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Estrogens, Estrogen Agonists/Antagonists, and Calcitonin

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ESTROGEN

It is well established that osteoporosis is more common in women than men and fracture risk increases dramatically after menopause. The relationship between estrogen deficiency and osteoporosis was first suggested in the mid-1900s when Albright showed that treatment with estrogen reversed the negative calcium balance in postmenopausal women. The positive effects of estrogen on peak bone mass and on bone loss have been demonstrated in both men and women. For years, estrogen was considered the treatment of choice for postmenopausal women and widely advocated for prevention of bone loss, with numerous trials showing prevention of bone loss in recently menopausal women and increased of bone mineral density (BMD) in women with postmenopausal osteoporosis. Part of the emphasis on estrogen therapy was the assumption of extraskeletal benefits (lower rates of cardiovascular events and dementia in women who chose to take estrogen compared with those who chose not to) and also that the benefits would be durable after estrogen was stopped.

The Women's Health Initiative (WHI) confirmed the value of estrogen administration (with or without a progestin) in the treatment of osteoporosis and reduction of risk for hip and other clinical fractures. However, the presumed extraskeletal benefits were not confirmed, and the effects on BMD and fracture reduction disappeared within a year of discontinuation of estrogen (loss of BMD of approximately 5% in the first year after stopping). Thus, it appears that estrogen has protective effects on the skeleton only for as long as it is taken. However, women who take estrogen and then stop should be no worse off compared with women who have never taken estrogen at all.

Following results of the WHI, estrogen treatment is recommended for relief of menopausal symptoms, but in the lowest dose and for the shortest time necessary. Most women are not sufficiently symptomatic at menopause to require estrogen therapy, and most who require estrogen will be able to stop after a few years. However, a minority will require estrogen long-term. For those women, estrogen may be sufficient for prevention and/or treatment of osteoporosis.

Several different forms of estrogen are available for therapeutic use (e.g., estradiol, conjugated estrogen esterified estrogens, etc.) as well as several routes of administration (e.g., oral, transdermal). In addition to different compounds and routes of administration, the dose can vary as well. After hysterectomy, estrogen can be use "unopposed"; however, for women who still have their uterus, "opposing" estrogen with a progestin (of which there are several,e.g., progesterone, medroxyprogesterone acetate) is recommended for protection against endometrial hyperplasia and endometrial carcinoma. The specific therapy that was shown to reduce fracture risk in WHI was orally administered conjugated estrogen, 0.625 mg daily (also effective was the combination of 0.625 mg conjugated estrogen plus medroxyprogesterone acetate 5 mg daily; however, there is little or no evidence that progestins have any effect on bone). It is likely, but

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not proven, that other estrogen preparations, as well as lower doses, might have beneficial effects on maintenance of BMD and reducing fracture risk.

Estrogens are considered by many to be "antiresorptive agents"; however, they reduce the rates of both bone resorption and bone formation but reduce resorption more than formation.

In summary, despite its important role in physiology and pathophysiology, estrogen is not recommended for prevention or treatment of postmenopausal osteoporosis, but should provide protection against bone loss and fractures for women who require estrogen from relief of menopausal symptoms.

ESTROGEN AGONISTS/ANTAGONISTS (SELECTIVE ESTROGEN RECEPTOR MODULATORS OR SERMS)

Tamoxifen, widely used for treatment and prevention of breast cancer, was thought of as an antiestrogen, based on the concept that a compound that blocked estrogen receptors in breast tissue would reduce the risk of recurrence or spread of breast cancer. Clinical trials of tamoxifen in postmenopausal women that were expected to show acceleration of bone loss actually showed modest gains in BMD, as well as decreases in bone turnover markers, establishing that this compound blocks the effect of estrogen in some tissues but acts like estrogen in others.

Rather than being an antiestrogen, tamoxifen and functionally related compounds are classified as estrogen agonists/antagonists, also known as selective estrogen receptor modulators (SERMs) and tissue-selective estrogens. They bind with estrogen receptors, activating estrogen pathways in some tissues and blocking them in others. Effects appear to be similar and consistent in some tissues (e.g., antagonists to estrogen in breast tissue and partial agonists in bone) but compound-specific in others (e.g., some stimulate the endometrium, while others are neutral, and still others are antagonists). The ideal compound would relieve menopausal symptoms (including vasomotor symptoms and vaginal dryness), maintain or increase BMD and reduce the risks of fractures at all skeletal sites, as well as reducing the risks of cardiovascular disease, dementia, genitourinary problems, and breast, endometrial, and ovarian cancer without increasing the risk of venous thromboembolic events. This "holy grail" has not yet been attained. Several promising compounds failed or have been limited because of safety concerns (tamoxifen increases the risk of endometrial hyperplasia and carcinoma) or because the skeletal effects were limited to reducing fractures in the spine, with no effect on nonvertebral sites.

Raloxifene, the first of these agents specifically marketed for positive bone effects and given orally in a dose of 60 mg daily, was shown to prevent bone loss in recently menopausal women and increase BMD in postmenopausal women, although the gains in BMD appear to be about half of what is observed with estrogen. The risk of new and worsening vertebral fractures was significantly reduced, but raloxifene has not been shown to have an effect on hip and nonvertebral fractures. Confirming a reduction in breast cancer noted in the osteoporosis study, raloxifene was shown in the Study of Tamoxifen and Raloxifene (STAR) trial to reduce the risk of breast cancer in postmenopausal women at increased risk of breast cancer and in postmenopausal women with osteoporosis. Raloxifene does not stimulate the endometrium. Although raloxifene has effects on lipids that suggest it might be cardioprotective (decreased triglycerides, total, and LDL cholesterol), no benefit was shown in the large Raloxifene Use for the Heart (RUTH) trial. The occurrence of stroke was not different between raloxifene and placebo groups; however, there were more fatal strokes in the raloxifene group. Enthusiasm for the use of raloxifene has been limited because of the lack of evidence for protection against hip and other nonvertebral fractures, as well as side effects and safety concerns (increased menopausal symptoms, increased risk of venous thromboembolic events such a deep vein thrombosis, pulmonary embolus, and retinal vein thrombosis). The increase in venous thromboembolic events is similar to estrogen and is highest during the initial months of treatment.

Several estrogen agonists/antagonists have fallen by the wayside, while a few have made it into Phase 3 trials for osteoporosis. Commercialization of arzoxifene was abandoned because of lack of protection against hip and other nonvertebral fractures. Lasofoxifene and bazedoxifene are approved in Europe but not in the U.S. Bazedoxifene has been studied in combination with estrogen, with the estrogen improving vasomotor symptoms and vulvovaginal atrophy.

CALCITONIN

In humans, calcitonin is a 32-amino acid peptide produced by specialized C cells in the thyroid. Osteoclasts express receptors for calcitonin and respond to calcitonin with a rapid decrease in resorptive capacity. Unlike estrogen deficiency in adults, which has been shown to cause bone loss and increase fracture risk, there is no evidence for an important physiologic effect of calcitonin in adults, and patients with calcitonin deficiency (i.e., after total thyroidectomy) show no changes in skeletal status or mineral homeostasis. As a pharmacologic agent, human, eel, and salmon calcitonin have all been tried, but synthetic salmon calcitonin has been the major product in clinical use. Given by subcutaneous injection, salmon calcitonin has been use to treat Paget's disease, hypercalcemia, and osteoporosis but with significant side effects of injection site reactions, flushing, and nausea in up to 20% of patients. In women with osteoporosis who were at least 5 years postmenopausal, nasal spray salmon calcitonin in a dose of 200 IU daily was shown to reduce the

risk of vertebral fracture and was well tolerated; however, lower (100 IU/day) and higher (400 IU/day) doses did not show an anti-fracture effect. Changes in BMD and bone turnover markers were minimal. There have been small trials of salmon calcitonin treatment in men with osteoporosis and men and women with glucocorticoid-induced osteoporosis.

Some patients appear to develop resistance to calcitonin, which could be due to the development of tachyphylaxis or the development of neutralizing antibodies. Treatment with calcitonin may lead to a reduction in plasma lithium due to increased renal clearance of lithium.

Although not included in the approved indications for calcitonin, studies suggest a possible analgesic effect, possibly mediated through an increase in circulating and central nervous system (CNS) endorphins, which may be clinically useful in patients with acute painful vertebral fractures.

An oral form of calcitonin is being studies as possible treatment for osteoarthritis and osteoporosis.

SUMMARY

Estrogen is indicated for relief of menopausal symptoms; for women who are candidates for estrogen either short term or long term, bone effects may be considered a "side benefit." Raloxifene has a limited role for prevention and treatment of osteoporosis and for reducing the risk of breast cancer. Nasal spray calcitonin has questionable evidence for beneficial effects on BMD, bone turnover markers, or fracture risk, but may have a role in reducing pain in patients with acute painful vertebral fractures.

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