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Bone mineral density in Addison's disease: evidence for an effect of adrenal androgens on bone mass

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Abstract

It is unknown whether replacement doses of cortisone acetate and the absence of the small amounts of androgens secreted by the adrenal cortex may cause osteoporosis. This was studied in 35 patients (12 men and 23 women) suffering from primary adrenocortical failure and taking cortisone acetate 25-37·5 mg and fludrocortisone 50-100 μg daily. Bone mineral density was measured by single photon absorptiometry at the midshaft of the radius, representing cortical bone, and at the distal part of the radius, a site with a significant trabecular component. The bone mineral density was normal in premenopausal female patients as well as in male patients, showing that replacement doses of cortisone acetate do not affect bone mass. By contrast, in postmenopausal patients there was a dramatic bone loss in addition to the physiological postmenopausal decrease in bone mass.

This loss, combined with the low plasma concentrations of androstenedione, dehydroepiandrosterone, and testosterone (and low concentrations of oestrone of adrenal origin), indicates that adrenal androgens may be essential for the maintenance of bone mass in postmenopausal women with Addison's disease. In addition, these data indicate that the small amounts of androgens secreted by the adrenal cortex have a role in the maintenance of bone mass in normal postmenopausal women.

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Introduction

It is well known that supraphysiological amounts of glucocorticoids may induce osteoporosis. The question whether physiological doses of glucocorticoids are devoid of this side effect has not been settled, however, as we have discussed elsewhere with regard to rheumatoid arthritis.[1] As rheumatoid arthritis may influence peripheral bone mass we sought to resolve this problem by studying patients suffering from primary adrenocortical failure (Addison's disease) and receiving treatment with glucocorticoid substitutes. At the same time we investigated whether the adrenal androgens played a part in the maintenance of bone mass.

Patients and methods

Bone mineral content and bone width, expressed in g/cm and cm, respectively, were determined by single photon absorptiometry with a modified Norland-Cameron bone mineral analyser. The results are presented as the ratios of bone mineral content over bone width (g/cm²) or bone mineral density of the non-dominant arm of the patients. Measurements were made at two locations: 2 cm from the styloid process (distal radius) and two thirds of the way from elbow to wrist (midshaft radius). Cortical bone represents about 90% of the second scanning site, whereas trabecular bone accounts for about 27% of the first.[2] At least five scans were performed at each site. The precision of this method is around 2-4%.[3]

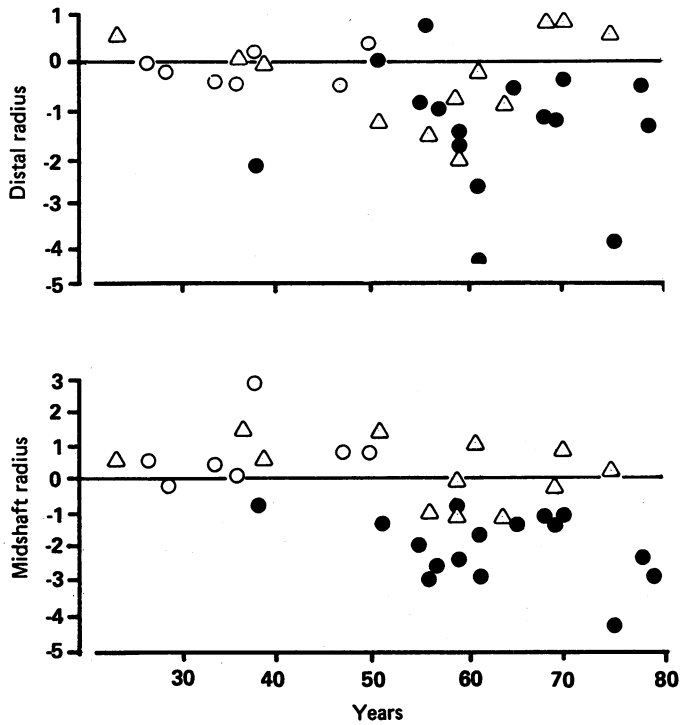
So that men and women of varying ages could be compared individual bone mineral density values were expressed as standard deviations (z scores) from the predicted mean for normal subjects, obtained from regression equations that predicted the bone density as a function of age, as described by Seeman *et al.*[4] Separate regression equations were used for men and women. The Mann-Whitney U test was used to compare the two groups.[5]

Thirty five patients (12 men and 23 women) suffering from Addison's disease (primary adrenocortical insufficiency) were studied. Nine of the men and two of the women has a history of tuberculosis. The other patients were considered to have the idiopathic form of the disease. Substitution treatment generally consisted of 25 mg of cortisone acetate and 50-100 µg fludrocortisone taken orally in the morning and 12·5 mg of cortisone acetate taken in the middle of the afternoon. All blood chemistries were normal. The mean (SEM) age of the men was 56 (4·4) years and the mean duration of the disease and treatment 11·6 (3·0) years. (Generally, the course of Addison's disease is such that diagnosis, leading to treatment, follows onset by only a few months.) The 23 women were divided in two different groups according to their hormonal state. There were 16 postmenopausal patients (63 (2·7) years, with a mean duration of disease and treatment of 12·1 (2·3) years) and seven premenopausal patients (37 (3·2) years, with a mean duration of disease and treatment of 7·0 (1·7) years). None of the postmenopausal patients was receiving treatment with gonadal hormone substitutes. Patients were compared with normal controls (154 women, 66 premenopausal and 88 postmenopausal, and 98 men) as described elsewhere.[6] The controls were volunteers or patients from the arthritis clinic who were being treated for benign extra-articular rheumatism and were devoid of any disease known to interfere with bone mass, such as diabetes and hyperthyroidism. The mean weight of the patients (61·4 (2·2) kg) was slightly but not significantly lower than that of the controls (66·8 (1·9) kg). Likewise, the weight/(height²) ratio of the patients was not statistically different from the ratio (or body mass index) of the controls (24·6 (1·0) *v* 25·5 (0·9)).[7] Concentrations in the plasma of oestrone, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulphate, and testosterone were determined by radioimmunoassay in 21 of the 23 female patients.[8-10] The same measurements were carried out in 15 premenopausal and 60 postmenopausal controls.

TABLE I—*Mean (SEM) bone mineral density of radius (expressed as Z score) determined by single photon absorptiometry in patients with primary adrenocortical insufficiency*

	Mean (SEM) age (years)	Distal radius	Midshaft radius
Men (n=12)	56 (4·3)	−0·40 (0·28)	0·21 (0·27)
Premenopausal women (n=7)	37 (3·2)	−0·18 (0·13)	0·77 (0·38)
Postmenopausal women (n=16)	63 (2·7)	−1·52 (0·34)*	−2·02 (0·24)*

*Difference from normal value p<0·001.



Bone mineral density (expressed as deviation from predicted mean or Z score for normal subjects) at distal and midshaft radii in postmenopausal women (●), premenopausal women (○), and men (△) with Addison's disease.

Results

WOMEN WITH ADDISON'S DISEASE

The bone mineral density in the premenopausal patients was not significantly different from that of the controls at the distal or midshaft radius (table I and figure). Table I shows, however, that there was a significant loss in bone mineral density in the postmenopausal patients, both at the distal and midshaft radii, compared with controls (p<0·001). The patient aged 38 (figure) deserves further comment. She had suffered from Addison's disease since the age of 30 but, for other reasons, had undergone medical castration as a result of external *x* ray treatment at the age of 25. The early menopause combined with Addison's disease had led to severe loss of bone mineral density similar to that found in patients in their 60s.

There was a negative correlation between bone mineral density and the duration of Addison's disease and its treatment in the postmenopausal women, at both the midshaft and distal radii, but this correlation did not quite reach significance, probably owing to the small number of patients.

Table II gives the data regarding the hormonal state of the female patients. In the patients with Addison's disease the concentrations of androstenedione, dehydroepiandrosterone, and testosterone both before and after menopause were significantly lower than those in the controls (p<0·01), whereas oestrone concentrations were not significantly different (p=0·051) from those in the controls. On the other hand, there was a significant decrease in

TABLE II—*Mean (SEM) results of plasma steroid concentrations in female patients with primary adrenocortical insufficiency receiving substitution treatment compared with controls*

	Oestrone (pmol/l)	Androstenedione (nmol/l)	Dehydroepiandrosterone Free (nmol/l)	Dehydroepiandrosterone Sulphate (µmol/l)	Testosterone (nmol/l)
Premenopausal controls (n=15)	193 (80)	3·23 (0·42)	7·57 (1·77)	3·2 (0·7)	1·34 (0·15)
Premenopausal patients with Addison's disease (n=6) p value	280 (88) NS	1·32 (0·17) <0·01	0·41 (0·06) <0·001	0·09 (0·01) <0·001	0·57 (0·06) <0·001
Postmenopausal controls (n=60)	110 (15)	2·66 (0·21)	5·05 (0·67)	1·53 (0·16)	1·03 (0·07)
Postmenopausal patients with Addison's disease (n=15) p value	77 (21) NS	0·54 (0·10) <0·001	0·55 (0·12) <0·001	0·13 (0·01) <0·001	0·39 (0·08) <0·001
P value for difference between premenopausal and postmenopausal women with Addison's disease	<0·01	<0·01	NS	NS	<0·05

TABLE III—*Mean (SEM) plasma steroid concentrations in patients with primary adrenocortical insufficiency receiving substitution treatment compared with controls**

	Weight (kg)	Oestrone (pmol/l)	Androstenedione (nmol/l)	Dehydroepiandrosterone Free (nmol/l)	Dehydroepiandrosterone Sulphate (μmol/l)	Testosterone (nmol/l)
Postmenopausal controls (n=25)	64·8 (1·7)	113 (17)	2·95 (0·42)	5·98 (1·35)	1·70 (0·28)	1·07 (0·13)
Postmenopausal patients with Addison's disease (n=14) p value	62·0 (2·9) NS	79 (24) <0·05	0·55 (0·11) <0·001	0·56 (0·13) <0·001	0·12 (0·01) <0·001	0·40 (0·08) <0·001

*Patients and controls who had undergone the menopause less than five years previously were excluded, and mean weights were adjusted accordingly.

the concentrations of oestrone, androstenedione, and testosterone in the postmenopausal compared with the premenopausal patients with Addison's disease ($p<0·05$). As it is well known that women take at least four years after the menopause to be free of any residual ovarian secretion of oestrone we excluded from the groups of women all those who had undergone the menopause less than five years previously.[11] As it is also known that oestrone concentrations are closely related to weight[11] we excluded from our control group those who weighed the most so that the two groups were comparable. Table III shows that the oestrone concentrations were thus significantly lower ($p=0·034$) in the patients than in the controls, all the other differences remaining significant. The exclusion of the two patients who had undergone the menopause less than five years previously did not affect the Z score as shown in table I.

MEN WITH ADDISON'S DISEASE

The bone mineral density among the men patients was not significantly different from that of the controls (table I). Bone mineral density was within one standard deviation of the mean at both the midshaft and distal radii in all the patients except three at the distal radius (figure). The importance of the low bone mineral density in these three patients remains uncertain, particularly as, like other men with Addison's disease, their testosterone concentrations were well within the normal range (20·7 (1·7) nmol/l, range 13·2-32 nmol/l (normal range 13-35 nmol/l)), thus excluding gonadal deficiency, which would have accounted for their bone loss. Two of these patients had a history of tuberculosis (which was common in the men but rare in the women). The treatment of tuberculosis is known, at least in some cases, to be complicated by the shoulder-hand syndrome.[12] In many cases the bone dystrophy is limited to a radiolucent zone in the metaphyseal aspect of the distal radius close to the distal scanning site, which leads to low bone mineral density values. The third patient with a low bone mineral density suffered concomitantly from diabetes mellitus, a condition sometimes complicated by bone loss.[13]

Discussion

In contrast to postmenopausal women with Addison's disease, premenopausal women with this condition have normal bone mineral density, as do most men with Addison's disease. From our data we may conclude that replacement doses of cortisone acetate, as given in patient's with Addison's disease (25-37·5 mg daily), do not affect bone mass when there is a normal secretion of ovarian oestrogens, as in the premenopausal women with Addison's disease, and of testicular androgens in the men. After the menopause, however, there is a significant loss of bone mineral density, in addition to the physiological bone loss associated with the menopause. The difference in bone mineral density between premenopausal and postmenopausal women could be caused by the lack of those minute amounts of androgens normally released by the adrenal cortex and the ovaries. Both the adrenal cortex and the ovary secrete androgens in normal premenopausal women, and in about half of all postmenopausal women the ovaries continue to secrete some testosterone and small amounts of androstenedione or dehydroepiandrosterone.[14] The adrenal androgens have not been implicated as determining factors in the maintenance of bone mass. This study suggests, however, that they are essential for the preservation of bone mass as the absence of functional adrenals is followed by a decrease in bone mass in postmenopausal women. Indeed, the concentrations of oestrone, which were normal as expected in the premenopausal patients, were significantly lower in the postmenopausal ones when the comparison was limited to women of similar weight who had undergone the menopause at least five years previously. In such patients oestrone concentrations result from peripheral aromatisation of androstenedione of adrenal origin.[15] Owing to adrenal failure, the concentrations of androstenedione and testosterone, low in premenopausal female patients, were even lower after the menopause ($p<0·05$) (table II), and concentrations of dehydroepiandrosterone, whether free or sulphate, were low in both groups.

In conclusion, replacement doses of cortisone acetate do not cause loss of bone mass, as indicated by measurements in men and premenopausal women treated for Addison's disease. The dramatic loss of bone mass noted in postmenopausal women might be caused by the lack of secretion of androgen of adrenal origin in addition to the menopausal hormonal state. This implies that the small amounts of androgens normally released by the adrenal cortex have a role in the maintenance of bone mass. In fact, this has been suggested as a pathogenetic mechanism for androstenedione in patients with accelerated postmenopausal osteoporosis by one group of investigators,[16] and more recently for dehydroepiandrosterone.[17]

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