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# THE EFFECTS OF OOPHORECTOMY ON SKELETAL METABOLISM

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**Summary**—The effects of oophorectomy on the biological indices of bone remodelling and the time-course of their changes are described. In the first few months following surgical menopause the measurement of the markers of bone remodelling indicates that the increase in osteogenesis is delayed compared with that of bone resorption; this prevalence of destruction over new bone deposition justifies the deficiency of skeletal balance, shortly after acute oestrogen deficiency.

The changes in bone remodelling are accompanied by an increase in serum calcium while serum immunoreactive parathyroid hormone levels remain unchanged or even decrease, suggesting a shift to right of the parathyroid gland set-point.

The reasons for the negative skeletal balance after oophorectomy might be sought therefore at bone tissue level, even if changes in responsiveness and/or of the parathyroid gland set-point could also be contributory.

## INTRODUCTION

Bone mass decreases physiologically with aging in both sexes [1]. In women, however, the rate of bone loss accelerates at the beginning of menopause [2] as soon as oestrogen synthesis decreases and serum levels of pituitary gonadotropins increases [3].

## BONE REMODELLING FOLLOWING OESTROGEN DEFICIENCY

The pathogenetic role of oestrogen deficiency has been well recognized; in a recent study we have in fact shown (Fig. 1) that 3 yr after natural menopause bone mineral density measured at an ultradistal radial point, was already reduced by about 13% compared with mean values of age-matched premenopausal women [4]. The loss of bone mass caused by oestrogen deficiency was accompanied by an increase in skeletal turnover revealed by the increment in both the bone resorption and formation markers. Secondly, and most important, all these metabolic changes are prevented by oestrogen replacement therapy [5].

The extent of bone loss appears to be correlated with the degree of oestrogen deficiency. In fact, in women with surgical menopause following oophorectomy, bone mineral density is lower than in subjects of the same age with physiological menopause lasting the same length of time (Fig. 2). The increment in skeletal turnover following surgical menopause caused by oophorectomy is even greater. In this case, measurement of the biological indices of bone remodelling indicates that the increase in osteogenesis is delayed compared with that of bone resorption (Fig. 3). The prevalence of destruction over new bone deposition justifies the deficiency of skeletal balance in the first few months following surgical menopause.

## THE PATHOGENESIS OF BONE LOSS

Three hypotheses have been postulated to explain the bone loss caused by oestrogen deficiency; in this context, the evaluation of the main parameters of skeletal metabolism, measured after oophorectomy, appears to be explanatory.

When the oestrogen level falls, the urinary excretion of hydroxyproline increases rapidly, reaching their maximum values 1–2 months after surgery, while serum immunoreactive parathyroid hormone (PTH) levels remain

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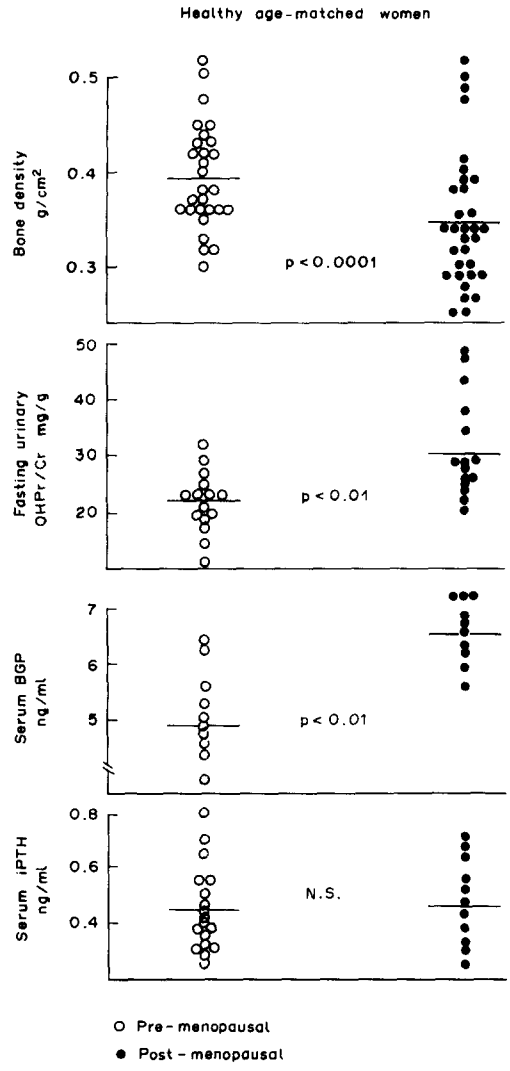


Fig. 1. Bone mineral density, bone remodelling indices and serum immunoreactive parathyroid hormone in healthy pre- and postmenopausal age-matched women.

unchanged or even decrease [6]. This observation excludes the possibility that the decreased intestinal calcium absorption and/or the reduced synthesis of $1,25(OH)_2D$ may represent

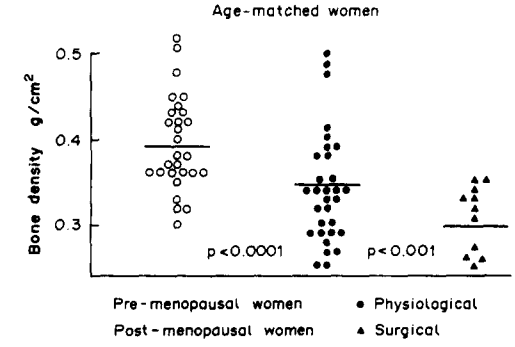


Fig. 2. Ultradistal radius bone density in pre- and postmenopausal (physiological and surgical) age-matched women.

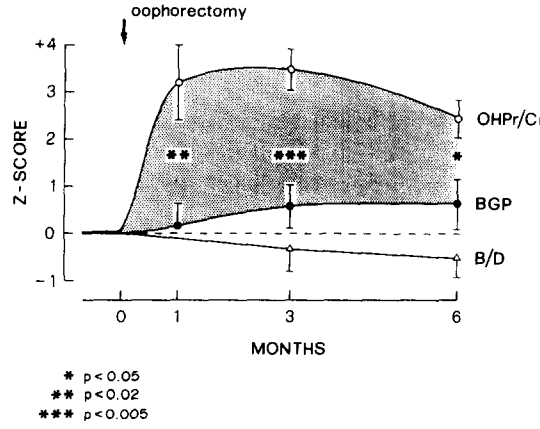


Fig. 3. The effect of oophorectomy on the behavior of serum osteocalcin (BGP) and hydroxyproline/creatinine ratio, both expressed as Z-score.

the first step of the mechanism leading to the increment in skeletal resorption, typical of the postmenopausal period.

On the contrary this observation suggests that the decreased synthesis of $1,25(OH)_2D_3$ is secondary to the reduction, for homeostatic reasons, of parathyroid gland secretion, supporting; the hypothesis that the loss of bone mass due to the lack of oestrogen is caused by a higher skeletal resorption, secondary to a greater responsiveness of bone to PTH [7].

It has recently been suggested that changes in calcium-phosphorus metabolism caused by oestrogen deficiency may be attributed to a shift to right of the parathyroid gland set-point [8]. In

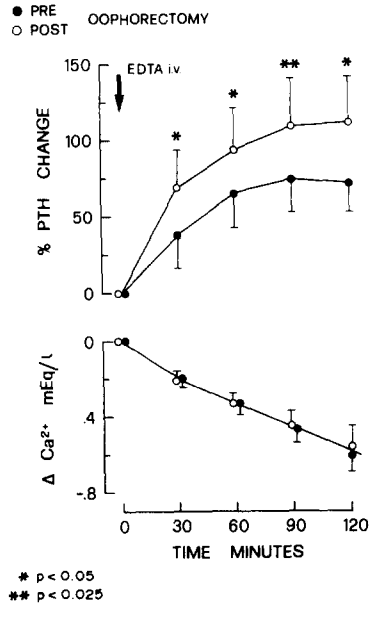


Fig. 4. The effect of $Na_2EDTA$ infusions on serum calcium and immunoreactive parathyroid hormone in normal women before and after oophorectomy.

fact, it is difficult to explain the lack of changes in serum PTH levels in the presence of both hypercalcemia which follows menopause and hypocalcemia induced by the administration of oestrogens. In other words, the increase in urinary calcium excretion observed immediately after menopause could be the consequence of hypercalcemia due to the shift of the parathyroid gland set-point to right; this is, in turn, responsible for the increased skeletal resorption necessary for the maintenance of calcium homeostasis. The finding that the regression slope between parathyroid hormone and blood calcium levels, which is observed after induced hypocalcemia, is significantly modified after oophorectomy is in agreement with this hypothesis (Fig. 4). After oophorectomy the regression slope in fact becomes steeper, thus suggesting higher sensitivity of parathyroid glands to calcium in absence of oestrogens [9].

The reasons for the negative skeletal balance caused by oestrogen deficiency should therefore be sought at the local level where oestrogen could act either indirectly by modulating the effects of the factors which stimulate bone resorption, or directly at the bone cellular level where receptors for these hormones have recently been discovered [10].

However changes in the responsiveness and/or of the parathyroid gland's set-point could also contribute to the establishment of a negative balance. The latter hypothesis might reconcile the different opinions concerning the relationships between the intestinal calcium absorption, $1,25(OH)_2D$ and bone resorption. In fact, a higher sensitivity of parathyroid glands to calcium implies a higher instability of the homeostatic system and therefore higher PTH serum levels when serum calcium tends to fall or vice versa, higher inhibition of serum PTH when serum calcium increases.

Consequently, in presence of decreased intestinal calcium absorption caused by oestrogen deficiency, an increased sensitivity of parathyroid glands may cause higher serum PTH levels and higher bone resorption.

## PREVENTION OF BONE LOSS

Oestrogen replacement therapy is the most pathophysiological approach to the prevention of bone loss following oophorectomy. However a recent study from our laboratory suggests that also the administration of calcitonin at a dose of 100 IU injected every other day for 12 months is able to prevent the loss of skeletal mass caused by ovarian surgery [11]. Calcitonin treatment if begun early, may therefore represent a valid alternative to oestrogen therapy at least in patients in whom the latter treatment is contraindicated.

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