

CHANGES IN SERUM CALCIUM AND PHOSPHORUS DURING STILBOESTROL TREATMENT OF OSTEOPOROSIS

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The value of oestrogens in the treatment of osteoporosis has been shown by two main types of evidence. Firstly, increased calcium retention, due to a reduction in both faecal and urinary excretion, has been shown by metabolic balance studies (Reifenstein and Albright 1947). Secondly, the progress of the disease, as judged by height loss and bone density, is arrested (Henneman and Wallach 1957), and furthermore the loss of height which normally occurs in post-menopausal women can be prevented by oestrogens (Hernberg 1960). However, oestrogens have never been shown to increase bone density and their mode of action is uncertain.

Oestrogens have been shown to stimulate osteogenesis in many different species, and to reverse in this way the osteoporosis which follows orchidectomy and adrenalectomy in rats (Caldwell 1962). Most workers have assumed that this action also occurs in man, and that the reduction in calcium excretion is secondary to a direct action on bone. An alternative theory has been put forward by Nordin (1958) in an attempt to explain the effect of oestrogens in the context of a general hypothesis that osteoporosis is usually due to calcium deficiency (Nordin 1960). He suggested that the reduction in calcium excretion might be a primary action which would lead, in terms of this hypothesis, to a reduction in bone resorption.

It should be possible to distinguish between these two theories quite simply, because if increased net calcium deposition in bone were secondary to a reduction in calcium excretion there should be a slight rise in serum calcium, whereas if the reduced excretion were secondary to increased calcium deposition, there should be a slight fall in serum calcium.

With this in mind, a retrospective study of the changes in serum calcium and phosphorus in patients with osteoporosis treated with oestrogens was undertaken.

METHODS

The records of all patients with post-menopausal osteoporosis who had attended the Royal National Orthopaedic Hospital were examined. In forty-one cases the diagnosis (based on radiological appearances and absence of signs of other causes of bone rarefaction) was acceptable and there was at least one determination of serum calcium and phosphorus before and after treatment. From these cases all available readings were abstracted and allocated to one of two groups: 1) "off treatment" and 2) "on treatment." Most patients had been given stilboestrol 0.5 milligram or 1 milligram daily, and some had been given methyl testosterone 5 milligrams or 10 milligrams daily in addition. No distinction was made between these régimes. Most patients had been instructed to take tablets for four weeks and then stop for one week and continue in this cycle. As the interval between tests was usually not a multiple of five weeks, it was often impossible to correlate the time of the tests with the stage in the cycle; so in the "on treatment" group the tablets may have been stopped up to one week before blood was taken. In patients who had had intermittent courses of treatment the result was allocated to the "off treatment" group if the tablets had been stopped more than two weeks before blood was taken.

RESULTS

In the "on treatment" group there was a substantial reduction (approximately 15 per cent) in mean serum phosphorus, and a smaller reduction (approximately 3 per cent) in mean serum calcium (Table I). Both changes were statistically significant.

DISCUSSION

The fall in serum phosphorus was less than in a previous report from this unit, in which the mean level fell from 3.78 milligrams per 100 millilitres to 2.82 milligrams per 100 millilitres in thirty-one patients (Nassim, Saville and Mulligan 1956). This is probably because of the method of allocation used in the present study; if the effect of stilboestrol on serum phosphorus persisted for more than two weeks after it was stopped (Bogdonoff, Shock and Parsons 1954), the difference between the two groups would be underestimated (Table II). The fall in serum calcium was small, but a much greater change would be unlikely in the presence of normal parathyroid function.

TABLE I
CHANGES IN SERUM CALCIUM AND PHOSPHORUS WITH STILBOESTROL TREATMENT
Results expressed in milligrams per 100 millilitres

	Serum calcium		Serum phosphorus	
	Off treatment	On treatment	Off treatment	On treatment
Number of readings	152	165	181	196
Mean	9.65	9.37	3.63	3.04
Range	8.3-10.9	8.0-11.0	2.5-4.5	2.1-4.2
Difference in means (Δ)	0.28		0.59	
Standard error of difference (S.E.)	0.0652		0.0436	
Δ /S.E.	4.3		13.5	

TABLE II
CHANGES IN SERUM CALCIUM AND PHOSPHORUS IN AGED MEN GIVEN STILBOESTROL
Results expressed in milligrams per 100 millilitres

	Before treatment (Milligrams per 100 millilitres)	During treatment (Milligrams per 100 millilitres)	After treatment (Milligrams per 100 millilitres)
Calcium	9.66	9.40	9.73
Phosphorus	2.88	2.77	2.54

Each figure is the mean of two or three readings obtained over a twenty-day period from each of six patients.
Calculated from data of Bogdonoff, Shock and Parsons (1954).

As far as I know no attention to this particular point has been given before, but in Bogdonoff, Shock and Parsons's (1954) paper on the effect of stilboestrol in aged men, sufficient facts were included for comparative calculations to be made. The fall in serum calcium was of similar magnitude although not statistically significant (Table II). A similar fall in both serum calcium and phosphorus was found in a patient with fibrocystic disease of the pancreas who retained calcium under the influence of 19 nor-testosterone phenyl propionate (Parfitt, Nassim, Collins and Hilb 1962).

Although in need of confirmation by a prospective study, the results are consistent with the theory that the changes in calcium balance which occur with stilboestrol are secondary to a direct effect on bone, and do not support the alternative theory of Nordin.

SUMMARY

1. The changes in serum calcium and phosphorus which occurred in forty-one patients with post-menopausal osteoporosis during treatment with stilboestrol were examined.

2. There was a fall of approximately 15 per cent in mean serum phosphorus and of approximately 3 per cent in mean serum calcium.
3. The fall in serum calcium is considered to furnish some evidence against the theory that the primary action of stilboestrol is a reduction in calcium excretion.

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