# Is Routine Use of Estrogen Indicated in Postmenopausal Women?

## An Affirmative View

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Postmenopausally the ovarian follicles are no longer active and do not secrete estradiol into the circulation. Circulating estradiol levels are therefore nearly always less than 55 pmol/L (15 pg/mL). The weak androgen androstenedione, produced mainly by the adrenal gland, continues to be secreted postmenopausally and is converted to estrone in peripheral fat tissue. Unless a woman is obese, however, the amount of estrone secreted into the circulation is not sufficient to maintain premenopausal physiologic levels of circulating estrogen. For this reason, nearly all postmenopausal women, except those who are obese, have some degree of estrogen deficiency during the one third of their average lifespan that occurs in US women after the menopause. This estrogen deficiency adversely affects many organ systems in the body. To prevent these adverse changes, nearly all postmenopausal women should receive exogenous estrogen to maintain the physiologic circulating levels of estrogen that existed premenopausally.

## NEEDS FOR ESTROGEN BY ORGAN SYSTEM

### Genital Tract

Estrogenic target tissues in the genital tract are derived from the urogenital sinus and the müllerian ducts. Estrogen stimulates their growth, and lack of estrogen causes them to become atrophic. The atrophy of the vaginal epithelium, called atrophic vaginitis, can produce symptoms of itching, bleeding, and dyspareunia as well as stenosis of the upper vagina. The vulva also becomes atrophic. Shrinkage of the vulvar tissue, kraurosis vulvae, can cause pruritus and pain. The ligaments that support the uterus lose their normal tone, which can result in uterine prolapse. The elastic tissue in the vagina also loses its tone, and hernias can develop in the anterior (cystocele) and posterior (rectocele) vaginal wall that can lead to difficulties in micturition and defecation. These local problems can be prevented by administering systemic exogenous estrogen therapy starting at the time of the menopause. No agent other than estrogen can prevent vaginal and vulvar atrophy and maintain the normal tone of the supporting structures of the uterus and vagina.

### Urinary Changes

The urethra and lower portion of the bladder are also derived from the urogenital sinus. They, too, have estrogen receptors and become atrophic when estrogen levels fall. Atrophy of the bladder and urethra mucosa can cause dysuria and the other symptoms that constitute the urethral syndrome (also known as senile urethritis).[1] Alterations in the pressure in the urethra and bladder can produce symptoms of urgency incontinence, stress incontinence, and urinary frequency.[2] Each of these symptoms can be prevented or relieved by treatment with exogenous estrogen.[3–5]

### Central Nervous System

Estrogen deficiency produces several changes in the central nervous system. The pathognomonic symptom of the

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menopause is the hot flush, a sudden explosive physiologic phenomenon that lasts for about 4 minutes and usually occurs several times a day, most frequently during sleep.[6,7] The hot flush appears to be due to changes in the hypothalamic temperature regulator, resulting from periodic alterations in higher centers of the central nervous system. In an attempt to adjust to this change and release heat from the body, skin blood flow and perspiration are increased. The cause of the hot flush is triggered by a change in estrogen levels, and the more abrupt the change, the more severe the symptomatology. Thus, flushes are most frequent in the first 2 years after the menopause, after which they decline in frequency.

The optimal treatment for hot flushes, as shown in randomized, double-blind, placebo-control studies, is the administration of exogenous estrogen.[8,9] This treatment is superior to placebo therapy or other agents such as progestins or clonidine. Certain adverse mental symptoms occur more frequently postmenopausally, such as anxiety and depression. It has been shown in several double-blind randomized studies with psychologic testing that these symptoms are relieved more with exogenous estrogen than with placebo,[10–12] and estrogen-treated women are more optimistic and worry less.

## Skin Changes

About 90% of the dermis of the skin is composed of the protein collagen, and the amount of collagen synthesis has been shown to be directly related to the levels of circulating estrogen. Postmenopausally, biopsies of skin have shown that women not treated by estrogen have steadily decreasing amounts of collagen in the dermis; when treated with estrogen, however, the premenopausal amount of collagen in the dermis is maintained.[13] Thus, skin thickness is unaltered postmenopausally in estrogen-treated women, while women not treated with estrogen develop a thinner skin with a greater amount of wrinkling.

## Postmenopausal Osteoporosis

Postmenopausal osteoporosis is an asymptomatic reduction in bone density that can result in fractures when the bone density is reduced more than 15%. The process begins at the menopause and affects the trabecular bone in the spine and distal radius more rapidly than the cortical bone in the axial skeleton. Postmenopausal osteoporosis affects about 25% of white and Oriental women and thus affects about 5 million of the estimated 30 million postmenopausal women in the United States today. This disorder is uncommon in blacks as well as obese whites and is more prevalent in thin women.

Fractures start occurring in trabecular bone, namely, the thoracic spine and distal radius, about 10 years postmenopausally, when bone density is decreased about 15%, and their incidence steadily increases after the age of 60 years.[14] Because bone loss occurs at a slower rate in cortical bone, osteoporotic hip fractures start occurring at about the age of 70 years and increase at an exponential rate after the age of 80 years. It was estimated in 1987 that there were 300,000 hip fractures in the United States, nearly all in women, with a mortality rate within 6 months of about 10%, making it the 12th leading cause of death among women.[15] Acute health care costs are estimated to be about $4 billion per year, with about one third of the individuals with hip fractures being discharged to nursing homes requiring custodial care for an additional $2 billion per year in cost.

The mechanism by which estrogen deficiency produces osteoporosis has not been completely determined, but it is believed that in premenopausal women, estrogens inhibit the action of parathyroid hormone on bone, reducing the rate of bone resorption. Postmenopausally, with decreased estrogen levels, the rate of bone resorption is increased and more calcium is excreted in the urine.[16] A cohort study of a group of women who had oophorectomies when they were in their 30s and were randomly treated with either estrogen or placebo showed after 10 years that the estrogen-treated women had no significant decrease in bone density, whereas the placebo group had a decrease in bone density each year.[17] Bone density studies 15 years after oophorectomy revealed that the estrogen-treated group had significantly greater bone density in both the lumbar spine and the femoral neck than the group receiving placebo.[18]

Numerous case-control studies have shown that estrogen treatment for more than 5 years postmenopausally significantly reduces the risk of developing fractures in trabecular bone, the wrist, and the vertebral column as well as in cortical bone in the hip.[14,19] Postmenopausal estrogen decreases the incidence of fractures in postmenopausal women to about the same rate as occurs in men of the same age. Several studies have shown that dietary calcium supplementation does not prevent postmenopausal bone loss and that it is necessary to administer estrogen to prevent this bone loss.[20–22]

## Cardiovascular System

The major beneficial effect of estrogen replacement is its effect on the cardiovascular system. Estrogen replacement has been shown in numerous case-control and cohort studies to reduce the incidence of both myocardial infarction and stroke. Since deaths from cardiovascular disease account for the majority of deaths among women in the postmenopausal age group, reduction in the incidence of myocardial infarction, the major cause of mortality in this age group, results in estrogen replacement therapy being asso-

ciated with a longer lifespan by women who ingest these agents.[23]

Although the amount of estrogen used in estrogen replacement therapy (ERT) is about 20 times greater than the amount of estrogen used in low-dose oral contraceptive therapy, the orally administered natural estrogens used for ERT are only about 1% as potent as ethinylestradiol, the synthetic estrogen in oral contraceptives, in terms of increasing hepatic globulin production.[24] Because of these differences in potency, the usual dose of estrogen in ERT produces only one-fifth to one-tenth the effect on globulin production, as do low-dose oral contraceptives, and thus ERT does not cause a clinically important increase in angiotensinogen, which may raise blood pressure or the globulins involved in the clotting process.[25]

Epidemiologic studies have confirmed that, in contrast to oral contraceptives, estrogen replacement therapy is not associated with an increased incidence of venous thrombosis, thrombophlebitis, or pulmonary embolism.[26] Furthermore, both longitudinal and cross-sectional studies have shown that postmenopausal estrogen replacement does not raise systolic or diastolic blood pressure in both normotensive and hypertensive women.[27–29] Thus, there is no reason not to prescribe postmenopausal estrogen replacement therapy to women with elevated blood pressure.

About 10 case-control and 15 cohort studies have examined the relationship between postmenopausal estrogen replacement and cardiovascular disease, particularly myocardial infarction. Nearly all of these studies have shown reduction in both the crude and adjusted relative risk to about 0.5 for estrogen users.[30] A recent nationwide study at lipid research clinics found that the cardiovascular disease death rate per 10,000 women was significantly reduced in each decade of life from age 50 to age 80 years, with an overall age-adjusted relative risk of death from cardiovascular disease in estrogen users to be 0.34.[31] A recent cohort study found that the risk ratio of mortality from stroke in women using estrogen was 0.5, with a significantly decreased risk existing up to the age of 85 years.[32] The most likely mechanism of action for this protective effect of estrogen replacement on cardiovascular disease is that oral estrogen increases levels of the cardioprotective high-density lipoprotein cholesterol and decreases levels of the deleterious low-density lipoprotein cholesterol fraction.[33]

## ADVERSE EFFECTS OF ESTROGEN REPLACEMENT

Numerous case-control studies have been undertaken investigating the relationship of exogenous postmenopausal estrogen replacement to breast cancer. The vast majority of these studies show risk ratios that do not vary significantly from 1.0, indicating neither an increased or decreased risk of estrogen upon breast cancer.[34] Since 1975, however, there have been numerous studies showing that postmenopausal estrogen use increases the risk of endometrial cancer, and the increased risk is related to both dosage and duration of use.[35] The type of cancer associated with exogenous estrogen is usually very well differentiated, however. After hysterectomy the age-adjusted mortality rate in estrogen users who develop this cancer is no different from that of a control group using estrogen who did not develop cancer and is much greater than the mortality rate of women developing endometrial cancer who do not take estrogen.[36] Nevertheless, most clinicians are prescribing progestins to women who are taking estrogens postmenopausally and have a uterus because the progestin opposes the effect of estrogen upon endometrial receptors and thus diminishes the incidence of hyperplasia as well as cancer.[37,38]

Although progestins have a beneficial effect on the endometrium, they have an adverse effect on lipids, reversing the beneficial effect of estrogen upon the high-density lipoproteins and causing these lipids to return to pretreatment levels.[39] For this reason many individuals are prescribing a lower dose but a longer duration of progestin therapy instead of the sequential regimen of high-dose progestin for 10 to 12 days per month that is utilized by many clinicians in the United States, which produces periodic withdrawal bleeding in the majority of women. Several recent reports indicate that daily administration of estrogen and a low dose of progestin reduces the incidence of bleeding and maintains an atrophic endometrium. Most authorities do not recommend that progestin therapy be used in women who have had a hysterectomy so that the maximum beneficial effect on cardiovascular disease can be continued.

## CONTRAINDICATIONS TO ESTROGEN REPLACEMENT THERAPY

Contraindications to estrogen replacement include acute liver disease, previously diagnosed breast or endometrial cancer, and probably active thrombophlebitis or thromboembolic disorders. Relative contraindications include chronic liver disease, obesity, and possibly a history of thromboembolism. For all individuals without these contraindications, it would appear prudent to advise that they take estrogen replacement therapy as long as they live to prevent the problems caused by this hormone deficiency.

## SUMMARY

A study of age-adjusted all causes of mortality has shown that estrogen nonusers are three times as likely to die of all causes compared with users.[24] The benefit of estrogen is

greatest in women who have had their ovaries removed, but benefit also occurs in those who have had a hysterectomy as well as those with intact pelvic organs. A recent British study also reported that women taking estrogen were less likely to die of all causes.[40]

Because of the many benefits of estrogen replacement therapy improving both the quality and quantity of life, all women who have this postmenopausal hormone deficiency, except possibly those who are obese, should receive estrogen replacement. The beneficial effects of estrogen replacement therapy are many and there are very few adverse effects.

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# An Opposing View

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It does make good sense to treat all menopausal women with estrogen if one believes that the menopause is an endocrinopathy. This philosophy has been perpetuated by the term applied to hormone use in this population: *estrogen replacement therapy*. This term, however, is a misnomer for two main reasons. First, all women become "estrogen deficient" as they mature into their postreproductive years[1]; the prescribing of estrogen to these women is therefore better described as "additive therapy." This point extends beyond semantics, for estrogen replacement therapy becomes pharmacologic treatment as opposed to an attempt to replace physiologically a sex steroid that should be present. In this context, the postmenopausal loss of estrogen production is not too dissimilar to the age-related increase in the peripheral resistance of insulin and its delayed response to glucose loading.[2] Most aging individuals do not develop diabetes or experience its potential cardiovascular or other complications. The same is true for the majority of otherwise healthy menopausal women who do not receive estrogens postmenopausally. A significant minority of individuals, however, have an accelerated or aberrant response to age-related changes in metabolism, and these individuals will benefit from specific hormone therapy—be it insulin or estrogen.

These age-related changes are quite different from the pathologic deprivation of sex steroids in surgically or prematurely menopausal women. Under these circumstances, it is appropriate to think in terms of physiologic replacement therapy and to prescribe estrogen and progesterone or progestins in a cyclic fashion in an attempt to mimic the normal menstrual cycle. As a corollary, juvenile and certain maturity-onset diabetics obviously need insulin.

There is a second reason that estrogen replacement therapy is a misnomer. It has been conclusively established that unopposed long-term estrogen therapy significantly increases the likelihood of endometrial hyperplasia and cancer, but that this side effect can be eliminated by the concurrent use of either cyclic or continuous progestin therapy.[3] Most women experience a natural menopause. The title of this article should therefore read, "Is Routine Use of Estrogen Plus Progestins Indicated in Postmenopausal Women?" The addition of progestins raises at least two confounding metabolic and one practical clinical issue: What adverse effects does long-term progestin use have on lipid, lipoprotein, and insulin metabolism? What will the compliance rate be in women experiencing cyclic withdrawal bleeding given the two more important long-term reasons for hormonal therapy: the prevention of osteoporosis and cardiovascular disease.

## WHY PRESCRIBE HORMONES?

Few physicians will disagree with the need, safety, and efficacy of estrogens in the treatment of menopause-related hot flushes, vasomotor symptoms, atrophic vaginitis, and certain higher-center-initiated problems such as insomnia, depression, mood swings, etc. The main issue, however, involves the use of estrogen for the prevention or treatment of osteoporosis and cardiovascular disease. Both of these syndromes are complex and multifactorial. The bottom line is women develop osteoporosis because they have significantly reduced bone mass[4] and atherogenic disease (probably) because of disturbances in lipid and lipoprotein metabolism.[5] Both conditions are modulated by the presence or absence of estrogen, but both are also heavily influenced by the individual's genetic makeup, lifestyle, social habits, and physical activity. Women who enter their menopause with adequate bone mass do not develop osteoporosis. Women who are normotensive, have appropriate lipid and lipoprotein profiles, are physically active, and do not smoke are unlikely to experience significant atherogenic disease. Why then should one treat all postmenopausal women with estrogen therapy?

### Cardiovascular Protection

Epidemiological studies have established that the incidence of coronary artery disease in untreated menopausal women is three times greater than in premenopausal women.[6] Whereas this is probably true for women with untreated premature menopause,[7] there are many who

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doubt a causal relationship in naturally menopausal women.[8] The reality is that there is no clear change in female mortality from ischemic heart disease as women enter the menopause as there is from other hormonally related diseases such as breast cancer. The approximation of the mortality rates for cardiovascular disease in men and women as they age is thought by some to be a decrease in the rate of increase in men rather than a speeding up of the rate of increase in women.[8]

Women with myocardial infarction do, on average, experience an earlier menopause. Smoking plays an important confounding role; in a study of nurses' health habits, for example, the median age at menopause was 52.4 years among women who had never smoked and decreased, according to the amount smoked, to 50.4 years in women who smoked 35 or more cigarettes per day.[9] Other lifestyle factors also have an impact on the incidence of coronary heart disease. A recent review article found a significant and graded relationship between physical inactivity and the risk of coronary heart disease. Physically inactive persons had a median risk ratio of 1.9, that is, a 90% excess risk.[10]

Given the above, there are numerous studies that attest to the protective role of hormones against ischemic heart disease. Two illustrative studies are those of Ross et al[11] (case-control), who reported a relative risk of ischemic heart disease in treated vs untreated women of 0.4, and Bush et al[7] (cohort study) with an all-cause mortality risk ratio of 0.4 in hormone- vs nonhormone-treated women. The treatment in all of these studies was estrogen alone, and although not proven, the beneficial results were thought to be due to the lowering action of estrogen on cholesterol and low-density lipoprotein (LDL) cholesterol and its stimulating effect on high-density lipoprotein (HDL) cholesterol synthesis. The addition of a progestin, even the less potent medroxyprogesterone acetate, may neutralize this effect. In an 18-month prospective study evaluating untreated naturally menopausal women and two matched groups of estrogen-treated (conjugated equine estrogen, 0.625 mg or 1.25 mg/d) subjects, the addition of a 7-day course of medroxyprogesterone acetate (10 mg/d for 1 week) was found to inhibit an anticipated increase in HDL cholesterol and a lowering of serum cholesterol.[12]

Hormone replacement therapy also affects carbohydrate metabolism. Whereas the early glucogenic effect of estrogen usually normalizes when treatment exceeds 1 year, progestins have a potential diabetic effect. Progestins stimulate a progressive hyperglycemia and hyperinsulinemia after 6 months of treatment.[13] The role of hyperinsulinism in the pathogenesis of atherogenic disease is well established.[14] Despite the promising cardioprotective effect of treatment with estrogen alone, the data on combination hormone additive therapy are incomplete. It may well be that this form of hormone replacement compromises rather than aids in protecting women against ischemic heart disease.

## Osteoporosis Prevention

Cross-sectional studies have suggested that about 50% of the age-related loss of vertebral bone may be due to ovarian senescence.[15] It is therefore not surprising that estrogen therapy reverses this process and prevents bone loss in postmenopausal women. A small increase in bone mass during the rapid phase of bone loss in the immediate postmenopausal period may occur. This protective effect is true of most estrogens, provided an adequate dose is given. The benefit is seen in both the spine and the femoral neck.[16] As a consequence, epidemiologic studies have recorded a significant reduction in both vertebral and hip factors. It has been suggested that estrogen therapy for a given period of time would delay the onset of accelerated bone loss by an equal period of time.[16]

Although the means whereby estrogen exerts its protective effect is unclear, the net result is an increase in bone mass, as was clearly demonstrated by Ettinger et al,[17] who reported both an increase in bone mineral and a reduced fracture rate in estrogen-treated vs control patients. As noted previously, bone mass is inversely proportional to the risk of fracture. Why then should one treat all women with estrogen if the majority of untreated postmenopausal women have adequate bone mass and do not develop osteoporosis?

The selective use of estrogen for the prevention of osteoporosis is a viable alternative to routine treatment. Bone mineral (mass) can be quantified with photon absorptiometry. Despite editorials criticizing this approach,[18,19] experts from institutions recognized for their expertise and experience in bone mineral metabolism[20] and consensual opinions from organizations such as The National Osteoporosis Foundation, The Society of Nuclear Medicine, and The American College of Nuclear Physicians[21] have endorsed the use of bone densitometry for a number of indications, one of which includes "deciding whether to begin preventive treatment in a woman at menopause."[20] The authors of this statement acknowledge that "estrogen replacement prevents the transient accelerated phase of bone loss . . . ," but they add that estrogens have " . . . significant side effects and [are] not tolerated by some women." Furthermore, "bone densitometry is of great value in helping to make this decision," ie, the decision whether to start a woman on estrogen.[20]

Much of the controversy has centered on the suitability of single- vs dual-photon absorptiometry and whether one should screen all women. This issue is beyond the scope of this article; however, Ross et al,[22] in an elegant and exten-

sive study, have illustrated both the practicality and the reliability of using peripheral bone densitometry (of both the os calcis and the distal radius) as a means of detecting individuals with bone demineralization who do not have overt fractures (osteopenia). Furthermore, these tests were predictive of future fracture. Prospective follow-up of 536 Japanese-American women demonstrated 14 new spine fractures in osteopenic women, whereas none occurred in the nonosteopenic group. The author[23] has had similar experience in clinical research and practice, and advocates the use of peripheral bone densitometry as the most cost-effective initial intervention. By using both midshaft and distal radial measurements, it was possible to classify correctly 86.3% of unselected women who had both single- and dual-photon absorptiometry. Only 7.8% of osteopenic women were incorrectly classified as having normal bone mass and 5.9% as falsely positive. Patients proven to be osteopenic by this method need to be further evaluated by the more costly but more site-specific dual-photon absorptiometry, together with x-ray examinations and blood and urine tests. Bone-density testing thus allows for the individualized use of estrogen.[23] It also enhances patient compliance with recommended treatment. In a study involving over 700 participants, 86.4% of the women who were tested and found to have low bone mass altered their lifestyles, compared with 68.7% of women with normal bone mass and only 53.8% of the unscreened population.[24]

## ALTERNATIVES TO HORMONE ADDITIVE THERAPY: ENHANCING THE QUALITY OF LIFE

### Nutrition

There appears to be a threshold for serum cholesterol levels below which cardiovascular disease rarely develops. This threshold has been found to lie somewhere between 3.20 and 4.25 mmol/L (125 and 165 mg/dL), as found in populations where coronary heart disease is rare, for example, in Japan. In Japanese women, the mortality rate is 50 per 100,000 versus 264 per 100,000 in the United States.[25] The American Heart Association advocates a reduction in the total fat intake in the diet to 30% of calories, the saturated fatty acid content to below 10% of calories, and the cholesterol intake to less than 300 mg/d. Recommendations similar to this have been accepted by men and have had a dramatic impact on the incidence of cardiovascular disease. Thus, Walker[26] reported a significant decrease in cardiovascular disease in men by increased physical activity, reductions in smoking (by 27.1%), a reduced intake of cholesterol-rich foods (by 38.8%), and an increased intake of potentially cardioprotective foods such as vegetable fat (57.6%) and fish (22.6%). During the period 1963 to 1981, there was an age-specific decrease in coronary-associated mortality—due to lifestyle modification—that ranged from 44.8% (at age 35 to 44 years) to 38% (at age 55 to 64 years). These results suggest that "the pragmatic view contends that atherosclerosis is predominantly the result of lifestyle in most affluent societies and that modification of this environment is the rational way to prevent coronary heart disease."[26] There is no reason why women could not benefit from lifestyle modification, too.

### Exercise

Active life expectancy, ie, the portion of independent living, can be enhanced by physical fitness. Studies in aging men have shown that the decline in weight-adjusted $\dot{V}O_2$ max (a measure of aerobic capacity) is significantly less for physically active ($0.65 \pm 1.5$ mL $min^{-1}$ $kg^{-1}$ $y^{-1}$) as compared with sedentary men ($-1.32 \pm 0.85$ mL $min^{-1}$ $kg^{-1}$ $y^{-1}$).[27] Improved physical conditioning is especially noticeable at submaximal workloads common to everyday activity: extraction of oxygen becomes more efficient, substrate needs of exercised muscle are lessened, and myocardial oxygen requirements and blood pressure are reduced.[28]

In addition to enhancing quality of life, physical activity is inversely related to the risk of both coronary heart disease and cancer.[29–31] Ekelund et al[31] followed 4276 men aged 30 to 69 years prospectively for an average of 8.5 years. The heart rate during submaximal exercise and the duration of exercise on treadmill testing were used as measures of physical fitness. The relative risk from cardiovascular death and that from coronary heart disease was 2.7 and 3.2 in physically fit men when compared with their unfit peers. Further analysis showed that the protective effect of physical fitness was achieved other than by improved blood pressure and serum lipids. Factors responsible for this improved prognosis were speculated to be an increase in stroke volume, an increased extraction of oxygen from the blood, and an inhibition of blood coagulation, primarily by lowering the ability of platelets to aggregate and an increase in fibrinolysis. Estrogen therapy as such does not have a positive influence on any of these factors. It is yet to be proven that women will also benefit from physical fitness in the same way as men.

One of the arguments against exercise is the intensity of effort that is needed to achieve a cardioprotective effect. Paffenbarger et al[29] recorded a 21% lower risk of death when the distance of walking was increased from 3 miles to 9 miles or more per week. In another study,[32] moderate leisure time activity—yard work, dancing, swimming, and home exercise—was associated with a 63% reduction in death from coronary heart disease when compared with a more sedentary group of cohorts. Death rates are decreased as physical activity is increased from 2100 to 8400 kJ (500 to 2000 kcal) a week.[29]

**TABLE 1. RESPONSE OF CLIMACTERIC WOMEN (MEAN AGE 56 YEARS) TO INTENSIVE STRUCTURED EXERCISE**

| Group | No. | Mean Maximal Oxygen Uptake (mL/kg/min) | | | | Percent Difference Baseline/12 mo |
|---|---|---|---|---|---|---|
| | | Baseline | 3 mo | 6 mo | 12 mo | |
| Nautilus | 13 | 26.0 | 26.1 | 26.5 | 26.2 | 0.8 |
| Treadmill | 10 | 27.1 | 29.5 | 30.5 | 29.5 | 8.9 |
| Ergometer | 10 | 26.7 | 38.9 | 30.2 | 30.0 | 12.4 |
| Control | 14 | 26.5 | 26.1 | 25.9 | 26.2 | −1.1 |
| Hormone | 16 | 26.6 | 26.3 | 26.4 | 25.1 | −5.6 |

The lifetime appearance of cancers of the reproductive tract (uterus, ovaries, cervix, vagina) and the breast in former college athletes was found to be reduced by a relative risk factor of 2.5 and 1.9, respectively, when compared with nonathletes. The athletes had a much later menarche, an earlier menopause, and were less fat. Obesity is associated with an increase in extra glandular conversion of androgen to estrogen, a decrease in sex-binding globulin, and therefore a higher percentage of free plasma estradiol. The latter may be related to an increased risk of breast and endometrial cancer. Athletes (as a group) also eat less fat; dietary fat is associated with an increased risk for cancer. A comparable reduction in cancer risk with physical exercise has not been reported in women treated with hormones alone.

Most of the training effects of regular exercise are similar in old age as in youth. Thus, 75-year-old men can readily increase their quadriceps muscle strength 10% to 20% and achieve a similar improvement in maximal oxygen uptake after several weeks of endurance training.[33] Regular exercise also modulates age-related glucose intolerance[34] and may be helpful in preserving bone mass. The role of exercise in the promotion of new bone by stimulating the bone remodeling cycle has been recently extensively reviewed.[35] One of the more recent studies confirmed that 9 months of weight-bearing exercise—walking, jogging, and stair climbing at 70% to 90% of maximal oxygen uptake for 50 to 60 minutes three times a week—increased the bone mineral content of the lumbar vertebrae in sedentary postmenopausal women by 5.2%. The control group lost 1.4% of their bone mass.[36] Despite such studies, the optimal amount and type of exercise needed to maintain or, it is hoped, to increase bone mass still needs to be defined.

It is far easier to take an estrogen pill than to exercise. Even so, although estrogen improves the lipid profile in postmenopausal women and modulates the rate of bone loss, estrogen does not increase the bone mass, improve glucose tolerance, or enhance aerobic power or physical fitness. These points were clearly illustrated in three studies performed recently at The Center for Climacteric Studies in Gainesville. As reflected in Table 1 and Table 2, women who had combination hormone-additive therapy alone—conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg, both on a daily basis—exhibited a progressive loss in $VO_2$ max and in total exercise time when compared with women undergoing structured exercise. This finding was especially true for women who exercised aerobically.[37] In a second study, walking on a treadmill for 20 minutes at 75% to 80% of maximal heart rate three or four times a week significantly improved insulin metabolism (especially the first phase of insulin release) in trained, but not in unexercised control postmenopausal women. As noted previously, progestins induce a peripheral insulin resistance[38] (Table 3). In a final study,* surgically menopausal women who were treated with 0.625 mg of conjugated equine estrogen and 1500 mg of calcium per day maintained their bone mass when observed over a 1-year period of time; the addition of muscle-strengthening exercises using Nautilus variable-resistance machines in similarly treated women increased the bone mass in the exercised group by 8.4% in the lumbar and dorsal vertebrae (as measured by dual-photon absorptiometry) and by 3.8% in the distal radius (measured by single-photon absorptiometry). The results of this study are most encouraging and add substance to the concept of a combined approach to the prevention of osteoporosis: estrogen (endogenous or exogenous) to modulate osteoblast activity, gravitational muscle-strengthening ex-

** The results of this study are in preparation for publication. Information is available from the author on request.*

**TABLE 2. RESPONSE OF CLIMACTERIC WOMEN (MEAN AGE 56 YEARS) TO INTENSIVE STRUCTURED EXERCISE**

| Group | No. | Mean Total Exercise Time (min:sec) | | | | Percent Difference Baseline/12 mo |
|---|---|---|---|---|---|---|
| | | Baseline | 3 mo | 6 mo | 12 mo | |
| Nautilus | 13 | 12.1 | 12.2 | 12.9 | 12.5 | 5.3 |
| Treadmill | 10 | 12.5 | 14.2 | 15.2 | 15.3 | 21.5 |
| Ergometer | 10 | 13.0 | 14.1 | 14.5 | 15.2 | 17.4 |
| Control | 14 | 12.2 | 11.6 | 12.2 | 12.1 | −0.95 |
| Hormone | 16 | 13.4 | 12.6 | 13.0 | 12.3 | −7.7 |

**TABLE 3. EFFECT OF EXERCISE ON INSULIN METABOLISM IN POSTMENOPAUSAL WOMEN**

| Exercise Modality | Fasting Glucose mmol/L (mg/dL) | Fasting Insulin pmol/L (μU/mL | Insulin Area Under the Curve pmol/L min (μU/mL/min) | | |
|---|---|---|---|---|---|
| | | | At 5 min | At 10 min | At 30 min |
| Control (n = 9) | 5.7 ± 0.2 (102 ± 4) | 60 ± 30 (8.4 ± 3.8) | 585 ± 290 (81.6 ± 40.6) | 1555 ± 635 (216.9 ± 88.4) | 8690 ± 2030 (1211.3 ± 282) |
| Treadmill (n = 7) | 5.4 ± 0.4 (97 ± 8) | 60 ± 20 (8.7 ± 2.8) | 325 ± 60 (45.5 ± 8.3)* | 900 ± 120 (125.1 ± 16.1)* | 5950 ± 1875 (829.4 ± 261.4) |
| Nautilus (n = 9) | 5.6 ± 0.27 (101 ± 5) | 55 ± 20 (7.6 ± 3.2) | 415 ± 175 (58.0 ± 24.2) | 1200 ± 475 (166.9 ± 66.5) | 7095 ± 2950 (989.1 ± 411.1) |

*P = .05 compared with control

ercises to stimulate osteoblast activity and new bone formation, and adequate calcium to mineralize the newly formed osteoid.[24,39]

## CONCLUSIONS

The clinical appearance of osteoporosis and artherogenic disease manifests 15 or more years after the menopause; preventive measures, such as good nutrition, exercise, and a healthy lifestyle, should ideally begin at least 15 years before the menopause. Although lack of estrogen can accelerate these conditions, both are complex multifactorial disorders that can be positively influenced by nonsteroidal means. There is a definite and important role for hormone use: replacement therapy for all premature or surgically menopausal women (since this is a pathologic state) and selective additive therapy for naturally menopausal women at high risk for atherogenic disease or osteoporosis. In addition, hormone therapy should not be withheld from menopausal women who elect to take hormones or who will not exercise or control their diet and weight, etc, as long as there is no contraindication to their use. Patients must, however, be given the facts. The menopause is a natural life event; postmenopausal health can be achieved without the need for hormone therapy.

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