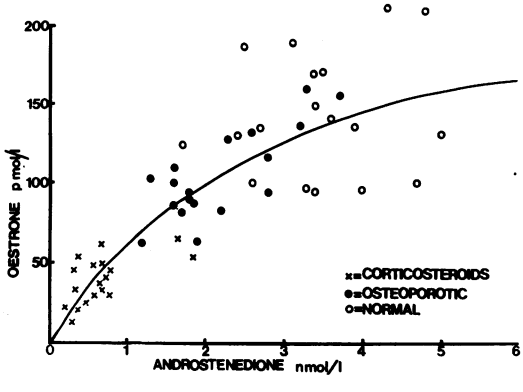

Figure 3. The relation between plasma androstenedione and oestrone levels in the same patients as Figure 1

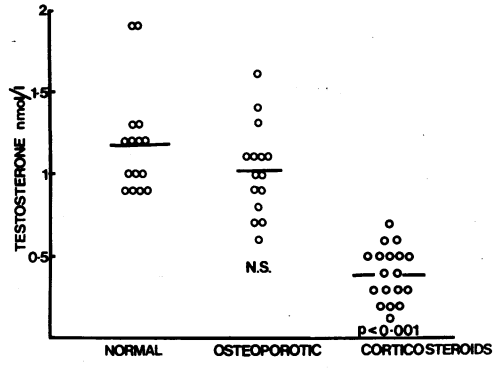

Figure 4. Plasma testosterone levels in 15 of the matched normal and osteoporotic pairs from Figure 1 and in the 18 corticosteroid-treated cases

Plasma oestrone levels in the same three groups are shown in Figure 2. The mean plasma oestrone is significantly lower in the osteoporotic than the normal subjects and significantly lower in the corticosteroid-treated cases than in the osteoporotics.

The relation between the oestrone and androstenedione values in these three groups of cases is shown in Figure 3. The data fall around the curvilinear relationship between plasma androstenedione and plasma oestrone (Pelc *et al.* 1978).

The plasma testosterone values in 15 of the normal and osteoporotic subjects in whom they are available and in the 18 corticosteroid-treated cases, are shown in Figure 4. The difference between the normal and osteoporotic subjects is not significant but the mean value in the corticosteroid group is significantly reduced.

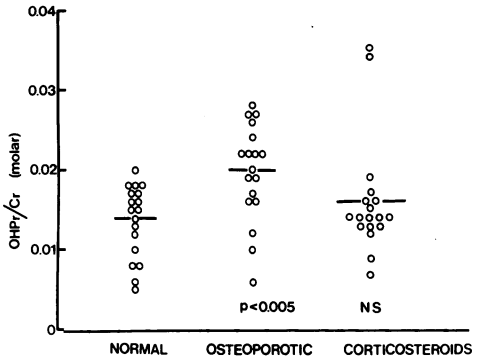

Figure 5. Fasting urinary hydroxyproline/creatinine ratios in the same cases as Figure 1.

The urinary hydroxyproline data are shown in Figure 5. The mean hydroxyproline/creatinine ratio is significantly higher in the osteoporotic than the normal subjects; the mean value in the corticosteroid-treated cases is intermediate between the two.

Discussion

Our data tend to confirm our previous suggestion that osteoporotic postmenopausal women are more 'oestrogen deficient' than normal postmenopausal women. (These observations do not agree with those of Bartizal *et al.* (1976) who reported no difference in total serum oestrogen as between osteoporotic and nonosteoporotic postmenopausal women.) Since androstenedione is the principal source of oestrone in postmenopausal women, it is likely that this reduced plasma oestrone level in osteoporosis is secondary to the low plasma androstenedione level. Whether these in turn are the result of reduced ovarian stromal secretion (Vermeulen 1976) or reduced adrenal secretion of androstenedione, remains to be established. It is interesting to note in this connection that although the mean plasma testosterone level is slightly reduced in the osteoporotic subjects, the difference between the two groups is not significant. However, there is a very marked reduction in plasma testosterone level in the corticosteroid-treated cases.

We regard the low plasma oestrone level in osteoporosis as a risk factor, since osteoporosis is almost certainly a multifactorial disease in which many risk factors operate. A low plasma oestrone level is an important risk factor because it apparently makes the bone particularly vulnerable to resorption by parathyroid hormone and/or $1,25(OH)_2D_3$. It therefore seems logical to suggest that the very low plasma oestrone levels in postmenopausal women on corticosteroid therapy, which are of course secondary to pituitary suppression and consequent low androstenedione levels, may explain why postmenopausal women are so particularly prone to corticosteroid-induced osteoporosis. Whether the androstenedione level is of any importance in its own right or simply as a precursor of oestrone we do not know. Although the

corticosteroid-treated cases are older and further from the menopause than the other two groups, these differences cannot possibly explain their extremely low hormone levels which are very abnormal for women of any age.

The malabsorption of calcium in osteoporosis which we (Gallagher, Aaron, Horsman, Marshall *et al.* 1973) and others (Saville 1973) have previously reported, represents another risk factor and is probably due to a reduced plasma $1,25(OH)_2D_3$ level (Gallagher *et al.* 1976). Corticosteroid-treated cases are also exposed to this additional risk factor, though not necessarily for the same reason, and we have previously reported (Gallagher, Aaron, Horsman, Wilkinson & Nordin 1973) that it is the corticosteroid-treated cases with osteoporosis which have the lowest calcium absorption rates.

The raised hydroxyproline excretion in the osteoporotic cases reflects their increased rate of bone resorption (Nordin *et al.* 1975). However, although the corticosteroid-treated group includes many osteoporotic subjects, their hydroxyproline excretion is not as high as it is in the osteoporotic group. The explanation is that bone can be lost at many different rates of bone turnover. Hydroxyproline excretion reflects total bone resorption rate but is only a function of bone balance if the bone formation rate is held constant. In patients on corticosteroid therapy, the bone formation rate is low (Crilly *et al.* 1978) and the urinary hydroxyproline in this group is therefore inappropriately high and represents a state of negative bone balance. This would, of course, be expected in a group of subjects who are so prone to develop osteoporosis.

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