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Tissue-Specific Estrogens — The Promise for the Future

As life expectancy continues to increase, women will soon be postmenopausal for one third of their lives. The human and economic costs of this increased longevity in an estrogen-deficient state are substantial. They include a projected increase in cardiovascular events, the leading cause of death among postmenopausal women, and in osteoporotic hip fractures, which are associated with a 20 percent mortality rate within the first year. However, despite the well-established efficacy of estrogens in protecting women against cardiovascular disease and maintaining bone density and reducing fractures, less than one fifth of postmenopausal women ever take them.[1] Furthermore, the proportion who take estrogen for a prolonged period — an important prerequisite for efficacy — is even smaller because of the reluctance of physicians to prescribe estrogens and of women to accept such a prescription. This reluctance is based on the high incidence of side effects: vaginal bleeding, breast swelling and tenderness, and an increased risk of endometrial and breast cancer.[1] Hence the pressing need for "designer estrogens," a growing family of compounds also known as selective estrogen-receptor modulators. These tissue-specific estrogens were designed to preserve the beneficial effects of estrogens, including protection against cardiovascular diseases and osteoporosis, but to have no undesired effects on the reproductive organs.

Raloxifene is one of these compounds. In ovariectomized rats it maintains bone mineral density and improves the serum lipid profile but has little estrogenic action on breast or uterine tissue.[2] In humans, too, it has a favorable effect on bone remodeling and serum lipid concentrations. In this issue of the *Journal*, Delmas et al. report a two-year randomized, placebo-controlled, dose-ranging trial of raloxifene in 601 normal white postmenopausal women.[3] At a dose of 60 mg per day, raloxifene maintained bone mineral density, lowered serum concentrations of total and low-density lipoprotein (LDL) cholesterol, and did not stimulate the endometrium. Specifically, the bone mineral density of the lumbar spine, total hip, femoral neck, and total body increased slightly (1.2 to 1.6 percent) in response to treatment with raloxifene. Serum concentrations of total cholesterol decreased by 6.4 percent and those of LDL

cholesterol decreased by 10 percent after three months, with no significant change thereafter. Serum concentrations of triglycerides and high-density lipoprotein (HDL) cholesterol did not change.

These beneficial effects on the skeleton and serum lipid profile are similar to those of tamoxifen[4,5] — which, however, causes endometrial stimulation — but are less strong than those of estrogen. Unlike estrogen, none of the selective estrogen-receptor modulators, including raloxifene, increase the serum concentrations of HDL cholesterol, an independent marker of protection against cardiovascular disease. The protective cardiovascular effect of estrogen is also partially mediated by an estrogen-induced vasodilatory effect and an antioxidant effect on lipoproteins that decreases their atherogenic potential. Similarly, raloxifene also inhibits LDL oxidation[6]; however, its effect on vascular tone is undetermined. The beneficial skeletal effect of raloxifene seems to be due mostly to an antiresorptive action on bone, thus inducing a positive calcium balance when administered over a long period at a dose of 60 mg per day.[7] Like estrogen, tamoxifen decreases plasma antithrombin III and fibrinogen concentrations; the effect of raloxifene on these substances and on the incidence of thrombophlebitis is not known.

The key role of estrogen and its receptor in the normal physiology of the skeleton and the reproductive organs is illustrated in two human syndromes, aromatase deficiency and estrogen-receptor–gene defect. Both are characterized by severe estrogen deficiency, the former because little estrogen is produced and the latter because of resistance to its action. Affected patients have incomplete epiphyseal fusion, with continued linear growth into adulthood, osteoporosis, and lack of sexual development in addition to insulin resistance.[8,9]

The central role of the estrogen receptor in skeletal physiology is further illustrated by studies aimed at elucidating the mechanism (or mechanisms) of action of estrogens and antiestrogens. Estrogens bind to the estrogen receptor, inducing a conformational change that leads to activation of gene transcription through specific estrogen-response elements of target genes. Transcriptional activation of these genes is thought to occur through two distinct domains of the estrogen receptor, AF-1 and AF-2. Differential activation of these two domains by estrogens and antiestrogens explains the tissue selectivity of the latter. Peptide growth factors stimulate estrogen-dependent transcriptional activation of estrogen-response elements and are themselves activated by the estrogen receptor. Indeed, estrogens and raloxifene may partially maintain bone mass through regulation of the gene for transforming growth factor β (TGF-β) by means of the estrogen receptor. Deletion of the ligand-binding domain of the estrogen receptor abolishes both estradiol- and raloxifene-induced activation of the TGF-β promoter. However, deletion of the AF-1 domain of the estrogen receptor abolishes estradiol- but not raloxifene-induced TGF-β activation, and deletion of the AF-2 domain abolishes raloxifene- but not estradiol-induced activation of the TGF-β promoter.[10]

The promising results of the study by Delmas et al. pave the way for important additional investigations. Despite the beneficial effects of raloxifene on bone mineral density and the serum lipid profile, its effect in preventing fractures and cardiovascular events is yet to be determined. The absence of vaginal bleeding and of endometrial or breast stimulation reported by Delmas et al. in women receiving raloxifene, as well as preliminary results demonstrating a decrease in the risk of breast cancer (reported

at the National Osteoporosis Foundation Meeting in Washington, D.C., in June 1997), are added benefits that should improve compliance among women taking this new type of hormone-replacement therapy. However, 25 percent of the women in the trial reported by Delmas et al. discontinued therapy. The proportions were similar in all treatment groups, as were the proportions experiencing hot flashes. The absence of an increase in hot flashes among the women given raloxifene is surprising; an increase, such as occurs with tamoxifen, might have been expected.

The favorable effect of raloxifene on bone mineral density and serum lipid concentrations and the absence of any effect on endometrial histology are quite encouraging. The decrease in estrogen-related adverse effects with the selective estrogen-receptor modulators in general and raloxifene in particular should improve compliance and decrease the incidence of cardiovascular events and fractures while not increasing breast cancer. The challenge is to realize this promise.

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