Women and Exercise: Physiology and Sports Medicine

2nd Edition

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CHAPTER 11

Menopause*†

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MENOPAUSE IN PERSPECTIVE

Menopause is a natural phenomenon that usually lasts about 1 week—the duration of the last menstrual period. It is the biologic marker of the gradual but persistent decrease in ovarian steroidogenesis that precedes the cessation of menstruation by about 15 years and that postdates that event by a similar duration. This period of reproductive senescence is known as the climacteric. The differentiation between "menopause" and the "climacteric" involves more than semantics, since it serves to illustrate that the midlife physical and psychologic needs of women extend over a 30-year continuum. There are two additional features of note: (1) the attenuation in endocrine function of the ovarian follicle affects many systems remote from the reproductive tract; and (2) the climacteric occurs at a time when certain age-related changes become apparent, so that one must differentiate between biologically induced and chronologically induced pathophysiology.

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†Although, as discussed at the beginning of this chapter, the period is more properly called the "climacteric," "menopause" is certainly the more commonly used term.

The date of menopause can be accurately pinpointed, but it is a retrospective diagnosis: a year of amenorrhea has to pass before the clinical diagnosis can be confirmed. The mean age of onset of menopause in western societies is 51 years.[1] The climacteric may be empirically but pragmatically categorized into three decades of clinical presentation and need (Fig. 11–1): the early climacteric (age 35 to 45), premenopausal and postmenopausal periods (age 46 to 55), and the late climacteric (56 to 65).[2] Contrary to the theory that follicular depletion is the cause of menopause, primordial follicles are frequently found in the ovaries of postmenopausal women, but they are unable to respond to stimulation of the pituitary gonadotropins—FSH and LH. The resultant alteration in ovarian function brings about the dysfunctional uterine bleeding patterns that characterize this phase. As the climacteric progresses, the decrease in estradiol production results in menopause and in a number of so-called hormone-dependent symptoms such as hot flushes and changes in temperament, mood, and sleeping patterns. The late climacteric is often associated with conditions resulting from chronic estrogen deprivation—chronic atrophic vaginitis, the urethral syndrome, and urinary incontinence.

Although the conditions just listed have an impact on an individual's quality of life, none is life-threatening. There are, however, two asymptomatic potential complications of the late climacteric that may have a serious adverse effect and that are responsible for much of the morbidity and mortality associated with older age in women: osteoporosis and atherogenic disease. In the United States, the total number of hip fractures among white women was 158,000 in 1986, and this number is expected to increase to 252,000 in the year 2020 and to 367,000 by the year 2040.[3] Of this figure, approximately 12% to 20% will die as a result of factors directly attributable to their hip fracture.[4] Only a third of the survivors will regain normal activity.[5] Of all hip fractures, 70% to 80% affect women. The total annual cost of hip fractures was approximately $7.2 billion in 1984, and this cost, adjusted for 5% inflation,

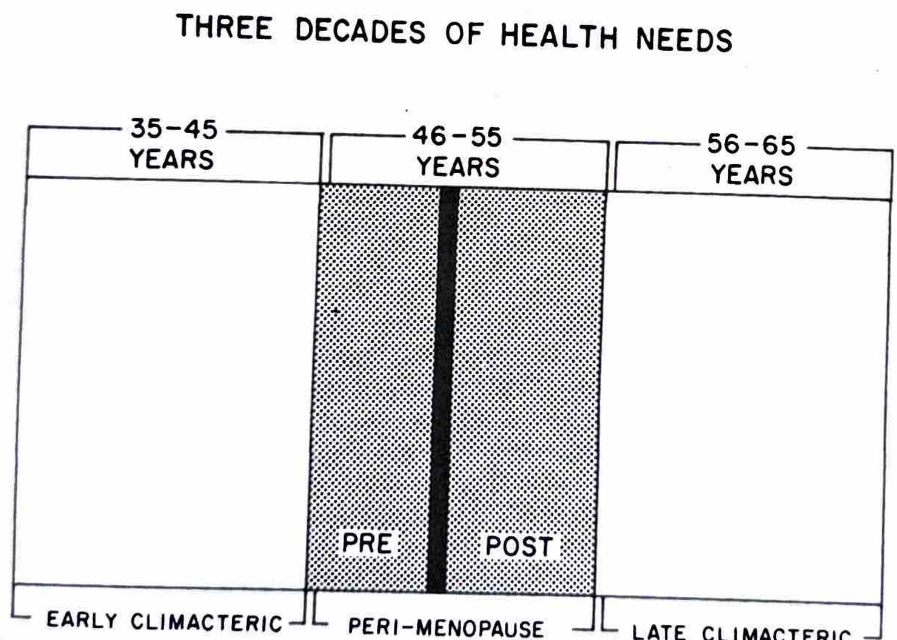

Figure 11–1. Diagrammatic representation of the menopause as a single event in the larger context of the climacteric. (From Notelovitz[2] with permission.)

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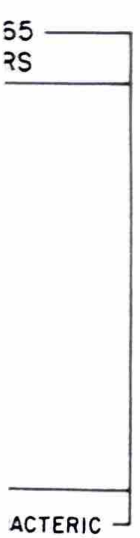

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is expected to increase to $240 billion by 2040.[3] This cost, of course, does not take into account the physical and psychologic pain suffered by these women.

In 1989, approximately 500,000 persons died from ischemic heart disease, the leading cause of death in the United States.[6] Annual health-care costs for cardiovascular disease alone exceed $135 billion, while the added costs of related injury and disability exceed $170 billion.[7] Cardiovascular disease has a significant influence on the well-being of the fastest-growing age group in the United States: an estimated 1000 individuals join the ranks of the elderly every day.[8] A woman aged 65 can now expect to live an additional 18.8 years (14.5 years for men).[9]

Exercise can play an important role in ensuring an appropriate quality of life in middle age and later, but to be maximally effective, it needs to be introduced as a premenopausal lifestyle—hence the emphasis on recognizing the climacteric as an important transitional phase in the pathogenesis of potentially preventable disease.

OSTEOPOROSIS AND BONE HEALTH

Osteoporosis is preventable. It is a condition that is relatively uncommon in men and in black women, owing in part to their having a greater bone mass. Cohn and coworkers[10] examined the skeletal and muscle mass of normal black women and found that their total body calcium was 16.7% higher than that of age-matched white women. More than half of this difference (9.7%) was calculated to be due to a greater muscle mass in the black women. Thus, despite the complexity of bone physiology, two practical issues need to be addressed: (1) women need to acquire as much bone as possible before menopause, and (2) the rate at which bone is lost thereafter needs to be modulated. Exercise plays a pivotal role, in that it is one of the few known means of stimulating new bone formation. Central to the entire issue is the fact that bone is a living tissue and needs to be treated as such.

Osteogenesis: A Brief Overview

Bone formation depends upon a five-stage cycle that results in "old" bone being removed and replaced with "new" bone. Normally, this process is coupled; the amount of old bone removed is replaced with an equal amount of freshly formed bone. Initiation of the cycle is dependent upon the recruitment and activation of osteoclasts. This activity usually takes place on the inner aspect of the bone's surface—the endosteal layer—and results in the dissolution of bone mineral and collagen, and the formation of a cavity. Resorption ceases when the mean depth of the cavity reaches 60 μm (trabecular bone) and 100 μm (cortical bone) from the surface.[11] At this point, mononuclear cells lay down a highly mineralized, collagen-poor bone matrix known as cement substance. It is from this surface that new bone is laid down by osteoblasts. These cells probably originate from bone marrow stromal cells (preosteoblasts), thereby sharing the ability of another cell type, the fibroblasts, to synthesize collagen.[11] The stimulus for osteoblast recruitment may be mechanical owing to humoral and/or locally produced substances (for example, human skeletal growth and other bone growth factors).[12]

The osteoblasts are responsible for the synthesis of collagen, which is the main component of newly formed bone matrix, or osteoid. The latter matures and is later mineralized by a process that largely depends on an adequate supply of calcium and phosphate and the formation of hydroxyapatite crystals.[10] At a microstructural level, numerous small crystallites of hydroxyapatite may be seen in intimate juxtaposition and in highly organized geometric arrangements with collagen fibrils.[11]

The elastic and tensile strength of bone depends in large measure on this interrelationship. Another very important determinant of the mechanical strength of bone is the orientation of the collagen fibrils in the bone matrix and the three-dimensional network of plates and bars found especially in trabecular bone (such as vertebrae), and to a lesser extent in cortical bone (for example, the radius), resulting in a scaffoldlike arrangement of vertical and horizontal trabeculae (Fig. 11-2). Interruption of this support system—for example, loss of horizontal trabeculae as a result of aging—can impair the structural integrity of the bone and result in

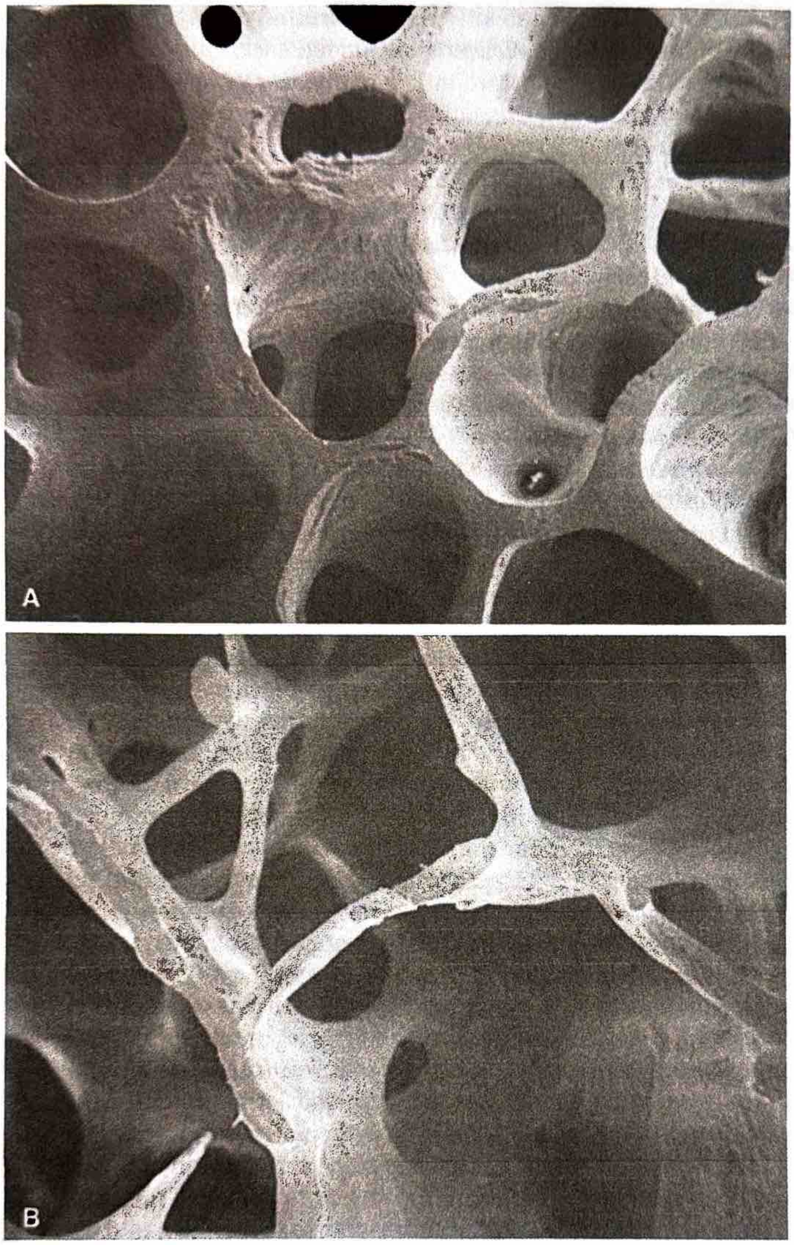

Figure 11-2. Scanning electron micrograph of an iliac crest biopsy from (*A*) a normal subject and (*B*) a woman with osteoporosis. Contrast the normal contiguous vertical and horizontal trabeculae with the thinning decreased number and loss of continuity of the trabecular plates in osteoporosis. (From Dempster DW, et al: A simple method for correlative light and scanning electron microscopy of human iliac crest bone biopsies: Qualitative observations in normal and osteoporotic subjects. J Bone Min Res 1(1):15, 1986, with permission.)

fracture, even in the presence of a relatively normal amount of bone mineral.[13] This is an important consideration when prescribing exercise for older women.

Types and Rates of Bone Loss

As mentioned above, there are two types of bone: cortical and trabecular. Cortical (compact) bone is found primarily in the appendicular skeleton (for example, in the femur, tibia, and fibula of the lower limbs, and in the humerus, ulna, and radius of the arms). Cortical bone constitutes 80% of the total skeleton but is metabolically less active than trabecular bone. About 10% of the cortical bone is remodeled each year.

Trabecular (cancellous) bone is found in the axial skeleton, primarily in the vertebral bodies (70% to 95%), with lesser concentrations in areas such as the neck of the femur (25% to 35%) and the distal radius (5% to 20%). The remodeling process is far more active in trabecular bone, in part because the architectural arrangement of the bone plates provides a larger exposed surface area for exchange with the extracellular compartment. Approximately 40% of trabecular bone is remodeled each year. Because of this greater activity, vertebral osteoporosis occurs more frequently than hip (cortical-related) fractures. It may also account for the increased susceptibility of the vertebrae to the bone mineral loss noted in female long-distance runners.[14]

After longitudinal bone growth has been completed, the bone mineral content and mass of bone further increase until about the age of 35 years, at which point the individual is said to have achieved her maximal cortical bone mass. From this age until the onset of menopause, it is considered normal for women to lose at least 0.12% of cortical bone per year (as measured by single- and dual-photon absorptiometry); after menopause and until age 65, the rate of bone loss increases to at least 1% per year, slowing down after age 65 to 0.18% per year. This "physiologic" bone loss averages out to a 25% decrease in cortical bone mass over the 30 years from age 50 to age 80.[13] Trabecular bone accrual reaches its maximum during the mid to late 20s and is followed thereafter by a linear loss of bone.[15] Others maintain that the trabecular bone loss pattern equals that of cortical bone, with a loss of at least 0.19% per year before menopause and at least 1.1% thereafter. Thus an estimated 31.7% of trabecular bone is lost during the 50-year span between 30 and 80 years of age.[13] The greater the bone mineral content at bone mass maturity (maximum), of course, the more an individual can afford to lose, so there is a need to focus on the accrual of bone during youth rather than on the treatment of a reduced bone mass in the postmenopausal period.

How to Acquire More Bone

Mechanical force plays an important role in bone formation and function, but it is not known how much exercise is needed and whether there is an optimal form of exercise for bone accrual. It has been postulated[16] that there is a physiologic "band" of activity that is site-specific: immobilization can lead to severe bone loss at some sites, whereas repeated loading at appropriate strain magnitudes can result in bone hypertrophy. The frequency and degree of activity is important: repeated and prolonged exercise causes bone fatigue and microscopic fractures.[16] Given appropriate intervals between periods of exercise, however, normal bone turnover will repair these microfractures and even strengthen the bone.[16] Excessive activity is known to have an adverse effect, with stress fractures a common reality in long-distance runners.[16]

Gravity. Bone mineral is lost with the inactivity of simple bed rest. The average rate appears to be 4% per month during the early phase of bed rest; although subjects with higher initial bone mass lose bone more rapidly than those with lower values, all immobilized patients seem to end up with a similar bone mass.[17] Lack of force on bones plays a major role in bone loss, with trabecular bone being more sensitive than cortical bone. Three hours a day of quiet standing is partially effective in restoring bone mineral, while 4 hours of walking prevents the bone loss associated with 20 hours of bed rest.

Osteogenesis in long bones requires mechanical stress; when electrodes are placed on opposite sides of bone, bending results in a negative electrical potential on the concave side relative to the convex side.[18] The resulting piezoelectricity stimulates new bone cell growth. It is therefore not surprising that isometric or horizontal exercise—which does not "bend" bone and thereby stimulate this piezoelectricity—is not able to restore bone loss associated with immobilization.

Systemic versus Local Effect. It is important to differentiate the amount of exercise needed to maintain bone mass from that needed to increase it. This difference is well illustrated by a study that compared male professional tennis players with age-matched casual tennis players. The former group was found to have an overall greater bone mass, but in addition, the cortical thickness in the playing arm of the professional tennis players was 34.9% greater than in the nondominant arm. The same was found in female professional tennis players; cortical thickness in the dominant arm was 28.4% greater than in the nondominant arm.[19] Exercise thus seems to have both a systemic and a local effect and appears to be related to the type of exercise performed. When combined with the effect of gravity, weight-bearing activity is more osteogenic than weight-supported exercises such as swimming. However, both male and female swimmers have been shown to have greater vertebral bone mineral content than do their sedentary counterparts of the same sex.[20] Although the differences between male swimmers and sedentary men were statistically significant, the differences between female swimmers and sedentary women did not achieve significance, probably because of the smaller numbers of women studied (58 male swimmers, 78 sedentary men; 35 female swimmers, 20 sedentary women).

Age. Age is yet another significant factor: bone mass accrual occurs more readily in "growing" than in "mature" bone.[21] Both animal experimentation and clinical experience have shown that the accumulation of appropriate mechanical damage can stimulate bone hypertrophy. This requires the exposure of adult bone to cyclic strain levels of 2000 microstrain or more.[22] However, there is an optimal level beyond which increasing strain levels will no longer enhance bone mass and may even have a negative effect.[22] Thus, the type and intensity of exercise prescribed must be tailored to the age of the individual.

Exercise Prescription. In presenting an osteogenic exercise program, two additional criteria should be met: (1) the activity should be diverse and vigorous, but nonrepetitive,[23] and (2) the exercise program should be enjoyable, in order to ensure long-term compliance. In addition, a program that will simultaneously improve cardiovascular fitness would provide an added incentive and advantage. By extrapolating from animal data,[24] it has been suggested that aerobic exercise at an intensity associated with 65% to 80% of maximal heart rate is osteogenic.

Exercise and Osteogenesis: Clinical Research

Several investigators have studied the effects of exercise programs upon bone mineral density in postmenopausal women, using various protocols for exercise. Some of these studies have included hormone replacement therapy in the protocol, and some have also quantified calcium intake. Disparate results reflect differences in protocols and populations.

When interpreting the efficacy of a given program, the method of bone strength measurement needs to be considered. Most assessments are based on radiologic techniques, single- and dual-photon absorptiometry, and/or CT scanning. A qualitative improvement in bone strength resulting from aerobic exercise may also derive from an engineering rather than a biologic principle—an increase in bone width. Radial expansion of long bones is an important determinant of bone strength. The so-called cross-sectional moment of inertia (CSMI) is what determines bone's resistance to bending. An increase in the external diameter of the bone, brought about by increased periosteal (outer layer) new bone formation, can compensate for the inevitable loss in the quality of bone tissue that occurs with aging. Cavanaugh and Cann[25] have demonstrated that a moderate brisk walking program of 1 year's duration does not prevent loss of vertebral bone density in early postmenopausal women. Kirk and colleagues[26] reported similar vertebral bone densities for postmenopausal runners and age-matched sedentary women. Although the calcium intake of the runners was higher (1145 mg/d versus 707 mg/d), neither group consumed adequate amounts by current standards. These data suggest that exercise cannot compensate for an estrogen deficiency in preventing bone loss.

Relatively brief exercise programs have been shown to have a positive effect on vertebral bone mineral. Sixteen healthy women (mean age 61 ± 6 years) participated in an exercise program that involved walking, running, and calisthenics for 1 hour twice weekly. At the end of 8 months, the vertebral bone mineral content (measured by dual-photon absorptiometry) increased by 3% to 5%, whereas in an age-matched control group it decreased by 2.7%. The bone mineral content of the distal radius, however, showed an average decrease of 3.5%.[27] The authors concluded that physical exercise inhibits or reverses bone loss from the lumbar vertebrae in normal women, but that the changes in the forearm were independent of these exercises.

These results are divergent from another study that examined bone mineralization by x-ray densitometry (middle phalanx of the fifth finger and os calcis) and photon absorptiometry (distal and midshaft) in 42 normally menstruating marathon runners (mean age 37.7 ± 0.82 years) and 38 sedentary controls (mean age 39.6 ± 1.0 years). Mean values of the mineral content and the bone density of the marathon runners' radial midshaft and middle phalanx (representative of cortical bone) were significantly greater, but the mean density of the os calcis (trabecular bone) was higher in the physically inactive women.[28] Women with moderate exercise had greater cortical but less trabecular bone mineral contents, indicating that the increase in cortical bone through exercise came at the "expense" of trabecular bone.

Although anatomically distinct, the metabolic functions of the cortical and trabecular bone compartments are shared—a gain in one compartment may be matched by a loss in another. These two studies raise the question: can one exercise too much, and if so, will this result in a compromise of the trabecular skeleton? Hypoestrogenic, amenorrheic runners have been shown to have a reduced amount of trabecular bone in their lumbar vertebrae (as measured by dual-photon absorptiometry) but normal or minimally reduced cortical bone (as measured by single-photon absorptiometry and radiogrammetry).[14,29–31] Lower bone density in these women correlates with estrogen deficiency, inadequate dietary calcium, and reduced body weight. Calcium intake obviously plays a very important role. When reported, calcium intake was inadequate in most osteopenic groups, regardless of estrogen and exercise status. The menstruating marathon runners referred to previously lost trabecular bone despite an intact hypothalamic pituitary ovarian axis; another study has shown that physically active women with anorexia nervosa (all of whom were amenorrheic and obviously hypoestrogenic) had significantly greater bone mass than a similar group of inactive anorectics.[32]

Unpublished results from a study at the Center for Climacteric Studies comparing different forms of exercise in natural and surgically menopausal women reflect on some of the aforementioned issues—age, type and intensity of exercise, and an "intact" estrogen milieu. Bone mineral content in this study was measured by dual-photon absorptiometry of the total skeleton. Naturally menopausal women participating in aerobic (walking on a treadmill, riding a stationary bicycle) and muscle-strengthening (Nautilus) exercises, none of whom were receiving hormonal therapy, had less bone loss over a 1-year period than did a control group that did not exercise. The controls lost 9.9% of their bone mineral content, compared with 3.8% in the Nautilus exercise group and 0.5% in the bicycle-riding group. The treadmill subjects gained 0.4%.[33]

Heikkinen and associates[34] showed that weight training for 40 minutes in one session per week was insufficient to enhance the beneficial effect of estrogen and progestogen on bone mineral density in postmenopausal women, nor was there any improvement in bone density in a control group not treated with hormonal therapy. However, a study performed at the Center for Climacteric Studies demonstrated increased bone mineral density of the spine when a group of surgically menopausal women were treated with both estrogen and intense Nautilus weight training for 45 to 60 min/wk, divided into three sessions.[35] In this study, the increase in vertebral bone mineral density (measured by dual-photon absorptiometry) was statistically significant for the estrogen-plus-Nautilus group, compared to baseline, but the increase did not reach statistical significance for the estrogen-only group, or for the between-group comparison (Fig. 11-3). It is likely that this lack of significance resulted from the small numbers studied ($n = 9$ for estrogen plus Nautilus; $n = 11$ for estrogen only). All subjects ingested a minimum of 1400 mg of calcium daily during the 12-month study. These studies suggest that an estrogen-replete state might be needed for an osteogenic effect in women involved in intense exercise programs, and that more moderate levels of activity can conserve and maintain bone independent of the estrogen milieu (Table 11-1). However, more studies are needed to delineate the frequency, intensity, and duration of exercise necessary.

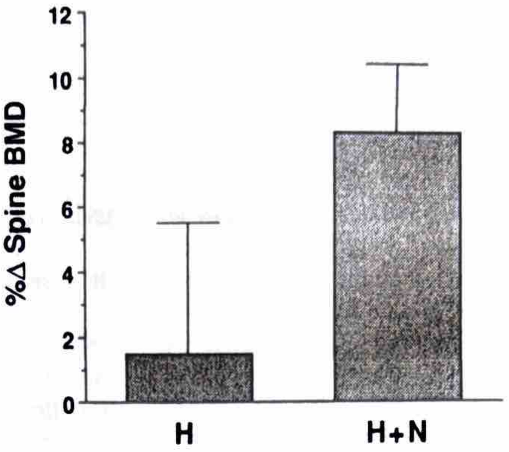

Figure 11-3. Percentage change (mean ± SEM) in the bone mineral density (BMD) of surgical menopausal women after 1 year of hormone therapy alone (H) or hormone therapy plus Nautilus exercise (H + N). The probability (one-tailed t-test) associated with the change in spine BMD measures within the exercising group was $p = 0.002$. The probability (one-tailed t-test) associated with the change in spine BMD measures within the hormone-only group was $p = 0.44$. Changes between groups were not significant. (From Notelovitz et al,[35] p 587, with permission.)

Exercise and Calcium Intake

The precise mechanism whereby exercise stimulates new bone formation is not clearly established. Mechanical load, muscular activity, and gravity serve as extracellular stimuli that are transmitted to bone cells to initiate their genetic program for growth and differentiation. Intermediaries include events such as the generation of piezoelectricity, which stimulates cyclic nucleotide

Table 11-1. EFFECT OF EXERCISE AND HORMONE REPLACEMENT THERAPY ON BONE MASS IN POSTMENOPAUSAL WOMEN

HRT*	Moderate Exercise (Aerobic)	Intense Exercise (Nautilus)	Effect on Bone Mass
No	Yes		0
No		Yes	0
Yes		Yes	+

*Hormone replacement therapy.
Source: From Notelovitz et al,[33] with permission.

activity, prostaglandin synthesis, and other matrix-derived bone growth factors.

It has been established that exercise is directly associated with the laying down of matrix on the remodeling surface of bone's trabeculae and cortices. The matrix is composed primarily of collagen. Chvapil and colleagues[36] showed that the amount and concentration of collagen in the femurs of adult rats increased with exercise, but there was no effect on the calcium content. This experiment illustrates a most important point: to benefit from exercise and its osteogenic stimulus, it is necessary to ensure an adequate supply of the substrate (mainly calcium) needed to mineralize and mature the newly formed bone. It is well known that fluoride therapy without simultaneous calcium supplementation will increase mineralization of the axial skeleton, but at the expense of the cortical bone and with an increase in hip fractures.[37] A similar situation may be true for exercise-induced osteogenesis, except that in this instance it is the cortical bone that benefits at the expense of the trabecular compartment. This may prove to be one of the reasons why the amenorrheic women reported by Drinkwater and associates[14] had lower spinal, but not cortical, bone mineral content when compared with the eumenorrheic controls. Although both groups met the current recommended dietary allowance of 800 mg of elemental calcium per day, the amenorrheic subjects fell short of the recommended amount needed to maintain calcium balance in low estrogen states (1500 mg), whereas the eumenorrheic women exceeded their daily requirement of 800 mg.

Established Osteoporosis

Exercise in women with established osteoporosis has to be modulated because pre-existing microfractures and discontinuity between the trabecular plates, especially in the axial skeleton, may be aggravated by weight-bearing exercise. Furthermore, even though individual fragments of the horizontal trabecular plates may be hypertrophied by exercise, the bone may not improve in strength in response to stress because their continuity (and hence structural integrity) has been lost. Nevertheless, light to moderate exercise in older women has resulted in an improvement of the cortical bone mass. Smith and co-workers[38] designed an exercise program for older women (mean age 81 years) that oriented activity (1.5 to 3.0 METs in intensity) around a chair. (One MET equals an oxygen uptake of 3.5 $mL \cdot min^{-1} \cdot kg^{-1}$, the average value of effort during chair rest.) Over 3 years, the exercise group demonstrated a 2.9% increase in midshaft radius bone mineral content, whereas a matched, nonexercising control group showed a 3.29% decrease.

Inadequate attention is given to the prescription of exercise for women with established osteoporosis, most of whom will present to the physician during the late climacteric. Key is discouraging activities that involve flexion of the back. Long-term follow-up of patients with radiologically confirmed osteoporosis revealed concurrent fractures in 16% of women practicing back extension exercises, 89% in a flexion program, 53% in a combined extension and flexion regimen, and 67% in a nonexercising control group.[39] Posture is also important. Avoidance of flexion during sedentary activities, such as sewing, can prevent further stress on already weakened vertebrae.[40] Instruction should also be given to avoid back straining by twisting, lifting, and making sudden, forceful movements. To remove the strain from the lower back when lifting or reaching lower objects, the large muscles of the legs (i.e., the hamstrings and quadriceps) should be used, by bending the knees and keeping the back vertical during these activities.

Walking is the safest form of exercise for women with osteoporosis. Also safe and effective are group activities such as square dancing, ballroom dancing, and folk dancing, as well as other activities such as riding a three-wheel bike or an exercycle. Swimming is an excellent exercise that allows patients to regain their confidence in being physically active, and at the same time allows them to increase the flexibility and mobility of their joints. Osteoporotic or markedly osteopenic women should be advised to avoid activities such as aerobic (jazz) dance classes that jar the spine and emphasize flexibility. In evaluating these women, care should be taken to test for balance and for orthostatic hypotension, and to advise them about practical measures such as the type of shoes they wear.

Additional information about bone concerns may be found in Chapter 5.

ATHEROGENIC DISEASE AND CARDIORESPIRATORY FITNESS

Premature cessation of ovarian function has been shown to increase the risk of myocardial infarction. Women who had a bilateral oophorectomy before age 35 were estimated to have a 7.2 times greater risk of being hospitalized for a myocardial infarction than age-matched normal premenopausal women.[41] Other studies have also observed high rates of coronary disease in women who experience an early menopause.[7,42,43] There is a general consensus that the postmenopausal period is associated with well-defined high-risk factors for atherogenesis: increased total plasma cholesterol and increased low-density lipoprotein (LDL) levels.[7] This is a biologic, not a chronologic, event. A Swedish study compared women aged 50 and older, of whom some were still menstruating and others had reached menopause; serum cholesterol and triglycerides were significantly higher in the postmenopausal group, and these levels increased with postmenopausal age.[44]

The pathogenesis of atherosclerosis is characterized by two factors: (1) endothelial desquamation with later smooth muscle cell proliferation, and (2) cholesterol deposition within these cells. Inhibition of LDL internalization and deposition in the smooth muscle cell by high-density lipoproteins (HDL) cholesterol is said to be a key factor in the prevention or slowing down of the atherogenic process.[45] Exercise has a beneficial effect on the lipoprotein moiety, especially regarding the HDL cholesterol.[46]

Physical inactivity has also been linked to atherogenic disease. Men who are physically active have fewer stigmata of coronary heart disease, and when they do occur, they are less severe and appear at an older age.[47] The same is true for women.[48] Despite some previous claims that physical inactivity contributed only indirectly to cardiovascular disease risk, there is now considerable evidence that low physical fitness stands as an independent risk factor, in both men and women, for all-cause mortality, cardiovascular disease mortality, and cancer mortality.[49,50] In addition to the direct role demonstrated after controlling for other known risk factors,[50] regular physical exercise probably also plays an indirect role by reducing other known risk factors for coronary heart disease, such as serum lipid concentrations and ratios,[51] hypertension,[51] hyperinsulinemia,[52] diabetes mellitus,[51,53,54] and abdominal fat.[55,56] The type, intensity, and duration of exercise linked to a potential decrease in coronary heart disease varies. There appears to be a threshold of activity needed to achieve a benefit. This has been estimated to be 300 kcal/d above normal activity and requires 30 to 60 minutes of moderately intensive exercise per day.[57] Earlier speculation that women,[58] especially older women, would not be able to achieve this goal has been disproved.

Based on the previous observations, two practical aspects of physical activity and cardiovascular health can be objectively measured: (1) the response of biochemical parameters such as cholesterol and HDL cholesterol, and (2) measures of physical fitness and exercise quantity—maximal oxygen uptake ($\dot{V}O_2max$) and total exercise time.

Lipids, Lipoproteins, and Exercise

The plasma lipoproteins are the means whereby endogenous synthesized lipids are transported in the circulation. They are classified according to their gravitational density into four basic classes: chylomicrons, very low density lipoproteins (VLDL), LDL, and HDL. The latter are frequently subfractionated into HDL_2 and the more dense HDL_3. The HDL_2 cholesterol component is higher in women[59] and is inversely related to the development of coronary heart disease.[60] Exercise stimulates HDL_2, which is higher in both male and female runners than in sedentary controls. In one study, for example, male runners had HDL_2 cholesterol values of 119 versus 53 mg/dL for sedentary men; in women the values for active and sedentary subjects were 218 versus 122 mg/dL.[59] The HDL-elevating effect of exercise is thought to be due to an increase in lipoprotein lipase, an enzyme responsible for the catabolism of triglyceride-rich lipoproteins. Lipoprotein lipase is found in greater concentrations in the skeletal muscle fibers (slow-twitch) of endurance athletes.[61]

The adverse effects of estrogen deficiency on low-density lipoprotein cholesterol levels tend to be offset by aerobic training. However, the beneficial effects of strenuous exercise on plasma apolipoprotein levels can be reversed, in premenopausal women, by exercise-induced amenorrhea and decreased serum estradiol levels.[62]

Table 11-2 lists the serum cholesterol values found in a cross-sectional study of women conducted at the Center for Climacteric Studies, showing an age- and menopause-related increase.[63] To determine whether this change would be improved by exercise, a group of 50 healthy women between the ages of 40 and 65 were invited to participate in a 12-week program of exercise, discussion sessions, or both. The discussion group served as the controls. Levels of serum cholesterol, triglycerides, total HDL, and HDL_{2a} and HDL_{2b} were monitored at baseline, at 6 weeks, and at 12 weeks. The exercise groups were instructed to walk-jog for 30 minutes (after a 15-minute warm-up session) and to pace their activity in order to maintain their heart rate at 70% to 80% of their predicted maximum heart rate. One exercise session each week was supervised by a group therapy leader, and the women exercised on their own during two other sessions per week. Cardiorespiratory function was determined at baseline and at 12 weeks by having subjects walk on a motorized treadmill until they declared fatigue or reached their predicted maximal heart rate. The exercising group had a significantly greater increase in $\dot{V}O_2max$, time spent on the treadmill, and time required to attain 90% of maximal oxygen consumption ($p < 0.01$), but did not show a statistically significant difference in the lipid or lipoprotein fractions at either 6 or 12 weeks.[64] This disappointing result was confirmed by Franklin and associates,[65] who exercised their subjects four times a week as part of a 12-week conditioning program. These discrepant results may be explained by the duration of the exercise program and intensity of the exercise. For example, when the weekly running mileage of 22 women was increased from 3.5 miles to 44.9 miles (over a 7-month period), their mean HDL cholesterol increased from 53.5 to 58.5 mg/dL ($p < 0.01$).[66]

In another study, hysterectomized postmenopausal women who exercised thrice weekly in 30-minute sessions of aerobic exercise at a minimum of 70% of maximal heart rate had a significant reduction in total serum cholesterol and LDL cholesterol.

Table 11-2. SERUM CHOLESTEROL (mg/dL) OF WOMEN, RELATED TO AGE AND MENOPAUSE

	Premenopausal		Postmenopausal		
Age range	35–45	46–55	46–55	56–65	66–75
N	30	24	23	24	10
Cholesterol (mean ± SEM)	170.5 ± 4.3	203.2 ± 7.6	233.8 ± 5.9	230.1 ± 6.9	238.8 ± 6.7

Source: From Notelovitz et al.[63]

However, this effect was not greater than that induced by oral estrogen alone.[67]

Like their younger counterparts, postmenopausal women who engage in regular endurance exercise have higher HDL cholesterol levels than inactive women.[68–70] Postmenopausal long-distance runners and joggers had significantly greater levels of HDL cholesterol compared with a control group of relatively inactive women—79.8, 73.5, and 61.8 mg/dL, respectively. The lipid-lipoprotein profiles were minimally affected by exercise in a simultaneously studied group of exercising premenopausal women,[70] raising the issue of whether it is possible to make "normal" *more* normal.

It appears that the cardioprotective HDL cholesterol level improves after only 3 months of moderate activity (e.g., running 10 to 15 miles/wk) or low-level activity (e.g., walking 30 miles/wk).[59] As with men, exercise training in women lowers total cholesterol slightly or not at all.[65,66]

Aerobic Power

With the advent of the "fitness craze," women have come into their own and have exploded the myth that women are "frail"; physical fitness in young women has now become socially acceptable and, in many circles, even desirable. Until fairly recently, however, it was felt that exercise would not benefit middle-aged people, and that the decline in cardiorespiratory function with aging would reduce the expected benefit from exercise.[58] Furthermore, it was postulated that menopause per se could be responsible for the decrease in aerobic power in women over the age of 50.[71,72]

As with men, cardiorespiratory fitness does decrease with age, but this decline is not related to the hormonal changes of the climacteric. Figure 11–4 shows that a decrement of 5.5% of $\dot{V}O_2$max occurred with each succeeding decade between ages 35 and 75 in a study of 163 healthy sedentary women.[73] This observation approximates with the generalization that sedentary individuals have a 1% loss of $\dot{V}O_2$max per year with age, especially after age 50. Women usually achieve maximal $\dot{V}O_2$max values in their 20s; by age 50 to 65 years, the values are decreased by almost 30%.[74] This loss of aerobic power is not related to menopause per se, however. In a recent study, women aged 45 to 55 had their $\dot{V}O_2$max predicted by means of a submaximal bicycle ergometer test.[73] They were divided into premenopausal and postmenopausal groups, as confirmed by hormonal analysis and by their menstrual pattern: postmenopausal women were required to have been amenorrheic for at least 1 year. As reflected in Table 11-3, serum LH and FSH were significantly higher in the postmenopausal women ($p < 0.0001$), and the estradiol and estrone levels were significantly lower ($p < 0.0001$). The premenopausal women were slightly younger (48.7 ± 0.4 years versus 52.2 ± 0.4), but the difference was not statistically significant. No significant difference was found in the estimated $\dot{V}O_2$max for the two groups ($p > 0.05$).[73]

The observed decline in $\dot{V}O_2$max with age probably reflects a loss of functional capacity due both to a natural age-related deterioration and to a decrease in physical activity. The age-associated reduction in cardiorespiratory efficiency at submaximal exercise, however, is due primarily to weight gain rather than to actual systems degeneration.[75] The rate of decline is slower in

Table 11–3. MEAN ESTIMATED MAXIMAL O_2 UPTAKE VALUES AND HORMONAL STATUS (± SD) OF PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN AGE 46–55 YR

Parameter	Premenopausal (n = 28)	Postmenopausal (n = 30)
Estimated $\dot{V}O_2$max (mL·kg⁻¹·min⁻¹)	27.4 ± 6.3	26.3 ± 4.7
LH (mIU/mL)	23.5 ± 3.6	62.8 ± 3.5
FSH (mIU/mL)	12.6 ± 2.6	55.7 ± 3.5
Estrone (pg/mL)	107.5 ± 11.5	62.9 ± 3.9
Estradiol (pg/mL)	146.2 ± 18.7	19.5 ± 3.5

Source: From Notelovitz et al,[73] with permission.

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meno-usal (= 28)	Postmenopausal (n = 30)
.4 ± 6.3	26.3 ± 4.7
.5 ± 3.6	62.8 ± 3.5
.6 ± 2.6	55.7 ± 3.5
.5 ± 11.5	62.9 ± 3.9
.2 ± 18.7	19.5 ± 3.5

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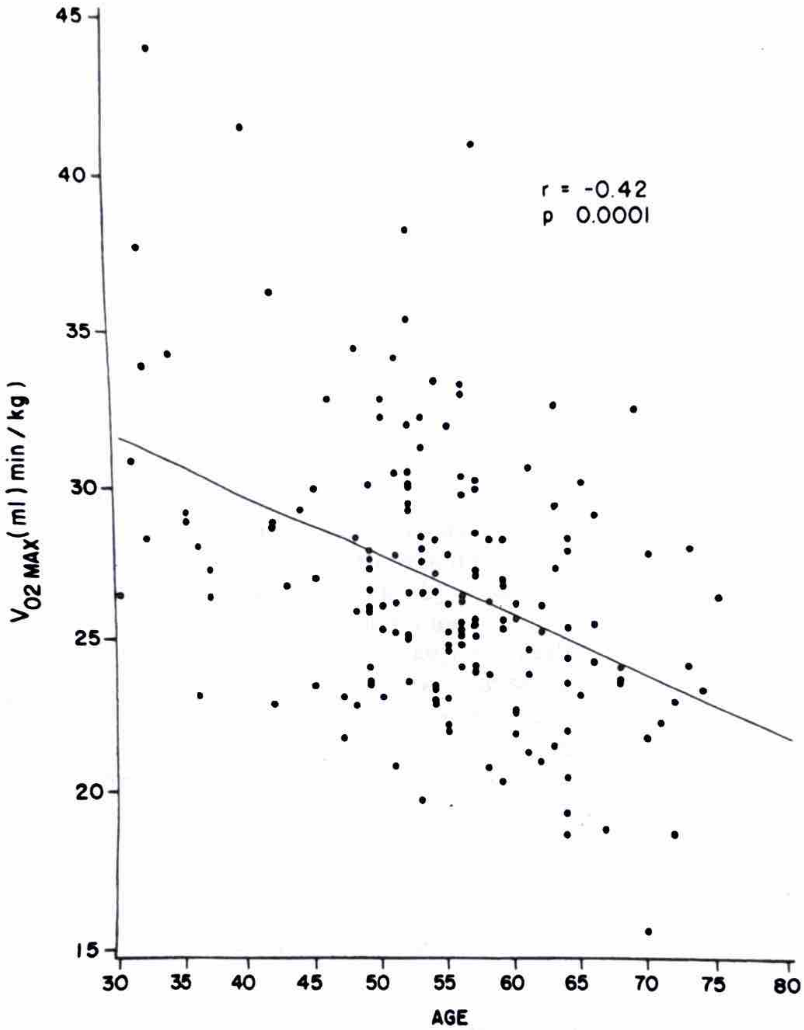

Figure 11–4. Measured $\dot{V}O_2max$ (mL·kg·min) in 163 healthy climacteric women, who first were screened for cardiovascular normalcy by a 12-lead ECG stress test and physical examination. The $\dot{V}O_2max$ was elicited using a modified Balke treadmill procedure, and was directly measured using a Beckman Metabolic Measurement Cart. (From Notelovitz et al.,[73] with permission.)

physically active men[76] and women.[76,77] This raises the issue of whether menopausal women can be efficiently trained. Premenopausal women (mean age 41 years) who trained for 9 weeks improved their $\dot{V}O_2max$ by 12.1%, while similarly trained postmenopausal women (mean age 57 years) improved their $\dot{V}O_2max$ by 19%.[78] This result has been confirmed by others,[79] including two studies conducted at the Center for Climacteric Studies in Gainesville, Florida. Moderate exercise (walk-jogging three times a week for 12 weeks) resulted in a significant increase in maximal oxygen consumption, time on the treadmill, and the time to reach 90% of maximal oxygen consumption, when compared with age-matched female controls who did not exercise.[80] More recently, 63 postmenopausal women were evaluated over a 1-year period, during a structured program that involved three weekly 20-minute treadmill, ergometer, or Nautilus (muscle-strengthening) sessions. Two nonexercising groups were

Table 11–4. RESPONSE OF CLIMACTERIC WOMEN—MEAN AGE 56 YR—TO INTENSIVE STRUCTURED EXERCISE,[81] MEAN (± SD) MAXIMAL O_2 UPTAKE ($mL \cdot kg^{-1} \cdot min^{-1}$)

Group	Age	n	Baseline	3 Mo	6 Mo	12 Mo	% Difference Baseline vs 12 Mo
Nautilus	59.3 ± 6.7	13	26.0 ± 5.2	26.1 ± 4.7	26.5 ± 4.0	26.2 ± 3.9	0.8
Treadmill	54.9 ± 6.9	10	27.1 ± 2.7	29.5 ± 2.8	30.5 ± 2.8	29.5 ± 2.4	8.9
Ergometer	55.9 ± 6.9	10	26.7 ± 4.7	28.9 ± 4.1	30.2 ± 4.1	30.0 ± 4.8	12.4
Control	62.0 ± 7.1	14	26.5 ± 4.7	26.1 ± 6.0	25.9 ± 5.9	26.2 ± 5.8	−1.1
Hormone	48.4 ± 7.2	16	26.6 ± 3.9	26.3 ± 3.7	26.4 ± 4.2	25.1 ± 3.9	−5.6

Source: From Notelovitz et al,[81] with permission.

included: an age-matched nontreatment group and a slightly younger group on hormone replacement therapy. Aerobically trained subjects were exercised at 70% to 85% of the maximal heart rate. Significant improvements in both $\dot{V}O_2max$ and time on the treadmill were recorded and maintained only by the bicycle and treadmill groups (Tables 11–4 and 11–5).[81]

The anticipated degree of improvement in aerobic power is inversely related to the subject's initial level of fitness, but at all initial levels, the greater the intensity and frequency of the training program, the greater the improvement. For example, the postmenopausal women in Cowan and Gregory's study[78] had a 19% improvement in $\dot{V}O_2max$ (from 12.6 $mL \cdot kg^{-1} \cdot min^{-1}$ to 15.0 $mL \cdot kg^{-1} \cdot min^{-1}$), compared with a 10.7% improvement in the Gainesville study[81] (from 26.9 $mL \cdot kg^{-1} \cdot min^{-1}$ to 29.8 $mL \cdot kg^{-1} \cdot min^{-1}$).

An intriguing observation in both of these studies is the considerably greater improvement in total exercise time versus $\dot{V}O_2max$. Cowan and Gregory[78] noted a 29.6% increase in total walking time; in the Gainesville study,[81] the time for treadmill walkers increased 21.5%, and for bicyclists, 17.4%. Premenopausal women exposed to the same exercise regimen had an improvement rate of 10.9% in total exercise time.[78] Since the heart rate and stroke volume response to exercise was appropriate in postmenopausal women, there is a possibility that the lesser percentage response in $\dot{V}O_2max$ compared with percentage improvement in exercise time might be accounted for by partially compromised lung ventilation, lung diffusion capacity for oxygen, and/or oxygen utilization by the tissues in the postmenopausal period.

Less attention has been directed to older women. When 10 healthy women of mean age 72.0 years exercised three times per week for 20 minutes per session, at 70% of maximum heart rate, for 26 weeks, maximum oxygen uptake increased 8.4% and total exercise time increased 25.4%, compared to a 6.1% decrease in maximum oxy-

Table 11–5. RESPONSE OF CLIMACTERIC WOMEN—MEAN AGE 56 YR—TO INTENSIVE STRUCTURED EXERCISE,[81] MEAN (±SD) TOTAL EXERCISE TIME (MIN)

Group	Age	n	Baseline	3 Mo	6 Mo	12 Mo	% Difference Baseline vs. 12 Mo
Nautilus	59.3 ± 6.7	13	12.1 ± 3.2	12.2 ± 2.5	12.9 ± 2.4	12.5 ± 2.4	5.3
Treadmill	54.9 ± 6.9	10	12.5 ± 1.6	14.2 ± 2.1	15.2 ± 2.0	15.3 ± 2.1	21.5
Ergometer	55.9 ± 7.9	10	13.0 ± 3.1	14.1 ± 3.0	14.5 ± 3.0	15.2 ± 3.3	17.4
Control	62.0 ± 7.1	14	12.2 ± 3.3	11.6 ± 3.6	12.2 ± 4.0	12.1 ± 3.4	−0.95
Hormones	48.4 ± 7.2	16	13.4 ± 2.4	12.6 ± 2.3	13.0 ± 2.3	12.3 ± 2.2	−7.7

Source: From Notelovitz et al,[81] with permission.

Table 11–6. IMPROVEMENT OF MAXIMAL O_2 UPTAKE FOLLOWING AEROBIC TRAINING PROGRAMS IN WOMEN OVER AGE 50

Author	n	Duration of Exercise per Session (min)	Frequency of Exercise per Week	Intensity of Exercise	Duration of Training Program (wk)	%Gain in Maximal O_2 Uptake
Kilbom[58]	13	30	2–3	70%*	7	8
Adams and DeVries[133]	17	50	3	85%†	12	20.8
Sidney et al.[134]	25	60	4	120–150‡	7	>30
Sidney and Shephard[135]	28	55	3	60–80%†	14	17
Cowan and Gregory[78]	14	50	4	80%†	9	18.9
Notelovitz et al[81]	10 (T)	20	3	70–85%†	52	8.9
	10 (E)	20	3	70–85%	52	12.4
Probart et al[82]	10	20	3	70%†	24	8.4

*$\dot{V}o_2$max.
†Maximum heart rate.
‡Heart rate.
T = treadmill; E = ergometer.
Source: Adapted from Cowan and Gregory.[78]

gen uptake and a 5.4% decrease in total exercise time in six age-matched controls who did not exercise.[82] These data and others (Table 11–6) indicate that older women can certainly expect to improve fitness and exercise capacity with aerobic training.

In the studies summarized in Table 11–6, the percentage gain in aerobic power ranges from 8% to 30%. With only one exception, the duration of these training programs was less than 14 weeks. The best improvement was obtained in programs whose duration of exercise exceeded 30 minutes in each session. The study that continued for 12 months demonstrated that most of the improvement attained by 12 months had been achieved by 3 months of training. These results, however, do not reflect the true potential of older women engaged in long-term, intensive exercise programs, nor do they consider a most important practical, real-life issue of exercise: compliance.

Measurements of aerobic fitness may help to motivate some sedentary women. Kirk and co-workers[26] reported higher levels of fitness (maximal oxygen consumption) among postmenopausal runners compared to age-matched sedentary women. In another cross-sectional study,[83] active women had a fitness gain of one decade when compared to sedentary women. The mean $\dot{V}o_2$max of active 40- to 49-year-old women was higher than sedentary 30- to 39-year-old women; active 50- to 59-year-old women had values similar to sedentary women in their 40s. One way of encouraging women to exercise is to use cardiorespiratory fitness assessments as a means of demonstrating improvement in aerobic function before the physical benefits of exercise are appreciated. Bruce and colleagues[84] reported that 63% of their patients attributed a change in one or more adverse health habits to a graded exercise test. Persons with an abnormal result were motivated the most.

Maximal oxygen uptake tests need to be performed in a specially equipped laboratory and are not suited to everyday clinical practice. Submaximal testing, on the other hand, is more suited to the practicing physician. Several studies have shown that predicted maximum $\dot{V}o_2$ values (using a bicycle ergometer) correlate well with observed maximal testing when corrected for age,[85,86] but none of these studies have involved climacteric women. To test this relationship in postmenopausal women, 29 women (mean age 55.6 ± 9.1 years) participating in an ongoing exercise program had both a maximal treadmill test and a submaximal ergometry test.[73] The interval between the two tests was less than 1 month, and the order of testing was randomly selected. The measured $\dot{V}O_2max$ was 28.6 ± 4.9 $mL \cdot kg^{-1} \cdot min^{-1}$, and the predicted $\dot{V}O_2max$ 32.5 ± 5.3 $mL \cdot kg^{-1} \cdot min^{-1}$. When the latter result was calculated using the recommended Åstrand age correction factor, the mean predicted $\dot{V}O_2max$ was 23.4 ± 4.9 $mL \cdot kg^{-1} \cdot min^{-1}$. This correlated closely with the directly measured result ($r = 0.789$; Fig. 11–5).

Submaximal testing can thus be used both as a screen to determine the cardiorespiratory fitness of climacteric women and as a way of monitoring the response to prescribed exercise. Patients at high risk for cardiovascular disease and those classified as having fair to poor fitness (as measured by ergometry) require more detailed evaluation before embarking on a prescribed exercise program. A nomogram is also very useful (Figs. 11–6 and 11–7); when used together with age-adjusted tables listing cardiorespiratory fitness for women (Table 11–7), potential exercise candidates can obtain a good index of both their current fitness status and the goals they should reach. Because postmenopausal women appear to show a greater response to a given exercise program in total exercise time than in maximum oxygen uptake, the total exercise nomogram (Fig. 11–7) may be used as the primary indicator of exercise response and improvement.

In view of the laziness inherent in most people, any program that can produce improved results for little effort is more likely to be successful and lead to a greater degree of compliance than a program that requires great effort and discipline. Schoenfeld and co-workers[87] examined the efficiency of walking with a backpack load as a method for improving physical fitness of sedentary men. They showed that it was possible to increase $\dot{V}O_2max$ by 15% to 30% by walking for 3 to 4 miles with a 3- or 6-kg backpack. When we compared the effects of treadmill walking with and without extra weight in a small group of postmenopausal women, we found greater improvement in the aerobic capacity of the load-bearing group.[88] However, confirmatory studies with larger numbers are needed to determine whether load-bearing enhances the efficacy of aerobic training or modifies the perceived effort.

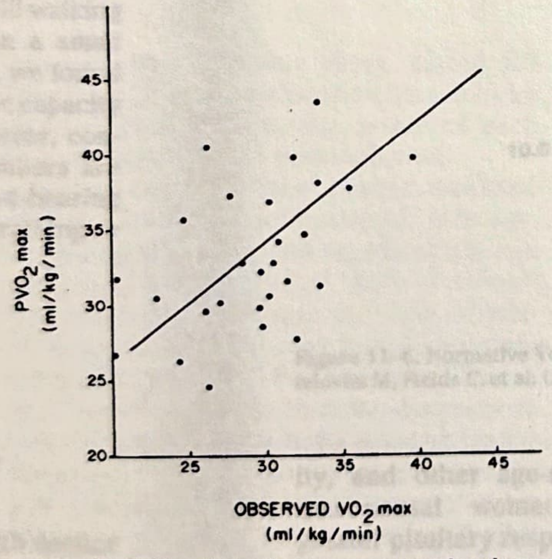

Figure 11–5. Correlation between measured and predicted $\dot{V}O_{2max}$ in climacteric women. (From Notelovitz et al.,[73] with permission.)

MUSCLE TISSUE AND STRENGTH

Age-Related Loss of Muscle Tissue and Strength

Muscle mass and muscle strength decline with aging, and muscle weakness can greatly reduce the quality of life and self-sufficiency of many older women. The age-related decline in lean body mass correlates with several changes: a decline in endogenous growth hormone (GH),[89] a decline in pituitary responsiveness to growth hormone releasing hormone (GHRH),[90] loss of muscle fibers,[91] neuromuscular alterations, inactiv-

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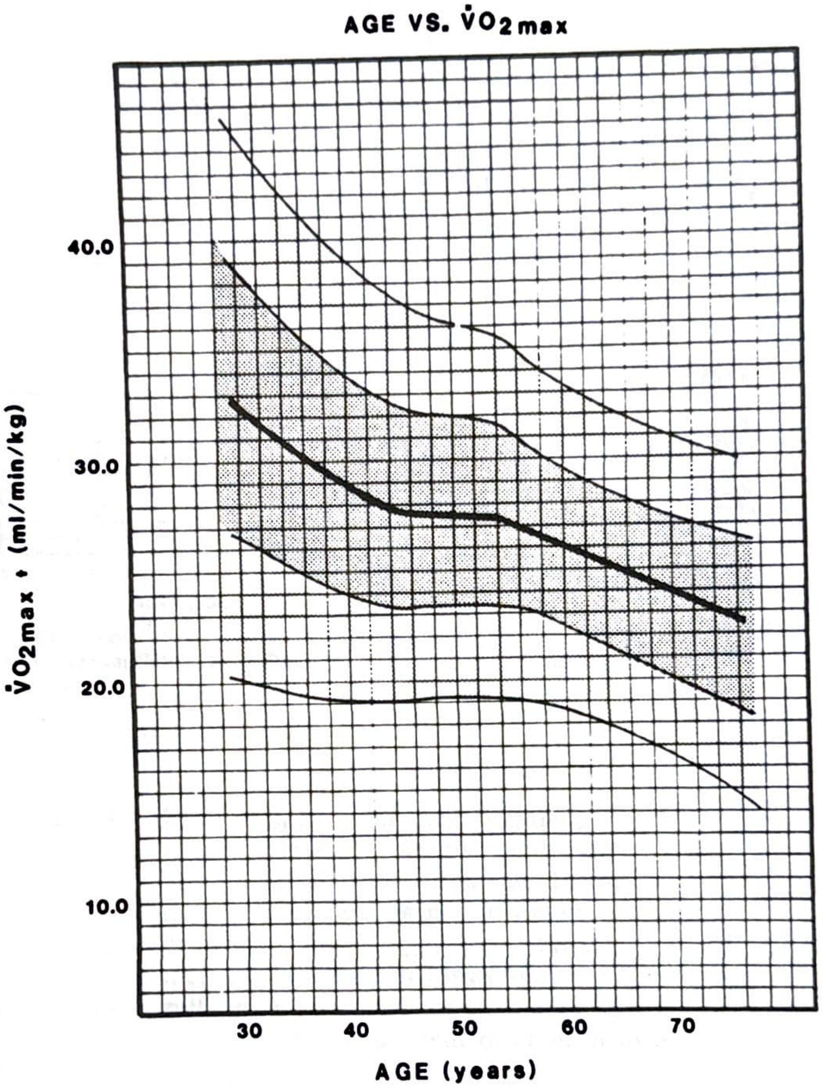

Figure 11–6. Normative $\dot{V}O_2$max values for climacteric women. Mean ± 1 and 2 SD for each age group. (From Notelovitz M, Fields C, et al: Unpublished data. Center for Climacteric Studies, Gainesville, FL, with permission.)

ity, and other age-related changes. Premenopausal women have significantly greater pituitary response to GHRH than do men of the same age, but postmenopausal women do not;[90] this finding suggests that postmenopausal estrogen deficiency accelerates the age-related decline in GH secretion and may also accelerate the loss of muscle tissue that occurs as women age. Although Rudman and his co-workers[92] reported that older men increased both lean body mass and skin thickness and de-

Table 11–7. GUIDELINES FOR FITNESS ASSESSMENT BY $\dot{V}O_2$max ($mL \cdot kg^{-1} \cdot min^{-1}$) OF HEALTHY WOMEN AGE 30–70

Age	Poor	Fair	Average	Good	Excellent
30–39	<20	20–27	28–33	33–44	45+
40–49	<17	17–23	24–30	31–41	42+
50–59	<15	15–20	21–27	28–37	38+
60–69	<13	13–17	18–23	24–34	35+

Source: Adapted from Exercise Testing and Training in Apparently Healthy Individuals: A Handbook for Physicians, published by the Committee on Exercise, The American Heart Association, Dallas, TX, 1972.

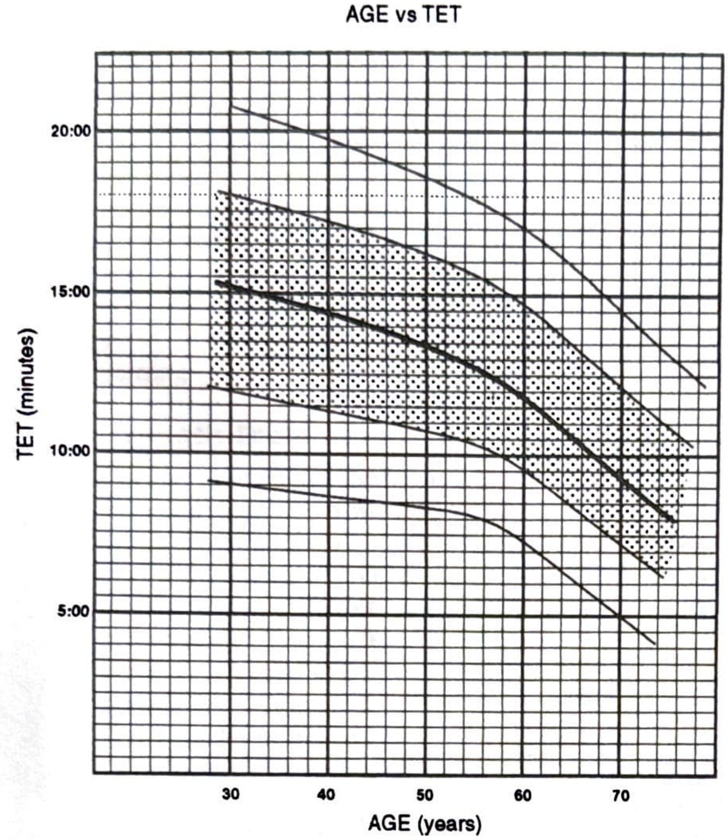

Figure 11-7. Normative total exercise time (TET) to exhaustion values for climacteric women, using modified Balke method. Mean ± 1 and 2 SD for each age group. (From Notelovitz M, Fields C, et al: Unpublished data. Center for Climacteric Studies, Gainesville, FL, with permission.)

creased adipose tissue mass during GH treatment, this has not been studied in older women. Furthermore, the safety of such therapy has not been demonstrated.

Several cross-sectional studies also have shown a loss of muscle strength with age, beginning after the third decade of life and amounting to a decline of 16.5% or more.[93] The loss is greater in women.[94] Loss of muscle tissue is related to a number of important metabolic activities. For example, Tzanoff and Norris[95] maintain that the decrease in muscle mass may be wholly responsible for the age-related decrease in basal metabolic rate (BMR). The average $\dot{V}O_2$max of older men was 22% lower when compared with younger men, but this difference decreased to only 8% when the values were expressed in terms of milliliters per kilogram per minute of muscle, as determined by 24-hour urine creatinine measurements. Increasing muscle mass can thus play an important role in determining energy expenditure: a 2-kg increase in a woman's lean body mass results in an additional expenditure of about 50 kcal/d, the equivalent of about 5 lb of body fat per year.

Muscle is also an important determinant of carbohydrate utilization. The rate of glucose removal from muscle is more rapid in physically active persons, and the amount of insulin needed is significantly reduced.[96] This effect is reputed to be due to the enhanced sensitivity of insulin receptors in skeletal (and adipose) tissue. Obesity and diabetes are two age-related conditions that

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are prevalent in the late climacteric. Van Dam and colleagues[96a] have shown improvement in glucose tolerance among postmenopausal women following aerobic exercise training.

Strength Training

Weight training in women has been shown to improve strength with a loss of adipose tissue and with relatively little muscle hypertrophy. These studies have involved young women, trained athletes, or both, however.[97–99] It is not known whether muscle strengthening exercises will enhance the metabolic function of postmenopausal skeletal muscle, and if so, to what degree. Extrapolation from data collected in male subjects suggests that the accumulation of greater mass will lead to greater energy expenditure. Strength training does not improve cardiorespiratory function (see Table 11–4), a finding confirmed by studies done in middle-aged men.[100] Weight training stresses muscles far more than do most aerobic exercises. It is safe to start an aerobic exercise program and then, many months later, to start lifting weights.

OTHER MENOPAUSAL PROBLEMS: VASOMOTOR SYMPTOMS

Very few studies have addressed the relationship between menopausal vasomotor symptoms ("hot flushes") and exercise. In one study, Hammar and co-workers[101] found vasomotor symptoms to be less common among exercising menopausal women than among inactive women. Since exercise has not been shown to relieve symptoms, however, this finding may reflect a self-selection bias, representing differences between the two groups questioned.

Although the etiology of the menopausal vasomotor flush remains enigmatic, estrogen remains the most effective form of therapy available.[102] When estrogen is contraindicated, medroxyprogesterone acetate[103] or megestrol acetate[104] (synthetic progestogens) will provide relief for most women. It should be noted that medroxyprogesterone acetate has not been approved, in the United States, for use in women with breast cancer.

OTHER AGE-RELATED CHANGES

Exercise and Adipose Tissue

Most people add adipose tissue with aging. There is no evidence that accumulation of adipose tissue is related to menopause, estrogen deficiency, or any other alterations in reproductive hormones, but many women first notice this accumulation around the time of menopause. Menopause also has not been shown to affect the distribution of body fat,[105] but there is a progressive age-related increase in upper and central body fat deposition, which tends to accelerate in postmenopausal women.[106] However, it remains to be shown whether this change is related to menopause, aging, or both.

Levels of adipose tissue lipoprotein lipase (LPL) correlate directly with body mass index (in kilograms per square meter of body surface) and affect the maintenance of adipocyte size, body weight, and obesity.[107] Adipocyte size is similar at mammary, abdominal, and femoral sites and is similar for premenopausal and postmenopausal women.[108] It has been shown[108] that femoral LPL activity is much higher among premenopausal women than among postmenopausal women and that, among premenopausal women, it is much higher than it is at mammary or abdominal locations. Treatment of postmenopausal women with estradiol and a progestogen leads to an increase in femoral LPL activity.[109] When percutaneous progesterone is applied to the femoral region of premenopausal women during the follicular phase of a natural menstrual cycle, LPL activity rises locally.[110] These data suggest that progesterone is an important determinant of femoral LPL activity.[111]

Regional fat distribution has achieved importance since it was demonstrated that abdominal fat is a risk factor for cardiovascular disease and diabetes, while femoral fat is not.[55,56] Aerobic exercise facilitates the loss of abdominal fat more readily than fat at other sites, and promotes fat loss more readily in men than in women.[112–115] It is fortunate that abdominal fat is so sensitive to exercise, since this facilitates reduction in disease risk. However, the relative resistance of femoral fat depots to exercise may discourage many women with a preponderance of femoral fat.

Inactivity is the most common cause of obesity, and it accelerates the accumulation of body fat that occurs naturally with aging. Cowan and Gregory[78] have reported a loss of body fat during a 9-week training program in women, confirming that exercise can certainly help older women to lose fat. Control of weight and body fat is discussed more thoroughly in Chapter 2.

Exercise and Osteoarthrosis

The articular cartilage that covers the bone ends in joints is rich in collagen and the mucopolysaccharide proteoglycan. This collagen layer acts as a barrier preventing the leakage of proteoglycan from the deeper layers into the joint space, and at the same time it inhibits potential harmful enzymes in the synovial fluid from perfusing into the deeper cartilage.[116] Loss or damage to the cartilage layer leads to joint degeneration and the development of osteoarthritis.

Osteoarthritis is a highly prevalent disease: 86% of women over the age of 65 show radiologic evidence of the condition,[117] although only 25% to 30% of individuals with diagnosed osteoarthritis are symptomatic. There are conflicting opinions regarding the role of microtrauma to the joint surface in the pathogenesis of osteoarthritis. Impulse loading causes trabecular microfracture with subsequent healing by sclerosis, resulting in stiffened bone that increases the stress on the articular cartilage, with eventual damage to the cartilage and joint degeneration. These changes appear on roentgenogram as osteophytes, sclerosis of the subchondral bone, cyst formation, and narrowing of the joint space.

Postmenopausal women have decreased amounts of collagen in skin and bone,[118] and it is most likely that the same is true for the collagen content of their articular surfaces. The collagen in the skin (and possibly also in the bone) of postmenopausal women is responsive to estrogen replacement. Although arthralgia is a common symptom in the late climacteric, a direct linkage between menopause and joint disease has not been established. However, a study has demonstrated that noncontraceptive hormonal therapy does help some women with rheumatoid arthritis.[119]

With the increased interest in jogging, a question arises of whether damage to the musculoskeletal-articular system exceeds the benefit of exercise. Lane and associates[120] recently studied female long-distance runners over age 50 and compared them with age-matched nonactive community controls. The female runners did have more sclerosis and spur formation in the weight-bearing areas of the spine and knees, but not in the hands. These changes were not found in men studied in the same and other investigations.[121]

Given the asymptomatic nature of these changes and the difficulty of extrapolating cross-sectional data into "real-life" terms, it cannot be concluded that jogging has an adverse effect on the joints of middle-aged women. The absence of joint changes in age-matched and hormone-replete men, however, suggests the possibility that an estrogen-primed articular surface (with an improved collagen content) might be similarly resilient to mechanical stress.

EXERCISE AND WELL-BEING

The administration of exogenous estrogens, especially parenteral estrogen therapy, to postmenopausal women is frequently associated with a mood-elevating effect. Exercise is also known to induce a state of well-being and, according to some

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studies, a reduction in symptoms such as depression and anxiety. The early work of Weber and Lee[122] demonstrated that vigorous activity in animals had a positive influence on psychologic measures and that this was probably due to alterations in brain neurotransmitter levels or activity, or both.[123] Studies in humans have been less clear, and there is some question whether the "runner's high" really exists.[124]

Part of the controversy lies in the fact that much of the research has been conducted in nondepressed subjects. Greist and colleagues[125] demonstrated that aerobic exercise performed for 12 weeks reduced depression (in patients complaining of mild to moderate depression) to a greater degree than traditional psychotherapy. Additional advantages noted by the authors included less expense, no need to use antidepressant medication, and the persistence of a depression-free state when evaluated 12 months later, whereas half the patients receiving psychotherapy returned earlier for additional treatment. The reader is referred to an excellent review by Dunn and Dishman[126] of the relationship between exercise and depression.

One of the most distressing symptoms expressed by menopausal women is anxiety. Vigorous physical activity reduces muscle tension and is also associated with a significant decrease in anxiety.[127] This effect was noted only when the exercise was intense enough to provoke significant elevations in plasma epinephrine and norepinephrine, however,[128] and did not occur if light to moderate exercise was performed.

Another common problem associated with the menopausal syndrome—insomnia—may be positively influenced by exercise. Healthy subjects who engaged in static exercise (e.g., contraction of a hand dynamometer at 40% of maximal level for 40 minutes, separated by a 10-minute rest at midsession) 2 hours before bedtime were shown to have a significantly reduced time to onset of sleep relative to nonexercise nights. The improvement in sleep was associated with increased slow-wave sleep and decreased movement time during sleep, factors that contribute to a "refreshing" sleep period.[129]

To evaluate the effect of exercise on psychologic well-being, preprogram and postprogram psychosocial measures were obtained by questionnaire and standardized tests in a group of healthy women (age 40 to 64 years) participating in a 12-week exercise program. Methods of evaluation included a self-report of physical activity, a somatization scale, the multidimensional health locus of control inventory, the Profile of Mood States Scale, and a social support questionnaire. Members of the exercised group were required to walk-jog for 30 minutes three times a week for 12 weeks, and they were compared with matched women participating in discussion groups and a nonintervention control group. The only noted apparent benefit of exercise was a decrease in intake of stimulants (e.g., coffee) among exercisers, whereas there was an increase in intake among the nonexercisers.[80] These results are similar to the report of Penny and Rust,[130] whose subjects participated in a walk-jog program involving 1½ miles of exercise twice a week for 15 weeks. A comparison of personality scales measured by the MMPI showed no difference from a control nonexercising group. Despite these negative results, discussions with individuals who exercised elicited commonly observed responses: "feeling better, enjoying social functions more, participating in more extracurricular activities, and not being tired at day's end."[130] The operative factors appear to be the frequency, intensity, and duration of exercise, and patience. The last is most important, as the benefits of exercise rarely occur before 10 weeks of training, the time when most individuals drop out of exercise programs.

In summary, although the chemical basis of the mood improvement induced by physical activity is not known, fairly strong evidence suggests that acute and chronic vigorous exercise is associated with an improvement in affective states, especially anxiety and moderate depression.

Psychomotor speed is one well-recognized behavior that is slowed by aging. This is especially true for response speed that occurs in reaction time, performance of tasks that require the coordination of two simultaneous movements, writing speed, and simple tasks such as tapping in place.[131] The quicker the response, the higher the perceptual speed score. Perceptual speed was evaluated in healthy aging women as part of a large study examining age-related changes, and a progressive decrease was noted with both chronologic and biologic aging.[63] As shown in Table 11-8, the perceptual speed score decreased from a mean score of 64.4 ± 2.1 in 40-year-old premenopausal women to 48.0 ± 2.6 in 68-year-old women ($p < 0.0001$; $r = -0.41$). An interesting observation is the difference in the perceptual speed score between premenopausal and postmenopausal women aged 46 to 55. Although the premenopausal women were only a few years younger, their mean perceptual speed score was significantly higher than that of the postmenopausal group, whose score was similar to the score of women 5 or more years past their menopause.

Further analysis of these data revealed that, within the groups, physical fitness was positively correlated with the perceptual speed score. The greater the degree of fitness, the more functionally competent the individual.[63] This raises the issue of whether exercise may prevent premature aging of the central nervous system and compensate for possible alterations in the neurohormonal milieu of postmenopausal women. A number of investigators have shown that people who exercise consistently have a faster reaction time, and that this difference is related to generalized rather than specific exercise. For example, the reactive speed of the fingers is improved in runners, who primarily exercise their legs.[132] It is not clear whether this exercise-induced improvement affects central nervous system processing time, or motor speed. As with the psychologic response to exercise, CNS function (e.g., short-term memory) that is not impaired in a particular individual cannot be expected to be improved by exercise. With this caveat in mind, it is fair to conclude that "exercise seems to be one way for people to achieve maximal plasticity in aging, approximating full vigor and consistency of performance until life's end."[132]

SUMMARY

"Menopause," an often-misused term, is actually the duration of a woman's final menstrual period. The 15 years leading up to and following this event are known more properly as the "climacteric."

Women lose a small percentage of bone as a natural phenomenon in the aging process. However, the greater the bone mineral content at bone mass maturity, the more one can afford to lose. Thus, women should be encouraged during, and even before, the early climacteric to accrue as much bone as possible, through an appropriate calcium intake and an osteogenic exercise program. Likewise, such practices can be used to avoid excessive bone loss during the climacteric. For women who have osteoporosis, a regimen of walking may be the safest type of

Table 11-8. CHANGES IN PERCEPTUAL SPEED SCORE ASSOCIATED WITH CHRONOLOGIC AND BIOLOGIC AGING IN WOMEN

	Premenopausal		Postmenopausal		
Age range	35–45	46–55	46–55	56–65	66–75
Mean age (± SEM)	40.9 ± 0.5	48.7 ± 0.4	52.2 ± 0.4	59.3 ± 0.5	68.5 ± 0.5
N	30	29	30	29	27
Perceptual speed score (mean ± SEM)	64.4 ± 2.1	61.1 ± 1.9	56.6 ± 1.8	55.3 ± 1.3	48.0 ± 2.6

Source: From Notelovitz et al,[63] with permission.

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exercise program. These women should avoid exercises that emphasize flexion of the back.

The postmenopausal period has been associated with an increased plasma total cholesterol level and an increased LDL level—both risk factors for atherosclerotic disease. A regular, long-term exercise program promotes beneficial changes in lipoprotein cholesterol levels, aerobic fitness, exercise time, and coronary heart disease risk.

Exercise also adds to a feeling of well-being and may counteract clinical depression and anxiety experienced by some women in this stage of life.

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