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METABOLIC EFFECTS OF CORTICOSTEROID THERAPY IN POST-MENOPAUSAL WOMEN

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SUMMARY

Vertebral compression fractures occur in about 8% of post-menopausal women and are associated with a diminished volume of trabecular bone as judged by iliac crest biopsy. These patients differ from age-matched controls in having significantly lower calcium absorption, plasma oestrone and androstenedione levels and lower plasma testosterone levels. Their urinary hydroxyproline is increased and their skin thickness is reduced. The low plasma oestrone levels do not appear to be due to impaired conversion of androstenedione to oestrone, but are probably the result of the low plasma androstenedione levels themselves. The increased bone resorption can be corrected by oestrogen therapy and the malabsorption of calcium can be corrected with 1α-OHD_3 or $1,25(OH)_2D_3$ therapy. Post-menopausal women on corticosteroid therapy have even lower plasma androgen and oestrogen levels due to suppression of ACTH secretion. This abnormality, combined with malabsorption of calcium secondary to corticosteroid therapy, probably explains the high incidence of osteoporosis in this population. The malabsorption of calcium can be corrected in this group also by vitamin D metabolites. The hormone levels can be raised by ACTH administration or by the oral administration of androstenedione or dehydroepiandrosterone.

Spinal osteoporosis is an important complication of corticosteroid therapy, which in our experience is particularly liable to occur in post-menopausal women. The present paper describes some biochemical and metabolic findings in this group of patients.

CLINICAL MATERIAL AND METHODS

The material comprises 45 post-menopausal women on doses of prednisolone ranging from 3 to 20 mg daily at the time of study for the following complaints: asthma 22, rheumatoid arthritis 8, systemic lupus erythematosis 2, polymyalgia rheumatica 6, polyneuritis 1, Sjogren's Disease 1, polymyositis 2, polyarteritis nodosa 1, and haemolytic anaemia 2.

Not all observations were made on all the patients and the numbers appearing in the figures and in the text therefore vary.

Plasma samples were collected after an overnight fast for estimation of oestrone, androstenedione and testosterone by conventional immunoassay techniques; calcium, creatinine and hydroxyproline by standard Auto-Analyzer procedures; 25-hydroxy vitamin D_3 ($25(OH)D_3$) as described by Morris and Peacock[1]. Radiocalcium absorption was estimated by measurement of plasma radioactivity following the oral administration of 5 μCi of radiocalcium in 20 mg of calcium carrier as calcium chloride in 250 ml of water [2]. Calcium balance and bone turnover studies were carried out by methods we have described elsewhere [2].

OBSERVATIONS

Radiocalcium absorption in 35 patients is illustrated in Fig. 1. In patients without vertebral crush fractures, most values fall within the normal range but in those with compression fractures the mean value is significantly lower and most of the values are at the bottom of the normal range or outside it. The mean duration of therapy was 8 years in each group. The mean ages and dose at time of absorption tests for the two groups was 61 and 8 mg for the normals and 65 years and 7.5 mg for the osteoporotics respectively. Net calcium absorption data determined by calcium balance are shown in Fig. 2. Results are expressed in standard deviation units from the net absorption that would normally be expected at the particular calcium intake. This confirms the malabsorption of calcium in these patients, particularly in those with spinal osteoporosis, though with these small numbers the difference between osteoporotic and those with normal bones is not significant.

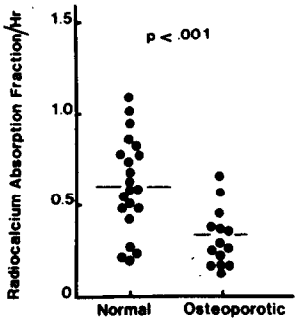

Fig. 1. Comparison of radiocalcium absorption between corticosteroid treated patients with normal bones and those with osteoporosis.

The relation between radiocalcium absorption and the fasting urinary hydroxyproline/creatinine ratio is shown in Fig. 3. It is clear that the highest hydroxyproline/creatinine ratios, representing the highest rate

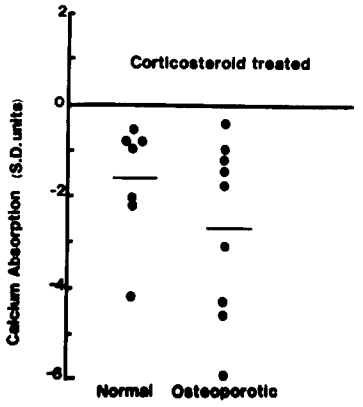

Fig. 2. Net calcium absorption in normal and oesteoporotic patients on corticosteroids, expressed in SD units to allow for variations in intake.

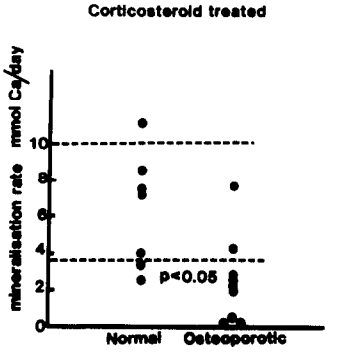

Fig. 4. Mineralization rate in normal and osteoporotic patients. Normal range is shown between the dotted lines.

of bone resorption relative to lean body mass, occur in the patients with the lowest calcium absorption. There is, however, no significant difference in hydroxyproline/creatinine ratios between osteoporotic and non-osteoporotic subjects.

Bone turnover data are illustrated in Fig. 4. The normal range of bone mineralization rate measured by our expanding pool technique is about 3.5 to 10 mmol/day and it is clear that most corticosteroid-treated women who have become osteoporotic lie below the normal range. Maintenance of a normal mineralization rate is associated with maintenance of a normal skeleton.

Plasma hormone measurements are illustrated in Fig. 5. The plasma androstenedione, oestrone, testosterone and oestradiol values are all extremely low and generally fall below the lower post-menopausal limit. Even in this small range of values there is a correlation between the androstenedione and oestrone levels (Fig. 6) but not between either of these and the plasma testosterone levels.

THERAPEUTIC IMPLICATIONS

The malabsorption of calcium in these patients is reversible with vitamin D which has been given in different forms and doses, viz. vitamin D_2 10,000–20,000 units (4 patients), 1α-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol 0.5–1 μg daily (4 patients) or 25-hydroxycholecalciferol 5–25 μg daily (3 patients) for periods varying from 3 weeks to 6 months. This treatment was followed by a significant rise in radiocalcium absorption and a significant fall in urinary hydroxyproline as shown in Fig. 7. The data suggest that the degree of improvement in the latter is related to the degree of improvement in the former.

Low plasma hormone levels can be corrected by administration of ACTH. The effect of the administration of Synacthen depot 0.5 mg 3 times weekly for 6 months on plasma androstenedione, oestrone and testosterone levels is shown in Fig. 8. This treatment caused skin pigmentation in a number of patients and fluid retention with peripheral oedema and did not appear to have any beneficial effect on any aspect of calcium metabolism.

An alternative approach has been to try and raise the plasma hormone levels by the administration of dehydroepiandrosterone (DHEA) in doses of 20 mg daily. The effect of this treatment on the plasma androstenedione and the plasma testosterone levels in 8 cases treated for at least 4 weeks is shown in Fig. 9. There was a significant rise in plasma sex hormone concentrations and the patients have reported a sense of increased wellbeing with no side effects, but we are not yet in a position to describe the effect

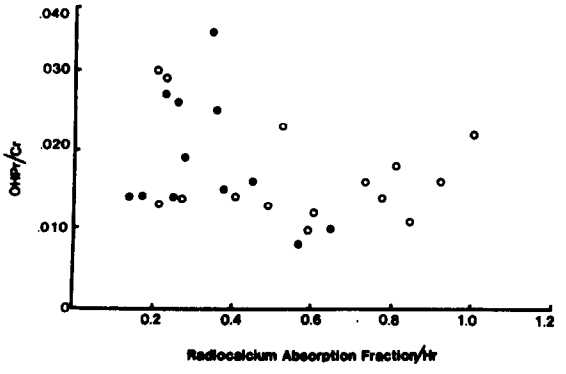

Fig. 3. Relationship between radiocalcium absorption and fasting hydroxyproline/creatinine ratio (OHPr/Cr) in patients on corticosteroids. Solid circles: osteoporotic, open circles: normal bones.

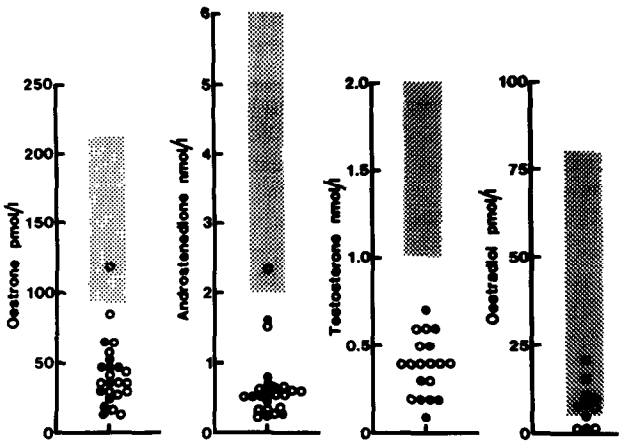

Fig. 5. Plasma sex hormone levels in corticosteroid treated patients. Normal post-menopausal ranges shown by shaded areas.

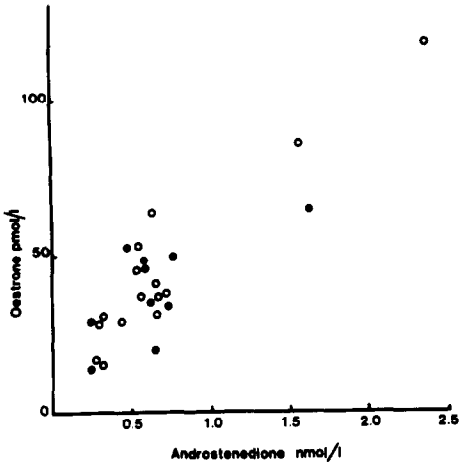

Fig. 6. Relationship between plasma androstenedione and oestrone in corticosteroid treated patients. Solid circles: osteoporotic, open circles: normal bones.

of this therapy on calcium and bone metabolism. Oestrone measurements on synacthen and DHEA are not yet available but as the androstenedione levels rise, a similar rise in oestrone is to be expected.

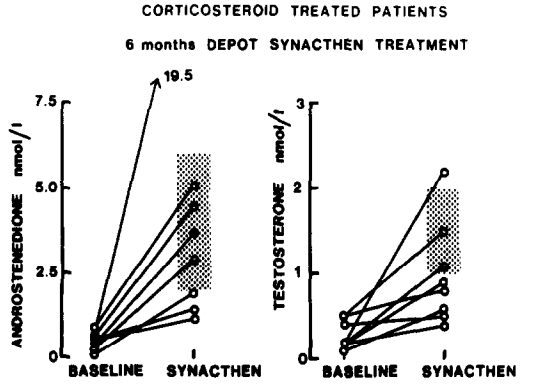

Fig. 8. Effect of synacthen treatment on androstenedione and testosterone levels in patients previously on oral corticosteroid treatment.

DISCUSSION

We have reported elsewhere that post-menopausal osteoporosis is associated with impaired calcium absorption [3] and low plasma concentrations of androstenedione and oestrone [4] and have suggested that malabsorption of calcium and severe oestrogen

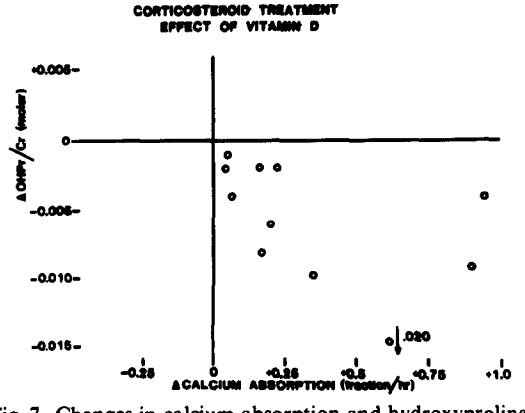

Fig. 7. Changes in calcium absorption and hydroxyproline excretion in patients treated with vitamin D.

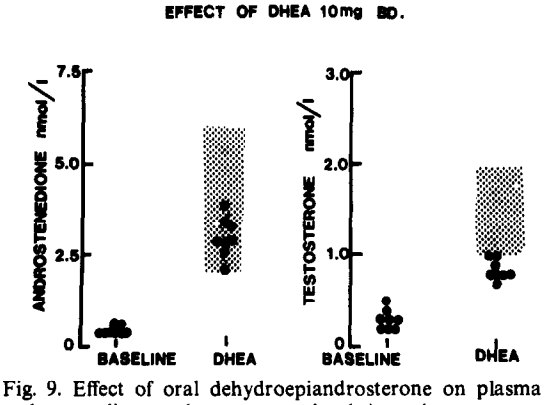

Fig. 9. Effect of oral dehydroepiandrosterone on plasma androstenedione and testosterone levels in patients concurrently taking oral corticosteroids.

deficiency are two important risk factors in spinal osteoporosis [5]. The present data show malabsorption of calcium is also a feature of corticosteroid-treated post-menopausal osteoporotic women particularly those with vertebral crush fractures. The inhibitory effect of corticosteroids on calcium absorption is well known [6, 7, 8] both in animals and man, but the mechanism of this is unknown. The plasma $25(OH)D_3$ levels in our patients are within the normal range. Avioli *et al* [9] have reported that corticosteroids may affect the metabolism of vitamin D to more polar metabolites, whilst Aloia *et al.* [10] found normal $25(OH)D_3$ levels in corticosteroid treated patients. Klein *et al.* [11] found that high dose corticosteroid lowered the $25(OH)D_3$ levels although most values remained within the normal range.

There is evidence that the malabsorption of calcium is due to a primary action of the corticosteroids on the gastrointestinal tract, independent of vitamin D metabolism [6, 8, 12, 13, 14]. If so, it might be expected that there would be stimulation of parathyroid hormone (PTH) secretion and therefore a rise in $1,25(OH)_2D_3$ production. Fucik *et al.* [15] have reported raised PTH levels in male patients on chronic corticosteroid treatment. Lukert *et al.* [8] have reported raised $1,25(OH)_2D_3$ levels in rats given corticosteroids and Kimberg *et al.* [6] have shown raised levels of calcium binding protein in the gut wall of cortisone treated rats despite poor transport of calcium. We are not aware of any published data of $1,25(OH)_2D_3$ levels in humans on corticosteroid treatment. The situation appears to contrast to that thought to exist in ordinary post-menopausal osteoporosis, where the malabsorption is held to be secondary to the increased bone resorption which leads to a rise in plasma calcium and suppression of PTH secretion and $1,25(OH)_2D_3$ production [16]. Whatever the mechanism, it appears that malabsorption of calcium contributes to corticosteroid-induced osteoporosis in post-menopausal women and it seems particularly significant that the patients with the lowest calcium absorption should be those with the highest urinary hydroxyproline excretion, i.e. those with the highest bone resorption. Moreover, the fact that high dose vitamin D lowers urinary hydroxyproline at the same time as it elevates calcium absorption suggests that malabsorption of calcium directly contributes to increased bone resorption in these patients. It is also of relevance that the osteoporotic patients are those with the low mineralization rate. This means that although the absolute rate of bone destruction, as reflected in the urinary hydroxyproline, does not differ between osteoporotic and non-osteoporotic corticosteroid-treated patients, the net rate of bone loss in the former must be greater.

Another factor which may contribute to negative calcium balance and loss of bone in these patients may be an effect of corticosteroids on tubular reabsorption of calcium. Evidence from humans concerning the influence of corticosteroids on calcium transport in the renal tubule is conflicting [17, 18]. Our calculated notional TmCa values (maximum reabsorptive rate of calcium) [19] in the patients studied here have been normal.

The factors predisposing to osteoporosis would be greatly enhanced by the severe oestrogen deficiency which is another feature of these cases and which is of course secondary to the suppression of the pituitary/adrenal axis by corticosteroid therapy leading to reduced secretion of androstenedione and consequently low plasma oestrone levels. By analogy again with animal experimentation, which show that oophorectomized rats are more susceptible to calcium deficiency than intact rats [20] it would be expected that patients with low plasma oestrogen levels would be more liable to lose bone in response to calcium stress than those with normal hormone levels. There is no difference in the hormone levels measured in the osteoporotic and normal patients on corticosteroids. It is probable that there is a general background of oestrogen deficiency against which the other factors play a determining role.

If these considerations are correct, corticosteroid-induced osteoporosis in post-menopausal women should be preventable or treatable in a variety of ways, alone or in combination. One way would be to improve calcium absorption by administration of vitamin D or one of its metabolites and this has certainly proved possible in a small series to whom we have given relatively large doses. That this may be beneficial is suggested by the fall in urinary hydroxyproline which has been observed with these cases. We have not, however, yet defined what is the best form of vitamin D or the optimum dose, nor do we have any useful information as to whether calcium supplements have any role to play.

Another approach is to correct the low plasma hormone levels. This we have done successfully with ACTH but have been disappointed with the result both in terms of the high incidence of side effects which were produced and the absence of any demonstrable improvement in calcium metabolism. We are therefore pursuing an alternative approach which is to raise the plasma hormone concentration by administering appropriate precursors. It appears that dehydroepiandrosterone may be useful compound in this connection, it certainly produces at a dose of 20 mg daily, a significant elevation of sex hormone levels to just below or into the lower end of the normal range. It is too early for us to say whether this substance at an appropriate dose, will have any beneficial effect upon bone or calcium metabolism.

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