Natural Estrogens:

A REVIEW of the PRIMARY LITERATURE

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Published data support the potential benefits of estradiol and estriol.

The average age of women at menopause has remained approximately 50.4 years for centuries.[1] Thus, women today may spend 30% of their lives with reduced ovarian hormonal concentrations. It is estimated that 75% to 85% may develop symptoms secondary to this hormonal decline that may require some form of hormonal replacement.[1] For years this has been accomplished by supplementation with synthetic estrogens. Synthetic estrogens, by definition, are not the same biological chemicals that exist in our bodies from birth but are only imitations that have similar characteristics. Unfortunately, synthetic estrogens also cause many unwanted side effects. Recently natural estrogens have been the topic of much discussion among health professionals. The natural estrogens, which include estrone, estradiol and estriol, are made up of the exact biological chemical composition that has been part of the make-up of mankind for millennia. In theory, treating hormonal deficiencies with natural estrogens should have many benefits over synthetic estrogens. In fact, countless books have been written on the subject and currently many patients do take natural estrogens for hormonal supplementation.

Many health professionals realize that natural-estrogen supplementation could have advantages over synthetic-estrogen therapies but the apparent lack of literature on the subject, combined with the busy schedule of a typical health professional and the questions surrounding natural estrogens, limits their use. The purpose of this review is to provide answers to many common questions about natural-estrogen supplementation based on information found in the current primary literature. To accomplish this, a literature search was conducted from 1966 through 1999 using the National Library of Medicine database, Medline. The most recently published studies were chosen for this review based on their ability to answer one of many common questions about natural estrogen replacement. Common inquiries include questions about cardiovascular effects, lipid metabolism, blood-clotting effects, bone resorption, urinary tract infections and skin aging. Other common questions address concurrent disease states such as hypertension and diabetes or routes of administration and dosage schedules. A brief synopsis discussing these issues forms the body of this review. Hopefully, this information will help physicians and pharmacists make the best professional choices for their patients concerning estrogen replacement therapy.

Cardiovascular Effects

Estradiol has a positive cardiovascular effect on postmenopausal women. The positive effects can be reached by using 2 mg/day of estradiol orally, 1 mg/day of estradiol sublingually or 50 µg/day transdermally. Patients will benefit even if they already have cardiovascular disease or have had a hysterectomy.[1-6]

Snabes and colleagues conducted a randomized, double-blind, placebo-controlled, crossover study of 31 healthy postmenopausal women volunteers to examine the effects of estradiol replacement therapy on cardiac structure and function. Subjects were given 2 mg of micronized estradiol or a placebo orally for 12 weeks, at which time echocardiography and Doppler techniques were used to assess the cardiac effects. Snabes and colleagues found that, while estradiol serum concentrations rose fifteenfold to 37.6 pmol/L, the treatment did not affect measurements of systolic function, diastolic function, left ventricular mass or pulmonary artery pressure at rest or during physical exertion ($p<0.01$). They concluded that estradiol replacement therapy, which results in physiologic serum concentrations, does not affect cardiac structure or function in normal postmenopausal women after 12 weeks of treatment.[2]

Rosano and colleagues conducted a randomized, double-blind study to examine the effect of estradiol on exercise-induced myocardial ischemia in women with coronary artery disease. Eleven women with confirmed coronary artery disease were given 1 mg of sublingual estradiol or a placebo 40 minutes prior to a treadmill exercise test. The time to 1 mm ST segment depression ($p<0.004$) and total exercise time ($p<0.01$) was increased by estradiol. Rosano and colleagues hypothesized that estradiol could lessen myocardial ischemia by reducing myocardial oxygen consumption through a decrease in the peripheral vascular resistance or by lowering preload. A possible alternative mechanism is a direct vasodilator effect on the coronary arteries. The authors concluded that this therapy could be a useful new treatment or an adjunct to existing therapy for stable angina in women. They also felt that this study may help explain some of the protection against coronary artery disease apparent in women before menopause and the protective effects of estradiol replacement therapy in postmenopausal women.[3]

Three other studies confirm the conclusions of Snabes and Rosano. The first, conducted by Volterrani and colleagues, also used 1 mg of sublingual estradiol and achieved similar results ($p<0.05$). Interestingly, six of the 11 patients in this study had undergone a hysterectomy.[4] The second, conducted by Riedel and colleagues, used blood-flow rates of the left common femoral artery in 23 postmenopausal women as an outcome measure of vascular response to 1 mg of sublingual estradiol. Estradiol induced a vasodilation of the femoral arteries compared to basal and placebo

measures ($p<0.001$).[5] The third, conducted by Cacciatore and colleagues, studied the long-term effects of oral and transdermal hormone replacement therapy (HRT) on carotid and uterine vascular impedance. This trial, which was conducted for one year, followed an open, randomized, controlled design and involved 63 postmenopausal patients who were assigned to use either estradiol 2 mg/day orally or transdermal estradiol 50 µg/day. Cacciatore and colleagues showed that both oral and transdermal estradiol are virtually identical in their ability to reduce carotid and uterine artery resistance to blood flow ($p<0.001$). They concluded that this long-term vascular effect may explain how estradiol protects women from cardiovascular disease.[6]

Lipid Metabolism

Estradiol has many positive effects on lipid metabolism. Estradiol, given orally or transdermally, reduces low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) cholesterol levels. In postmenopausal women, and even women who have had a hysterectomy, estradiol has been shown to reduce lipoprotein (A) (Lp(A)) levels, which are associated with an increased risk of coronary artery disease and cerebrovascular accidents. Doses of transdermal estradiol are critical to produce these positive effects and need to be at least 1 mg/day or higher to demonstrate this biological activity.

Karjalainen and colleagues investigated changes in plasma lipid and lipoprotein levels induced by oral estradiol valerate and transdermal estradiol gel in a controlled, double-blind, double-dummy study. The patients were 79 hysterectomized postmenopausal Caucasian women who were seeking hormone substitution therapy for climacteric symptoms. Patients received 2 mg/day of oral estradiol valerate or applied 1 mg of topical estradiol gel daily at bedtime. In the estradiol valerate group, total and LDL cholesterol were decreased and high-density lipoprotein (HDL) cholesterol and triglycerides were increased ($p<0.001$). In the estradiol gel group, plasma total, LDL and VLDL cholesterol and the ratio of LDL/HDL cholesterol were significantly decreased ($p<0.001$), but no change in HDL cholesterol and triglycerides was observed.[7] No serious adverse events related to the study treatments were noticed. Mild skin irritation was reported by three women in the oral placebo group and two in the estradiol gel group. Breast tenderness was reported by 14 women in the oral estradiol treatment group and eight women in the transdermal estradiol treatment group.

Haines and colleagues studied oral estradiol treatment to see if it was effective in lowering concentrations of Lp(A). The Lp(A) level is an independent risk factor for premature coronary artery disease and cerebrovascular accidents. Concentrations of this lipoprotein tend to increase after menopause. A double-blind, placebo-controlled, crossover study was conducted during a 12-month period in 100 postmenopausal women who had undergone hysterectomy. The women were randomized into two groups: group one received oral estradiol, 2 mg/day, for the first six months and placebo for the second; and group two received these treatments in the reverse order. Crossover analysis showed a 9.62% reduction in values of Lp(A) with estradiol treatment compared with a placebo during 12 months of treatment ($p<0.001$). No major side effects were noted.[8]

Elkik and colleagues studied the effects of percutaneous estradiol and conjugated estrogens on the level of plasma proteins and triglycerides in 18 postmenopausal women. Patients were randomized to receive either conjugated estrogens orally, 1.25 mg/day, or transdermal estradiol ointment 3 mg each evening. Both treatments were biologically effective and plasma triglycerides tended to increase in the conjugated estrogen group and to decrease in the transdermal group, though not significantly. However, plasma renin substrate and antithrombin III increased significantly ($p<0.01$) in the conjugated estrogen group. The authors concluded that the lesser toxicity of transdermal estradiol could be partially explained by the route of administration, since transdermally estradiol bypasses the liver. No major side effects were noted.[9]

Two other studies that were both conducted by Walsh and colleagues seem to contradict the conclusions of Elkik and colleagues. Walsh and colleagues conducted two studies comparing oral estrogens with transdermal estradiol in a dose of 0.1 mg applied twice weekly. These researchers concluded in each study that transdermal estradiol was ineffective in producing any positive effects on plasma lipoproteins. The conclusions are very suspicious and should not be taken seriously because the dose of transdermal estradiol was subtherapeutic. This is further supported by the fact that Walsh and colleagues never checked for estradiol blood levels in their studies; whereas Elkik and colleagues, Haines and colleagues and Karrjalainen and colleagues all conducted some form of double check to see if the treatments were biologically effective.[7-11]

Blood-Clotting Effects

Antithrombin III is the primary inhibitor of blood coagulation and its congenital deficiency is associated with severe and recurrent venous thrombosis. The association of oral contraceptive drugs and thrombosis has been known for a long time. Estrogen therapy has been considered a risk factor for thromboembolic events, especially in women with other risk factors such as antithrombin III deficiency. The key to preventing this adverse effect of estrogen therapy is to choose the correct route of administration. Oral estrogen therapy, supplanted with natural or synthetic hormones, will cause negative changes in coagulation and fibrinolytic parameters.[12-13] However, transdermal estrogen therapy does not modify these parameters and would be the preferred route of estrogen administration for women at risk for thromboembolism.[12]

Bonduki and colleagues conducted a prospective, randomized study to evaluate antithrombin III levels in 19 postmenopausal women receiving hormonal replacement. The patients received either continuous daily oral conjugated estrogen 0.625 mg or estradiol transdermally 50 µg daily. The antithrombin III levels in the conjugated estrogen group declined significantly ($p<0.05$), but the transdermal estradiol group remained unchanged.[12] In a double-

blind, randomized, prospective study, Conard and colleagues compared a placebo and oral micronized estradiol 2 mg/day during a six-month period. They found that, compared with a placebo, oral estradiol therapy resulted in a significant decrease in fibrinogen and a significant increase in plasminogen.[13] These conclusions are also supported by the work of Elkik and colleagues and their comparison of oral and transdermal estrogen therapy.[9] Therefore, transdermal estradiol administration may be more beneficial in terms of coagulation than oral conjugated estrogen therapy, especially in women with predisposing factors to thrombosis.[9,12]

Bone Resorption

Estradiol has a positive effect on the biochemical markers for bone resorption and on bone mineral density in oral and transdermal dosage forms.[14-16] Estriol may also have a positive effect on bone mineral density. However, estriol may not be as effective in reducing bone resorption in women with a history of hysterectomy.[17-18] No matter what dosage form of estrogen is chosen to prevent bone loss, it does seem clear that adjunctive therapy with some form of calcium supplementation is vital.

Reginster and colleagues, in a controlled, randomized group comparison, compared the effects of oral conjugated estrogen 0.625 mg/day and transdermal estradiol 50 µg/day on biochemical markers of bone resorption in 60 healthy menopausal women. In both groups they found that, after three months of therapy, hydroxyproline/creatinine ratios were significantly ($p<0.05$) reduced. Pyridinoline/creatinine ratios were also significantly ($p<0.01$) reduced. They concluded that both therapies were equally effective in reducing postmenopausal bone resorption. Five patients withdrew from this trial because of mastodynia and weight increase.[11]

Ettinger and colleagues studied low-dose oral estradiol in a double-blind, randomized, dose-ranging design. Over an 18-month period they studied the protective effects of dosages of 0.5 mg, 1 mg and 2 mg in 41 postmenopausal women. Each patient was also given 1500 mg of calcium carbonate daily. Using bone-density measurements, they concluded that micronized estradiol, taken orally, has a continuous skeletal dose-response effect in the range of 0.5 mg/day to 2.0 mg/day and that calcium intake positively modifies the skeletal response. No serious side effects were noted.[15]

Evans and colleagues studied low- and conventional-dose transdermal estradiol in 169 postmenopausal women with bone-status problems. Patients were given either 25 µg or 50 µg of topical estradiol daily. Bone mineral density was the main outcome measure; the authors concluded that transdermal estradiol is effective in preventing spinal bone loss at all postmenopausal ages and is capable of doing this in low dosages. Prevention of bone loss at the femoral neck is less certain and the average change in bone mineral density over three years was significantly lower ($p<0.001$) than in the lumbar spine. Evans and colleagues also found that the use of estradiol 50 µg/day is not associated with a greater response in bone mass. No significant side effects were noted.[16]

The effects of estriol on bone resorption have also been studied. Minaguchi and colleagues, in a multicenter, prospective, open trial, studied the effects of oral estriol on bone mineral density and bone metabolism in postmenopausal women. They treated 75 women for 50 weeks with 2 mg/day of estriol and 0.8 g/day of calcium lactate. They found that after 50 weeks the women's bone mineral density had increased 1.79% ($p<0.01$) compared to pretreatment levels.[17] In contrast, Devogelaer and colleagues found that oral estriol in a dose of 2 mg/day did not maintain bone mass, whereas 1.5 mg/day of estradiol did counteract bone loss. This may seem controversial but Devogelaer and colleagues studied hysterectomized women who did not receive any calcium supplementation during the two-year, double-blind study.[18] These changes in baseline calcium supplementation, combined with the different patient population, may explain the controversy.

Urinary Tract Infections

An estimated 10% to 15% of women more than 60 years of age have frequent urinary tract infections. Hormonally induced changes in the vaginal flora associated with menopause are thought to play an important part in the pathogenesis of urinary tract infections in older women. Estriol has been shown to be very effective at reducing chronic urinary tract infections and, when administered topically, works faster than when taken orally.[19-20]

Raz and Stamm studied 93 postmenopausal women with a history of recurrent urinary tract infections in a randomized, double-blind, placebo-controlled trial of a topically applied intravaginal estriol cream. Patients received 0.5 mg of estriol in a vaginal cream to be applied once each night for two weeks, followed by twice-weekly applications for eight months; the other group used a placebo cream in the same manner. The incidence of urinary tract infections in the estriol group was significantly reduced ($p<0.001$), compared with that in the placebo group. Lactobacilli were absent in all vaginal cultures before treatment and reappeared after one month in 61% of the estriol-treated women but in none of the placebo recipients ($p<0.001$). With estriol the mean vaginal pH declined from 5.5 to 3.8 ($p<0.001$), whereas there was no significant change with placebo. Ten women withdrew from this study because they experienced local side effects from the estriol treatment.[19]

Kirkengen and colleagues, in a block-randomized, double-blind, group-comparative, placebo-controlled study, assessed the effect of oral estriol on recurrent urinary tract infections in 40 postmenopausal women. Women were given a single morning dose of estriol 3 mg/day the first four weeks and 1 mg/day during the last eight weeks of the study or a matching placebo. During the first four weeks, there was no difference between estriol and placebo treatment. However, after four weeks of therapy, oral estriol therapy was significantly more effective ($p=0.05$) at reducing the number of urinary tract infections. No significant side effects were noted.[20]

Skin Aging

The coincidence of climacteric symptoms and the beginning of skin aging suggests that estrogen deficiency may be a common and important factor in the perimenopausal woman. Topical estradiol 0.01% and estriol 0.3% both combat the onset of skin aging. Schmidt and colleagues investigated whether topical treatment of the skin with estrogen could reverse some of the changes in the aging of skin. In this open-label study, 59 women applied 1 g of either 0.01% estradiol cream or 0.3% estriol cream daily for six months. The effects were compared with preclimacteric women with skin-aging symptoms. After treatment for six months, elasticity and firmness of the skin had markedly improved and the wrinkle depth and pore sizes had decreased by 61% or more in both estrogen groups ($p=0.05$). Furthermore, skin moisture and the number of collagen fibers had increased. No systemic hormonal side effects were noted.[21]

Hypertension

After menopause, both systolic and diastolic blood pressure become higher in women than in men of the same age, suggesting that estrogen deficiency may influence the age-related increase in blood pressure. Transdermal and oral estradiol both have blood pressure-lowering properties in postmenopausal women. Mercuro and colleagues studied 30 postmenopausal women affected by mild hypertension in a randomized, double-blind protocol. Subjects received patches of transdermal estradiol that delivered 100 µg/day or a matching placebo. Administration of estriol significantly ($p<0.05$) decreased 24-hour systolic and diastolic blood pressure and did not cause any side effects.[22] The effect of oral estradiol on blood pressure was examined by Van Ittersum and colleagues. In their randomized, controlled trial, 29 women were treated with 1 mg of estradiol daily and compared with a group that did not receive treatment. Changes in blood pressure differed significantly ($p=0.05$) between the two groups after one year. A decrease of more than 5 mm Hg was observed in the estradiol group, whereas an increase was found in the control group. No significant side effects were noted.[23]

Diabetes

Estrogen replacement therapy is associated with a decreased risk of cardiovascular disease in postmenopausal women. Patients with noninsulin-dependent diabetes mellitus have an increased cardiovascular risk. However, estrogen replacement therapy is only reluctantly prescribed for patients with noninsulin-dependent diabetes mellitus. Estrogen therapy should be prescribed in this population. Estrogen therapy administered orally and transdermally improves sensitivity in the liver, glycemic control, lipoprotein profiles and fibrinolysis in postmenopausal women with noninsulin-dependent diabetes mellitus.[24,25] Brussaard and colleagues, in a double-blind, randomized, placebo-controlled trial, studied the effect of 2 mg of oral estradiol given daily over six weeks in 40 postmenopausal women with noninsulin-dependent diabetes mellitus. The estrogen-treated group demonstrated a significant ($p<0.03$) decrease of hemoglobin bA1/c, LDL cholesterol, and apolipoprotein B levels.[24] In an open-label, randomized, crossover study, O'Sullivan and Ho compared the effects of oral and transdermal estrogen replacement on glucose tolerance. Nine patients were randomized to receive either 100 µg/day of transdermal estradiol or 1.25 mg/day of conjugated estrogen for 12 weeks and then crossed over to receive the alternative treatment for another 12 weeks. The authors found that mean glucose and insulin levels were maintained at an identical level during the hyperinsulinemic euglycemic clamp performed at pretreatment and during estrogen therapy. They concluded that the route of estrogen replacement therapy does not have a major impact on glucose metabolism in postmenopausal women. No significant side effects were noted.[25]

Conclusion

Estradiol and estriol have many potential benefits. Estradiol has a positive cardiovascular effect that can be achieved by using 2

mg/day orally, 1 mg/day sublingually or 50 µg/day transdermally.[2-6] Estradiol has been shown to reduce LDL, VLDL and Lp(A) when given orally or transdermally.[7-11] Transdermal estradiol also lowers antithrombin III levels, which are associated with severe and recurrent venous thrombosis.[9,12-13] Estradiol has a positive effect on bone mineral density in oral and transdermal dosage forms.[14-16] Chronic urinary tract infections can be reduced by supplementing estriol, which, when applied topically, works faster than when taken orally.[19-20] Estradiol has a positive effect on skin aging,[21] lowers blood pressure,[22-23] and improves glycemic control in patients with noninsulin-dependent diabetes mellitus.[24-25] Armed with this information, physicians and pharmacists can make well-informed professional decisions about estrogen replacement therapy for their patients.

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