Oestrogens and Osteoporosis*

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SUMMARY

The interrelationship between oestrogens, endogenous and exogenous, their effects on plasma calcium, phosphorus and alkaline phosphatase metabolism, and the pathogenesis of osteoporosis are reviewed. Aspects of research conducted by me at Groote Schuur Hospital, Cape Town are incorporated in the discussion. The current role of oestrogen therapy in the prevention of osteoporosis is presented. It is concluded that appropriate or specific oestrogens are of value in the prevention of osteoporosis but have little or no role to play once the process is fully developed. Finally, a plea is made for conservatism with ovaries during gynaecological operations on young females.

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Postmenopausal osteoporosis has been the subject of several reviews[1-4] and the present discussion is limited to defining the problem in terms of the relationship between oestrogen deficiency or oestrogen therapy, calcium and phosphorus metabolism and osteoporosis. The decreasing ovarian function of the climacteric is said to be a factor leading to the development of osteoporosis. The purpose of this article is to clarify these relationships. Aspects of research conducted at a Menopause Clinic, Groote Schuur Hospital, will be incorporated in the discussion.[5] Finally, some conclusions as to the current role of oestrogen therapy in the prevention of osteoporosis in postmenopausal or prematurely castrated females will be presented.

OSTEOPOROSIS—OBSCURE PATHOGENESIS

It was not until 1941 that Albright *et al.*[6] described osteoporosis as a clinical entity. Osteoporosis is a common clinical disorder which may cause backache or fracture in the elderly. It is characterized by a reduced amount of bony tissue per unit volume of bone in the affected part or parts of the skeleton. Unlike osteomalacia, there are no known specific biochemical abnormalities in osteoporosis and most authors agree that osteoporotic bone, while reduced in quantity, is essentially normal in chemical composition.[7]

The investigation of osteoporosis has been handicapped by the lack of satisfactory objective radiodiagnostic criteria. The Medical Research Council's Mineral Metabolism Unit has developed 2 quantitative measures.[8] The first method is X-ray densitometry and the second isotope densitometry. Lanzl and Strandjord[9] have also reported on a radio-isotopic device for measuring bone mineral. Unfortunately none of these techniques can give direct measurements; in this respect bone biopsy alone is the method of choice.

The pathogenesis of osteoporosis is obscure. The osteoporotic process commences or accelerates in women soon after the natural or induced menopause.[6,7,10-12] For this reason Albright *et al.*[6,13] attributed the condition to gonadal insufficiency resulting in a reduced rate of synthesis of bone collagen (matrix). This theory has not been substantiated by most isotope kinetic studies[14,15] and tends to be refuted by histological evidence suggesting bone resorption and normal bone formation.[2,3] This recent work, (reviewed by Nordin *et al.*)[16] demonstrating increased bone resorption possibly related to calcium deficiency[17] rather than decreased bone formation as the likely cause of osteoporosis, has cast doubt not only on the collagen theory but also on the role of the gonadal hormones.[18] Although doubt has been accentuated by the absence of convincing evidence that osteoporosis responds to treatment with gonadal hormones, it does appear that osteoporosis is related to endogenous oestrogen deficiency.[7] However, the evidence is circumstantial and not all workers are in agreement.[19,20] It seems that, although the osteoporosis of postmenopausal women may ultimately be due to hormonal deficiency, its immediate cause must lie in the regulation of calcium absorption or excretion.[7,21-23]

OESTROGENS AND CALCIUM METABOLISM

Factors as described above have focused attention on the menopause and therefore on the effects of the oestrogenic hormones on calcium metabolism. Jasani *et al.*[22] considered that careful measurement of plasma calcium might be one way of distinguishing whether the negative calcium balance of osteoporosis is secondary to a primary rise in bone resorption, or whether the rise in bone resorption is the result of an external negative calcium balance. They theorized that 'if the loss of oestrogenic activity has a direct effect upon bone resorption and increases the release of calcium into the plasma, it will tend to raise the serum calcium and so also the urinary calcium. If, on the other hand, oestrogens tend to increase either the renal tubular reabsorption of calcium or the absorption of calcium from the small intestine (or both) then deficiency of oestrogenic hormones (unless associated with an increased calcium intake) would tend to lower the plasma calcium and consequently increase the rate of bone resorption in order to maintain the plasma level. Thus the difference between these two processes is in their effect on plasma calcium (see Fig. 1).

'According to one hypothesis, oestrogens would tend to lower urinary calcium thereby raising the plasma level and reducing bone resorption; according to the other, oestrogens would tend to lower plasma calcium and so lower urinary calcium and improve calcium balance'.

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Their preliminary results suggested that oestrogens do not raise the plasma calcium and that the menopause (oestrogen deficiency) is associated with a slight rise in plasma and urinary calcium. They therefore suggested that oestrogenic hormones have an action on the blood/bone equilibrium antagonistic to that of parathyroid hormone

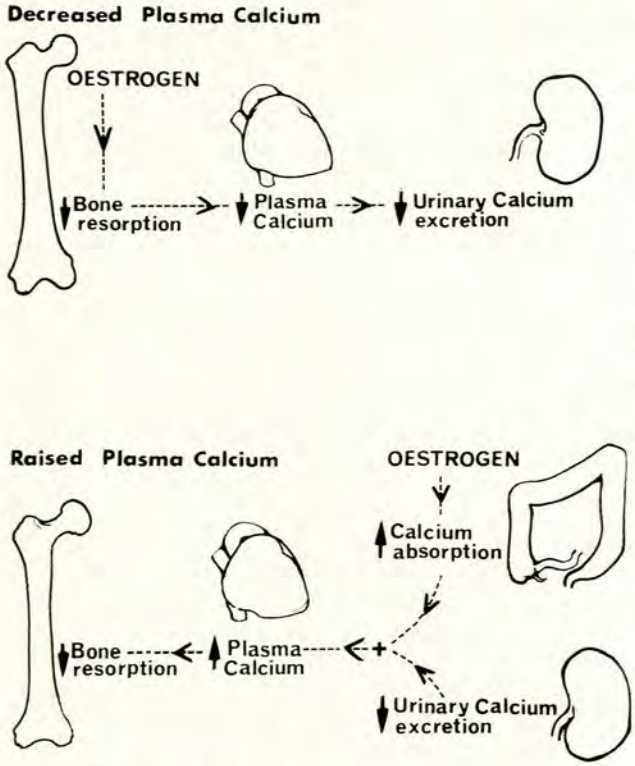

Fig. 1. Diagram of theoretical effect of oestrogen on plasma calcium.

and that a reduction of oestrogenic activity leads to a marginal elevation of plasma calcium and so to hypercalciuria and to negative calcium balance. They have suggested, moreover, that parathyroid hormone can break down bone more easily when oestrogens are not present. The degree of osteoporosis which this produces must depend upon the length of time which elapses before the subject re-adapts to the new situation.

A further report[23] showed a significant rise in plasma and urinary calcium and phosphorus values after the menopause. In the premenopausal women, fasting plasma calcium was 9·32 mg/100 ml and phosphorus 3·31 mg/100 ml. After the natural menopause the corresponding values were 9·62 and 3·52. After the artificial menopause the corresponding values were 9·81 and 3·62. The rise of plasma and urinary calcium was most apparent during the first years after the cessation of menstrual periods. They interpreted these changes to mean that the menopause is followed by a rise in bone resorption which leads to a rise in plasma and urinary calcium and phosphorus. Szymendera and Madajewicz[24] have reported similar findings.

Although the above biochemical changes can be reversed by oestrogenic hormones,[25] there is scant evidence of improvement of osteoporosis following such therapy. Lafferty *et al.*[18] found that oestrogens primarily reduce bone resorption and do not stimulate bone formation. In fact, after prolonged administration a secondary decline in bone formation occurred. Thus, despite publications[26,28,29] suggesting prophylactic oestrogen therapy and reports on relief of symptoms, there is little evidence of increased bone formation by densitometry, X-ray or histological studies.[1,18,20,27]

GROOTE SCHUUR STUDY

This study was planned to incorporate an investigation into plasma calcium, phosphorus and alkaline phosphatase levels. Thus there was no attempt to demonstrate the development of frank osteoporosis; rather an attempt was made to prove one step in the pathogenesis of the disease. The purpose was to compare oophorectomized to non-oophorectomized patients and then to study further the effect of various exogenous oestrogens on the above parameters.[5]

Plasma alkaline phosphatase levels were performed for the sake of completeness. There are two important causes for raised serum alkaline phosphatase activity: those diseases of bone in which there is increased osteoblastic activity; and the diseases of the liver, especially where there is obstruction to the outflow of bile.[30] These levels, therefore, have an established place in the investigation of suspected diseases of bone.

It is not the purpose of this article to present the detailed results, which are reported elsewhere,[5] but to summarize the more important and pertinent findings and define the place of such effects with regard to prevention and treatment of osteoporosis.

The principal aims of the study required a detailed clinical history and examination and the collection of material from varying groups of women whose samples would reflect an average physiological status for the group in question. The acquisition of this comprehensive material from sufficient patients and on repeated occasions over a period of 1 year for each patient posed a difficult organizational problem. Accordingly, a special Menopause Clinic was established in the Outpatient Department of Groote Schuur Hospital. This was conducted at a regular time each week for 2 years. The study comprised inpatients gathered for follow-up and outpatients who were recalled following a survey of the records of the Department of Gynaecology.

Patients were selected according to strict criteria. The only variable features related to the state of the ovaries and uterus. These groups included normal premenopausal females and patients who had undergone hysterectomy with and without bilateral oophorectomy.

Plasma calcium, inorganic phosphorus and alkaline phosphatase values were determined for patients in the above groups and then statistically compared. A group of 50 oophorectomized female volunteers were further observed for a period of 1 year, during which time control observations preceded single-blind cross-over administration of 2 forms of oestrogen and a placebo. The post-

oophorectomy groups were selected for detailed study because the climacteric cannot be accurately timed. Hence it is virtually impossible to collect a study group of human material at an accurately timed menopause other than in this way. Treatment was prescribed or changed according to Table I.

TABLE I. TREATMENT SCHEDULE FOR OOPHORECTOMY GROUP

Visit No.	Drug administered after investigation completed	Dosage (mg/day)	Time lapsed since previous visit (months)
1	Oestradiol valerate (Progynova, Schering)	4	—
2	Oestradiol valerate	4	1
3	Oestradiol valerate	4	2
4	Oestradiol valerate	4	3
5	Placebo—single-blind		3
6	Conjugated equine oestrogen (Premarin, Ayerst)	5	3

The results, in summary, were as follows.[5] Comparison between normal premenopausal patients and groups following hysterectomy with and without ovarian conservation showed no difference in the range of values of plasma calcium. Nevertheless, administration of conjugated equine oestrogen resulted in a significant lowering of the mean plasma calcium values ($P<0.0025$). In this effect conjugated oestrogen was also shown to be statistically superior to oestradiol valerate.

The plasma inorganic phosphorus values were more difficult to interpret. Although the findings suggest that the ovary is effective in either causing a reduction in or preventing an elevation of plasma inorganic phosphorus, it is impossible to place any strict interpretation on the results. Nevertheless, exogenous oestrogen replacement therapy was shown to be effective in reducing plasma inorganic phosphorus, and this property was common to both forms of oestrogen used.

The average values for alkaline phosphatase in all the groups investigated were well within the range of normality. This is supportive evidence that no patients admitted to the investigation were suffering any manifest forms of bone disease.

GENERAL DISCUSSION

Young and Nordin[23] demonstrated a significant rise in plasma and urinary calcium and phosphorus values after the menopause. In their premenopausal women, plasma calcium was 9·32 mg/100 ml and phosphorus 3·31 mg/100 ml (9·68 and 3·63 in the present study). After the artificial menopause the corresponding values were 9·81 and 3·62 mg/100 ml (9·68 and 3·63 in the present study). They found the rise of plasma and urinary calcium to be most apparent during the first years after the cessation of the menstrual periods. These findings were confirmed by Szymendera and Madajewicz.[24] Young and Nordin[23] interpreted these changes to mean that the menopause is followed by a rise in bone resorption which leads to a rise in plasma and urinary phosphorus. The phosphorus values of the Groote Schuur investigation[5] were similar and this interpretation is acceptable. The failure of the Groote Schuur investigation to confirm the changes in plasma calcium with menopause is inexplicable, especially in view of the fact that the methods of measurement were similar in both instances (Autoanalyzer) and the effect of oestrogen on plasma calcium was so dramatic in the present study.

The present investigation in fact demonstrated exogenous oestrogen therapy to be extremely effective in reducing plasma calcium and inorganic phosphorus values in oophorectomized females. These findings confirm those of Jasani *et al.*,[22] who found that a significant fall of plasma calcium could be demonstrated following oestrogen administration, provided the plasma calcium was measured by Autoanalyzer and not by flame-photometry. They suggested, as a result of their study, that oestrogenic hormones have an action on the blood/bone equilibrium antagonistic to the parathyroid hormone. The fall in plasma calcium and inorganic phosphorus has been shown to be due primarily to reduced bone resorption.[2,18] Referring back to Fig. 1 it now becomes obvious which mechanism for oestrogen control of plasma calcium is in fact operative. Jasani *et al.*[22] calculated that, since the sites of bone loss appear to be highly selective,[7] a negative calcium balance of only 50 mg daily for 5 years (15 - 20 g calcium) would be sufficient to destroy a significant amount of trabecular bone.

Taking into account the findings and discussion above, the conclusion of the present investigation is that exogenous oestrogen therapy tends to lower plasma calcium and inorganic phosphorus, presumably by inhibiting bone resorption. Such therapy is therefore of potential value in the prevention of oesteoporosis and is indicated, at least, in the premenopausal female who undergoes the operation of bilateral oophorectomy. These findings in relation to bone metabolism could be used as a reason for prescribing oestrogens prophylactically to all women for life from the menopause onwards.

An interesting observation of the present investigation[5] was the disparity in effect of the two forms of oestrogen administered. Conjugated equine oestrogen was extremely effective in reducing the plasma calcium levels whereas oestradiol valerate was statistically ineffective. Both oestrogens were effective in reducing plasma inorganic phosphorus, the conjugated oestrogens being slightly more effective. There are no satisfactory comparative trials in the literature. However, Young *et al.*[25] have shown that administration of ethinyl-oestradiol to postmenopausal women was associated with a small but significant fall in plasma calcium and phosphorus. Wallach and Henneman[29] suggested that diethylstilboestrol and conjugated equine oestrogens were prophylactic against postmenopausal osteoporosis, their observations being clinical and radiological. Hernberg[27] found a negligible reduction in height during ethinyl-oestradiol and hexoestrol treatment in comparison to control cases of the same age group. Neither Hernberg[27] nor Wallach and Henneman[29] included calcium kinetic studies in their investigations, nor did they differen-

tiate between the specific types of oestrogen used. In both instances all cases treated were analysed together as a single group. The present investigation is therefore considered of importance in indicating that certain oestrogens are more likely to be effective than others in the future management of oesteoporosis and a strict evaluation of all available oestrogenic substances is considered to be a subject for further research.

CONCLUSIONS

Exogenous oestrogen therapy tends to lower plasma calcium and inorganic phosphorus, presumably by inhibiting bone resorption. Such therapy is therefore of potential value in the prevention of osteoporosis and is indicated, at least, in the premenopausal female who undergoes the operation of bilateral oophorectomy. By similar argument it would appear in this instance that there is some cause for administration of appropriate oestrogens to all women from the menopause onwards.

It is stressed, however, that the possible mode of action of such oestrogen therapy is that of inhibition of bone resorption. Once frank osteoporosis has developed, it is extremely unlikely that exogeneous oestrogen replacement therapy has any role to play in the treatment. Thus exogenous oestrogens are of potential value in the prevention, but not the treatment of osteoporosis.

The discussion and findings presented are further[31] arguments in favour of conservatism with ovaries during gynaecological operations on young females.

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