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HORMONAL PREVENTION AND TREATMENT OF OSTEOPOROSIS—STATE OF THE ART 1990

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Summary—Osteoporosis is a growing disease, and attention should be directed to possible means of preventing and treating this disease. Osteoporosis may be caused by a number of diseases (secondary osteoporosis), but it most often occurs in otherwise healthy persons. The major risk factors are a low bone mass at skeletal maturity, and a rapid bone loss.

Postmenopausal bone loss may be prevented by hormone replacement therapy. All types of oestrogens and all administration forms are effective, as long as a sufficient serum concentration is obtained.

The greatest benefit of hormone replacement therapy is obtained if instituted right after the menopause, when the bone loss is most rapid. But oestrogen will also arrest the bone loss when instituted much later in life.

INTRODUCTION

Osteoporosis is a growing problem with overwhelming personal expenses. Furthermore, the cost to society will soon reach a level where the question is how this expense should be covered. Osteoporosis means low bone mass. It does not give any symptoms until the complications appear, i.e. bone fracture. The most characteristic osteoporotic fractures are the hip fracture, the spinal crush fracture and the forearm fracture. Osteoporotic fractures cause disability, pain, hospitalization, dependency and death.

Osteoporosis is more common in the elderly population and especially in women. It represents a major health problem. It is estimated that as many as 25 million American people, including 1 in 2–3 postmenopausal women, and virtually all very old people have sufficiently low bone mass to be at high risk of fracture.

Amplifying the tragedy of osteoporosis is the expansion of the most susceptible of the population, the aged, and an as yet unexplained increase in the age-adjusted incidence of hip fracture. It is evident that attention must be directed to possible means of preventing and treating this disease.

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PRIMARY AND SECONDARY OSTEOPOROSIS

Osteoporosis may be the result of a number of diseases or conditions known to influence the calcium metabolism (secondary osteoporosis), but occurs more commonly without a known underlying disease (primary osteoporosis). The pathogenesis of primary osteoporosis is thus obscure. Major determining factors are a low peak bone mass and/or a rapid bone loss.

PEAK BONE MASS

Peak bone mass is probably mostly determined by genetic factors [1], but environmental factors, such as diet [2] and exercise [3], may also play a role. Men have on the average a 20% higher peak bone mass than women [4].

BONE LOSS

It is generally believed that both men and women start to lose bone mass some time after peak bone mass has been reached [4–6]. This loss is small (3–5% per decade) and has been compared with the age-related loss of other functions, such as muscle mass [4]. Compared with muscle mass, men and women have the same peak bone mass; men do not lose more bone mass than muscle mass. In men this slow bone loss continues throughout life. The pathogenesis of the age-related bone loss is not clarified, and both genetic and environmental factors may play a role.

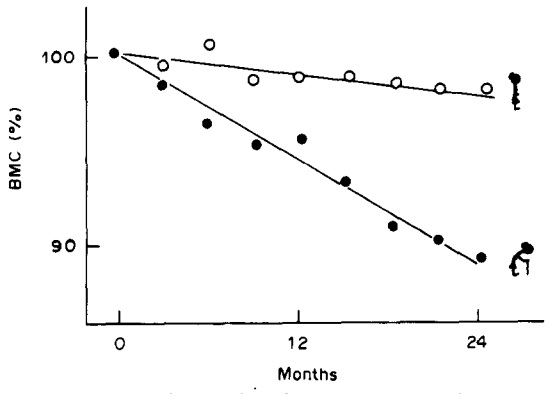

Fig. 1. Bone loss in two healthy postmenopausal women over 2 yr. (Copyright C. Christiansen, used with permission).

Whereas bone is lost at the same rate in men throughout life, in women it is accelerated in the years around the menopause [5–8]. The postmenopausal bone loss is independent of the age-related loss of muscle mass. All women are exposed to this accelerated bone loss, but the individual variation is wide (Fig. 1) [9]. On *average*, postmenopausal women lose approx. 2% of their bone mass a year, but more than a quarter of all postmenopausal women lose above 3% a year. The postmenopausal bone loss follows an exponential curve, and will thus level off after about 8 yr [6, 10]. The pathogenesis of the postmenopausal bone loss is still not understood, although its close relation to female sex hormones is widely established. Recent studies have furthermore suggested that estrogens have a direct action on bone via estrogen receptors [11, 12].

The difference in peak bone mass and bone loss between men and women explains why osteoporosis is much more common in women than in men. The individual variation in the postmenopausal bone loss may further explain why some, but not all women develop osteoporosis.

THE ESTROGEN ACTION ON BONE

Postmenopausal bone loss is mainly estrogen-dependent and is prevented completely by estrogen substitutional therapy [13, 14]. It is possible that postmenopausal bone loss may be aggravated by the same factors that may influence age-related bone loss, but correction of these factors will only affect the bone loss to a limited extent.

All conditions of estrogen deprivation result in loss of bone, i.e. natural or surgical menopause, drugs that inhibit the estrogen production/effect (LH-RH antagonists, anti-estrogens), or heavy exercise, or other conditions which provoke anovulation. The withdrawal of estrogen primarily affects the bone resorption, as shown by a rapid increase in the biochemical estimates of bone resorption [15]. Owing to the coupling of bone resorption and formation, bone formation will show a secondary increase, reflected by a delayed elevation in the biochemical estimates of bone formation [15].

It is self-evident that all kinds of bone loss are the result of an imbalance between bone resorption and bone formation, which implies that, in the case of postmenopausal bone loss, bone resorption is increased more than bone formation. The differences between the two processes seems to be greatest in the first few years after the menopause (where bone loss is largest), whereas in the long-term it moves towards a new steady-state at a higher level.

Postmenopausal estrogen therapy rapidly normalizes both the bone resorption and the formation, leading to a re-establishment of bone balance [16, 17].

The mechanism behind the estrogen action on bone is, as mentioned, unknown, but recent studies indicate that the effect is mediated via estrogen receptors located in osteoblasts [11, 12].

It is clear that all types of estrogen (synthetic, conjugated, human) prevent estrogen-dependent bone loss, if they are given in adequate doses [18–20]. In postmenopausal women, conjugated or human estrogen seems to be most appropriate, because they may produce less metabolic side effects. Human estrogens have furthermore been shown to be effective when given percutaneously [17] (Fig. 2) or by other

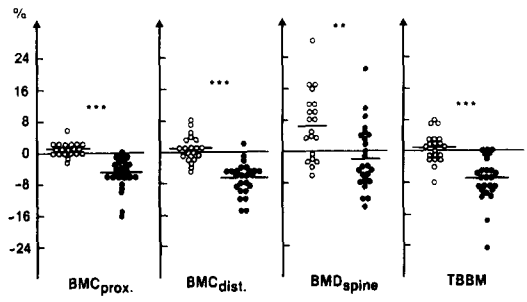

Fig. 2. The effect on bone mineral content in the distal ($BMC_{prox.}$) and ultradistal ($BMC_{dist.}$) parts of the forearm, the spine (BMD_{spine}), and total body bone mineral (TBBM) after 2 yr of treatment with percutaneous estradiol. (Copyright C. Christiansen, used with permission).

parenteral routes [21, 22], provided the serum concentration of estradiol is sufficient. The greatest benefit of estrogen therapy is obtained if it is instituted just after the menopause, when the bone loss is most rapid. But estrogen therapy will arrest the bone loss at whatever time of life it is instituted [23].

It is generally agreed that when oestrogen therapy is stopped the consequent bone loss will follow a curve similar to what it would have been had estrogen therapy never been instituted, i.e. the estrogen effect is life-long [13].

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