

SHORT COMMUNICATION

## Comparative effects of oestrogen and a progestogen on bone loss in postmenopausal women

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### Summary

1. The value of progestogen therapy in the prevention of postmenopausal bone loss was assessed in 30 women, by a preliminary randomized controlled trial of gestronol or mestranol, in comparison with a placebo.

2. When the skeletal response was measured by photon absorptiometry, bone mineral loss was prevented by both the oestrogen and the progestogen.

3. We confirm that mestranol significantly reduced the urinary output of hydroxyproline-containing peptide, but this did not occur during gestronol therapy, suggesting that progestogen has a different action on bone, perhaps stimulating bone formation.

Key words: bone, oestrogen, osteoporosis, progestogen.

### Introduction

Retrospective studies (Meema, Bunker & Meema, 1975) and prospective trials (Heaney & Recker, 1975; Lindsay, Aitken, Anderson, Hart, MacDonald & Clarke, 1976; Horsman, Nordin, Gallagher, Kirby, Milner & Simpson, 1977) have indicated that oestrogen replacement protects against postmenopausal bone loss. However, oestrogen therapy also causes metabolic effects which could create problems when oestrogens are prescribed over a long period (Poller, 1976; Goldman, 1976). In addition, there is considerable controversy at

present concerning the role of unopposed oestrogen in the production of endometrial carcinoma (Smith, Prentice, Thompson & Hermann, 1975; Gordan & Vaughan, 1976).

Some evidence suggests that progestogens may prevent bone loss in oophorectomized rats (Aitken, Armstrong & Anderson, 1972) and their effect on calcium, phosphate and hydroxyproline excretion in humans has been said to be similar to that of oestrogen (Gallagher & Nordin, 1975). We have therefore compared the effect of a pure progestogen with the effects of oestrogen or a placebo on bone mineral metabolism in postmenopausal women.

### Methods

Thirty-five consecutive patients referred to a menopausal clinic were assessed for treatment, all complaining of menopausal symptoms, with at least 6 months having elapsed since their last menstrual period. Five patients with contraindications to oestrogen therapy, or coexistent disease, were excluded. The remaining 30 patients were given, in a randomized order, mestranol, 40 µg/day, or gestronol hexanoate (19-nor-17-β-hydroxyprogesterone 17-caproate; Depostat, Schering), 200 mg by intramuscular injection monthly for 3 months and thereafter at 3 monthly intervals, or a placebo tablet preparation. Nine patients had had a hysterectomy and bilateral oophorectomy. By chance these patients were evenly divided among the groups.

Patients were reviewed at 1 month, 6 months and after 1 year. At the first visit and at one subsequent visit, fasting morning urine samples were obtained from each patient, and creatinine and hydroxyproline were measured (creatinine by

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Autoanalyzer method N-11; hydroxyproline by the method of Stegemann & Stalder, 1967). Results are presented as the ratio of molar concentrations of hydroxyproline to creatinine in urine from fasting patients. Patients were asked to eliminate high hydroxyproline-containing foods from their diet for 3 days before sampling, but otherwise no dietary restrictions were imposed. At the first visit and at 1 year, bone mineral content was assessed in duplicate at the mid-point of the third metacarpal, by a modification of the photon-absorption technique of Cameron and Sorenson (Cameron & Sorenson, 1963; Shimmins, Smith, Aitken, Anderson & Gillespie, 1972; Lindsay *et al.*, 1976).

Within each group comparisons were made by a paired *t*-test; comparison between groups was by Student's *t*-test. Values are given as mean  $\pm$  1 SE.

## Results

The mean ages and the mean number of years since menopause of the three groups were not significantly different and neither were the mean values of the metacarpal mineral content (Table 1). The average tablet consumptions of the two groups taking mestranol and placebo were 1.25 tablets/day and 1.31 tablets/day, which were not significantly different. The mean daily dose of mestranol was therefore  $25 \pm 1.02 \mu\text{g/day}$  and the mean calculated daily dose of gestronol was  $\sim 6 \pm 0.27 \text{ mg/day}$  for the first 3 months, and thereafter  $\sim 1 \text{ mg/day}$ .

The placebo-treated patients lost a significant amount of bone,  $1.7 \pm 0.50 \text{ mg/mm}$  during the year, equivalent to  $3.6 \pm 1\%$ , whereas during the same period the patients in the other two groups did not lose bone mineral (Table 1). In both these groups there was a slight, but insignificant increase in metacarpal mineral content during the trial, and by the end of 1 year, the mean bone mineral contents of both actively treated groups were significantly greater than that of the placebo-treated group ( $P < 0.05$ ).

Oestrogen treatment characteristically reduces urinary output of hydroxyproline (Young, Jasani, Smith & Nordin, 1968; Lindsay *et al.*, 1976). As expected, this occurred in the mestranol-treated group ( $P < 0.01$ ), the urinary hydroxyproline/creatinine ratio falling from  $2.07 \pm 0.2 \text{ mmol/mol}$  to  $1.21 \pm 0.1 \text{ mmol/mol}$ . Gestronol produced only a minimal reduction, which did not reach significance ( $2.30 \pm 0.2 \text{ mmol/mol}$  of creatinine before treatment;  $2.00 \pm 0.26 \text{ mmol/mol}$  after treatment). Hydroxyproline output in the placebo-treated group remained unaltered ( $2.20 \pm 0.26 \text{ mmol/mol}$  to  $2.16 \pm 0.2 \text{ mmol/mol}$  of creatinine).

Two patients in the placebo-treated group complained of nausea during the initial week of therapy, as did one patient receiving mestranol and two in the gestronol-treated group. One patient in the mestranol-treated group complained of cramp in the calves at night. This settled when the mestranol dose was reduced by one half to  $20 \mu\text{g}$  daily.

Three patients in the gestronol-treated group had slight vaginal bleeding approximately 3 weeks after their first injection. Gynaecological examination revealed no abnormality and bleeding did not recur. Two of these patients had suction curettage carried out after the bleeding had ceased and no aspirate was obtained. None of the patients receiving mestranol had vaginal bleeding during the 1 year's treatment, despite continuous therapy. In all of these patients treatment was stopped for 2 weeks after 1 year, and in one of the seven patients who had not previously undergone hysterectomy slight withdrawal bleeding occurred. Subsequently, therapy was continued with the addition of a progestogen given cyclically as norethisterone, 5 mg twice daily by mouth for 1 week every month.

## Discussion

Prevention of postmenopausal bone loss with oestrogen is now well established (Meema *et al.*, 1975; Lindsay *et al.*, 1976; Aitken, Hart &

TABLE 1. Initial bone mineral content and change during treatment  
Values are given as mean  $\pm$  SE; *n* = number of patients. n.s., Not significant

Treatment group	<i>n</i>	Age (years)	No. of years since menopause	Metacarpal bone mineral content (mg/mm)		Significance of change
				Initial	Mean yearly change	
Mestranol	10	46.9 $\pm$ 2.3	2.94 $\pm$ 0.82	45.0 $\pm$ 1.6	+0.6 $\pm$ 0.43	n.s.
Gestronol	10	45.1 $\pm$ 2.4	2.55 $\pm$ 0.81	44.1 $\pm$ 1.4	+0.1 $\pm$ 0.57	n.s.
Placebo	10	45.3 $\pm$ 1.9	2.72 $\pm$ 0.86	45.2 $\pm$ 1.9	-1.7 $\pm$ 0.50	$P < 0.01$

Lindsay, 1973; Horsman *et al.*, 1977). There is, however, little published evidence to support the use of progestogens in human females for this purpose.

In a strictly controlled rat experiment ethynodiol diacetate was shown to prevent bone loss after oophorectomy, but surprisingly oestrogen had no apparent effect (Aitken *et al.*, 1972). The progestogen apparently increased periosteal new bone formation without reducing bone resorption, and ash and calcium contents of femora increased significantly during progestogen therapy. In contrast, mice treated with a pure progestogen showed no effect on bone mineral retention, and their tibias showed histological evidence of loss of trabecular bone (Simmons & Cummins, 1968). This may be an example of difference in species sensitivity and it is therefore important to examine critically the effects of similar therapy in the human.

In our study the control patients lost an average of 1.7 mg/mm of bone during the year of observation, representing 3.6% of the initial bone mass. In a previous study oophorectomized patients lost 3.9% of bone mass every year (Aitken *et al.*, 1973). This rather high rate of bone loss appears to decline very rapidly when postmenopausal or oophorectomized patients are followed for a number of years (Lindsay *et al.*, 1976). A similar rate of bone loss from the ulna (3.5% per annum) was observed in the control patients in a separate trial conducted over 3 years (Horsman *et al.*, 1977).

We confirm that mestranol prevented postmenopausal bone loss (Lindsay *et al.*, 1976; Aitken *et al.*, 1973). Gestronol hexanoate with no oestrogenic or corticoid effects (Schering, personal communication), given by intramuscular injection, was also effective in inhibiting postmenopausal bone loss. However, we have studied only 10 patients in each group and followed them for only 1 year. More detailed and prolonged studies are required to confirm this effect of progestogen on bone and to establish if there is any interaction between the effects of progestogen and oestrogen when given in combination. Rat studies suggest that progestogen may antagonize the effect of oestrogen on bone (Aitken *et al.*, 1972).

The fact that gestronol did not significantly lower the urinary output of hydroxyproline suggests that the effect of progestogens on bone in humans may be similar to that in rats (Aitken *et al.*, 1972), with prevention of bone loss resulting from increased bone formation rather than the reduction of bone resorption which occurs after oestrogen therapy. The ideal preparation for

prevention of such bone loss may be a combination of oestrogen and progestogen, which might inhibit bone resorption and stimulate bone formation. This suggestion, however, requires further evaluation.

## References

- AITKEN, J.M., ARMSTRONG, E & ANDERSON, J.B. (1972) Osteoporosis after oophorectomy in the mature female rat and effect of oestrogen and/or progestogen replacement therapy in its prevention. *Journal of Endocrinology*, **55**, 79–87.
- AITKEN, J.M., HART, D.M. & LINDSAY, R. (1973) Oestrogen replacement therapy for the prevention of osteoporosis after oophorectomy. *British Medical Journal*, **ii**, 515–518.
- CAMERON, J.R. & SORENSON, J. (1963) Measurement of bone mineral *in vivo*: an improved method. *Science*, **142**, 230–232.
- GALLAGHER, J.C. & NORDIN, B.E.C. (1975) Effects of oestrogen and progestogen therapy on calcium metabolism in post-menopausal women. *Frontiers of Hormone Research*, **3**, 150–176.
- GOLDMAN, L. (1976) A dissident viewpoint. In: *The Management of the Menopause and Post-menopausal Years*, pp. 423–428. Ed. Campbell, S. M.T.P., Lancaster.
- GORDAN, G.S. & VAUGHAN, C. (1976) *Clinical Management of the Osteoporoses*. Publishing Sciences Inc., Acton, Mass.
- HEANEY, R.P. & RECKER, R.R. (1975) Oestrogen effects on bone remodelling at menopause (Abstract). *Clinical Research*, **23**, 535.
- HORSMAN, A., NORDIN, B.E.C., GALLAGHER, J.C., KIRBY, P.A., MILNER, R.M. & SIMPSON, M. (1977) Observations of sequential changes in bone mass in postmenopausal women: a controlled trial of oestrogen and calcium therapy. *Calcified Tissues Research*, **22** (Suppl. 2), 217–224.
- LINDSAY, R., AITKEN, J.M., ANDERSON, J.B., HART, D.M., MACDONALD, E.B. & CLARKE, A.C. (1976) Long-term prevention of post-menopausal osteoporosis by oestrogen. Evidence for an increased bone mass after delayed onset of oestrogen treatment. *Lancet*, **i**, 1038–1941.
- MEEMA, S., BUNKER, M.L. & MEMMA, H.E. (1975) Preventive effect of oestrogen on post-menopausal bone loss. *Archives of Internal Medicine*, **135**, 1436–1440.
- POLLER, L. (1976) A double blind cross-over study with conjugated equine oestrogens on blood clotting. In: *The Management of the Menopause and Post-menopausal Years*, pp. 313–320. Ed. Campbell, S. M.T.P., Lancaster.
- SHIMMINS, J., SMITH, D.A., AITKEN, J.M., ANDERSON, J.B. & GILLESPIE, F.C. (1972) The accuracy and reproducibility of bone mineral measurements *in vivo*. *Clinical Radiology*, **23**, 47–51.
- SIMMONS, D.J. & CUMMINS, H. (1968) Effect of the acetophenone-derivative of 16 $\alpha$ ,17 $\alpha$ -dihydroxyprogesterone (Deladroxone) and oestrogen (dihydroxyprogesterone-acetophenide) on  $^{85}\text{Sr}$  retention in rats and mice. *Proceedings of the Society for Experimental Biology and Medicine*, **128**, 1102–1106.
- SMITH, D.C., PRENTICE, R., THOMPSON, D.J. & HERMANN, W.L. (1975) Association of exogenous oestrogen and endometrial carcinoma. *New England Journal of Medicine*, **293**, 1164–1167.
- STEGEMANN, H. & STALDER, K. (1967) Determination of hydroxyproline. *Clinica Chitmica Acta*, **18**, 267–273.
- YOUNG, M.M., JASANI, C., SMITH, D.A. & NORDIN, B.E.C. (1968) Some effects of ethinyl oestradiol on calcium and phosphorus metabolism and homeostasis. *Clinical Science*, **34**, 411–417.