Estrogen replacement and skeletal muscle: mechanisms and population health

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Tiidus PM, Lowe DA, Brown M. Estrogen replacement and skeletal muscle: mechanisms and population health. J Appl Physiol 115: 569–578, 2013. First published July 18, 2013; doi:10.1152/japplphysiol.00629.2013.—There is a growing body of information supporting the beneficial effects of estrogen and estrogen-based hormone therapy (HT) on maintenance and enhancement of muscle mass, strength, and connective tissue. These effects are also evident in enhanced recovery from muscle atrophy or damage and have significant implications particularly for the muscular health of postmenopausal women. Evidence suggests that HT will also help maintain or increase muscle mass, improve postatrophy muscle recovery, and enhance muscle strength in aged females. This is important because this population, in particular, is at risk for a rapid onset of frailty. The potential benefits of estrogen and HT relative to skeletal muscle function and composition combined with other health-related enhancements associated with reduced risk of cardiovascular events, overall mortality, and metabolic dysfunction, as well as enhanced cognition and bone health cumulate in a strong argument for more widespread and prolonged consideration of HT if started proximal to menopausal onset in most women. Earlier reports of increased health risks with HT use in postmenopausal women has led to a decline in HT use. However, recent reevaluation regarding the health effects of HT indicates a general lack of risks and a number of significant health benefits of HT use when initiated at the onset of menopause. Although further research is still needed to fully delineate its mechanisms of action, the general use of HT by postmenopausal women, to enhance muscle mass and strength, as well as overall health, with initiation soon after the onset of menopause should be considered.

estrogen; hormone replacement; muscle; collagen; health

OVER THE PAST DECADE OR MORE, numerous potential beneficial effects of estrogen (17β-estradiol) have been identified in multiple tissues, including skeletal muscle. In addition, estrogen and estrogen-based hormone replacement therapy (HT) have been closely associated with the maintenance of metabolic health and improved body composition, enhanced neural protection, and regeneration and maintenance of skeletal health in both animal models and older females (33, 77, 79, 80). Estrogen has also been shown to affect spontaneous physical activity and eating behaviors, directly in rodents (21) and indirectly in humans (67). A lack of physical activity and excess body fat have both been identified as major risk factors contributing to cardiovascular compromise and premature death (36).

Life expectancy for women exceeds that of men in most Western civilizations and is at least 80 yr for women in most Western societies (69). Thus, over one-third of a typical female lifetime is spent in a sex hormone-deficient state. During the menopause, whether it occurs naturally or is chemically or surgically induced, the effects of diminished estrogen are immediately obvious on reproductive tissues and skin. However, estrogen receptors have been found in nearly all tissues and, thus, reduced estrogen in the middle age has effects throughout the entire body. While many of the negative consequences of diminished estrogen with aging have been identified, there is a substantial amount of research still needed (31).

This review will deal specifically with the effects of estrogen, as well as estrogen-based HT on skeletal muscle and connective tissue. One of the reasons for the relatively new interest in estrogenic effects on skeletal muscle was the identification of estrogen receptors (ER) in this tissue (38, 93, 94). Moreover, ER levels in skeletal muscle are responsive to endurance exercise training (39, 95) and to ovarian hormone status (3). Estrogen and HT interventions can also directly affect muscle strength and mass. This review of the current understanding of estrogenic influence on skeletal muscle and its mechanisms will also be related to current developments in the understanding of the health implications of HT, particularly in postmenopausal women. These issues will be discussed in the context of the potential beneficial effects of HT in this population. Many of these effects of estrogen on skeletal muscle may also be applicable to other populations, such as males and younger females with hysterectomy. However, there is less research available, particularly on estrogenic influence on skeletal muscle in males, and, hence, estrogenic influence in

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these populations will be inferred rather than directly discussed. A number of other related effects of estrogen and HT on metabolic, neural, and skeletal health have been reviewed elsewhere (31, 77) and will not be dealt with extensively in this review.

Frailty and muscle weakness are significant health issues, particularly in aging females (31). Women have a sharp decline in strength and muscle mass around the time of menopause (52, 64) compared with the more gradual loss of strength by men of similar age. It has been proposed that this greater decline in strength and muscle mass in postmenopausal women is directly due to estrogen deficiency, and this proposal has been supported by data showing that strength was preserved in postmenopausal women who were taking an estrogen-based HT (52). As women generally have relatively less muscle mass than men, a more rapid decline in muscle mass and strength in aging females makes them particularly vulnerable for age-related frailty and morbidity. It has been suggested that estrogen replacement via HT may be an important factor in preserving strength and prolonging independent living in older females by delaying or preventing a rapid decline in muscle mass and strength in older females (69). The evidence for, and mechanisms of, such estrogenic effects on skeletal muscle will be discussed. These potential benefits of estrogen and HT will also be related to our current understanding of potential health concerns associated with HT in older females.

Estrogen, HT, Muscle Mass, and Recovery from Muscle Atrophy and Damage

Animal-based studies have demonstrated species-specific effects of estrogen on muscle mass, with, for example, consistent anabolic effects seen in cattle (34, 65). However, developmental and ovariectomized rat models have not consistently seen positive influences of estrogen on muscle size (47, 68). For example, in immature growing rats, muscle size may decrease or increase less rapidly due to ovariectomy (86, 87), possibly as a result of reductions in levels of the proanabolic IGF-1 in muscle (87).

Recent findings have, however, consistently demonstrated a positive influence of estrogen or HT on muscle mass regain following muscle atrophy or injury in rodents and in resistance exercise-induced muscle mass gain, as well as muscle mass retention in aging human females. Following hind-limb unweighting-induced muscle atrophy in rats, several studies have reported that ovariectomy will inhibit and estrogen replacement will enhance muscle mass and functional recovery consequent to reweighting (8, 46, 72). Other recent data further suggest that a physical activity-based rehabilitation program following hind limb unweighting-induced muscle atrophy in rats will not optimally restore muscle mass in ovariectomized rats without estrogen replacement (7).

In aging human females, HT has also been demonstrated to have positive effects on muscle mass retention. Although research findings over the past 20 yr have reported conflicting results of HT on muscle mass in postmenopausal women (17, 71, 73), the preponderance of more recent evidence has “tipped the balance toward a positive and measurable impact of HT” (51) and have highlighted the “proanabolic” effects of HT on skeletal muscle (84). Several recent studies examining postmenopausal women showed significantly greater muscle mass in women taking HT relative to nonusers. One of the most compelling of these involved 13 pairs of monozygotic twin pairs aged 57–62, in which only one of each pair had been taking HT for average of about 7 yr (60). The HT twin had significantly greater muscle mass, less fat mass, and a tendency toward greater thigh muscle cross-sectional area. An additional randomized control study by this research group further confirmed the development of increased skeletal muscle and lean body mass in postmenopausal females aged 50–57 yr given HT over 1 yr relative to placebo-supplemented controls, who had no increases over this time period (54). These findings combined with previous studies demonstrating greater retention in lean body mass and muscle with HT in postmenopausal females (74) and greater gains in exercise-induced muscle mass and strength (71, 81), highlight the potential importance and effectiveness of HT in maintenance and resistance training-induced accretion of muscle mass in aging females. Table 1 summarizes the results of several relevant studies reflecting a diversity of results relative to HT and estrogen influence on muscle mass in postmenopausal females.

There are a number of mechanisms that are influenced by estrogen or HT, which may contribute to their potential ability to augment or maintain muscle mass or enhance repair in postmenopausal females. Dieli-Conwright et al. (12) reported greater resting levels in expression of quadriceps muscle mRNA of proanabolic markers, such as MyoD, myogenin, Myf5, and greater suppression of proteolytic markers, such as FOXO3A and MURF-1, as well as the negative growth regulator, myostatin, in 50–57-yr-old women taking HT relative to nonusers. These differences in muscle anabolic signaling between HT users and nonusers were further accentuated in response to a single bout of resistance exercise (12). This enhancement of a proanabolic environment in muscle at rest and following eccentric exercise in postmenopausal women using HT may be an important factor in helping to maintain muscle mass and strength in this population, as well as in enhancing the anabolic effects of resistance training. The mechanisms by which HT augments this anabolic signaling in skeletal muscle has yet to be fully determined.

The ability of estrogen and HT to diminish systemic and muscle inflammatory factors at rest and following exercise may also directly and indirectly affect muscle mass and exercise-induced muscle damage. It has been consistently demonstrated that estrogen replacement in ovariectomized rodents will result in diminished postexercise neutrophil infiltration into skeletal muscle (17, 32, 85). Earlier studies also clearly demonstrated that estrogen would diminish membrane disruption in isolated muscles as determined by loss of creatine kinase and that this was likely due to its effects on membrane stability, membrane fluidity, and antioxidant actions (4, 91). Reduced postexercise muscle creatine kinase loss has also been observed in young adult human females relative to males, with this effect being attributed to higher estrogen levels in females (78, 97).

Reduced postexercise disruption of muscle membranes by estrogen may directly or indirectly influence postexercise inflammatory responses and leukocyte infiltration into skeletal muscle (83). Estrogen administration in sedentary ovariectomized rats has also been reported to upregulate constitutive heat shock protein 72 (Hsp72) levels in muscles to levels that are induced by acute exercise (6). Because heat shock proteins can provide protection against exercise-induced muscle dam-
Table 1. Summary of hormone replacement therapy effects, including 17-β estradiol, on parameters related to skeletal muscle mass in postmenopausal women

<table>
<thead>
<tr>
<th>Study Group and Year</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Duration/Dose</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronkainen et al. (60)</td>
<td>13 postmenopausal twin pairs discordant for HT</td>
<td>• E2 only (n = 5)</td>
<td>• 1–2 mg E2 daily</td>
<td>Women on HT had nonsignificantly (6%) greater thigh muscle CSA</td>
</tr>
<tr>
<td>Sorenson et al. (74)</td>
<td>16 postmenopausal women 55 ± 3 yr</td>
<td>• Half of subjects placed on HT or placebo for 12 wk</td>
<td>• 4 mg E2 for 22 days, 1 mg E2 for 6 days</td>
<td>Placebo group lost significant (0.996 ± 1.58 kg) lean body mass</td>
</tr>
<tr>
<td>Qaisar et al. (57)</td>
<td>13 postmenopausal twin pairs discordant for HT</td>
<td>see Ronkainen et al.</td>
<td>see Ronkainen et al.</td>
<td>HT group gained significant (0.347 ± 0.858 kg) lean body mass</td>
</tr>
<tr>
<td>Taaffe et al. (81)</td>
<td>51 postmenopausal women 50–57 yr</td>
<td>• HT; n = 14</td>
<td>• 1–2 mg E2</td>
<td>Vastus lateralis single fiber CSA not different between twin pairs</td>
</tr>
<tr>
<td>Widrick et al. (92)</td>
<td>17 postmenopausal women 45–54 yr</td>
<td>Control; n = 15</td>
<td>Daily for 1 yr</td>
<td>Quadiceps and posterior thigh CSA significantly increased in HT and HT + Exercise groups</td>
</tr>
<tr>
<td>Skelton et al. (73)</td>
<td>102 women 5–15 yr postmenopause</td>
<td>• 8 women on HT</td>
<td>• 24 ± 5 mo</td>
<td>Single fiber CSA of type I and type II quadriceps fibers not different between groups</td>
</tr>
<tr>
<td>Sipila et al. (71)</td>
<td>80 postmenopausal women 50–57 yr</td>
<td>• 20 women in each of exercise, HT, exercise + HT, control groups</td>
<td>• 12 mo</td>
<td>Quadiceps CSA significantly increased in exercise and exercise HT groups</td>
</tr>
</tbody>
</table>

CSA, cross-sectional area; E2, estradiol, HT, hormone therapy.

The benefits of these estrogen-mediated reductions in muscle inflammation and enhanced regeneration may be reflected in the consistent reports of improved muscle recovery following disuse atrophy in rodent models, as previously noted (7, 8, 45, 46). Although these effects have been clearly demonstrated using in vitro and animal models, more applied research, particularly with aging females is needed to verify these benefits in human populations. In particular, the potential effects of estrogen and HT for enhancing regain of muscle mass and strength in older women following injury, immobi-
al, the ability of estrogen to upregulate constitutive Hsp72 expression in skeletal muscle may also afford muscle increased protection and, hence, limit inflammatory responses and exercise-induced damage (6).

In addition to its potential effects on muscle membranes and Hsp72 expression, estrogen may also influence postexercise muscle inflammatory responses via ER. For example, estrogen influence via activation of ERβ has been implicated in the downregulation of proinflammatory cytokines, such as TNF-α in injured skeletal muscle of rodents (89). HT will also reduce systemic and muscle levels of inflammatory interleukins in postmenopausal women in resting conditions and following eccentric exercise (1). In addition, estrogen administration has also been demonstrated to reduce postexercise muscle neutrophil infiltration in human males (41).

The limitation of secondary muscle damage and inflammation by estrogen and HT may also result in a more rapid recovery and repair of muscle. Estrogen may support more rapid recovery and repair of skeletal muscle by acting to reduce postinjury muscle necrosis, as has been reported in ovarioctomized mice (48). Estrogen may also induce upregulation of antiapoptotic signaling in muscle cells via ERK or p38 MAPK pathways (59). Estrogen also acts to enhance postischemic angiogenesis and revascularization in skeletal muscle, partially by estrogen-related receptor-γ-mediated augmentation of oxidative muscle fiber regeneration (43).
Estrogen may also play a regulatory role in other potential factors associated with muscle hypertrophy. IGF-1 is a positive regulator of growth-related muscle anabolism, as well as muscle repair (5, 9). However, the role of IGF-1 in resistance-induced muscle hypertrophy is controversial as robust hypertrophy can occur via activation of signaling pathways in animal models lacking IGF-1 receptors (76). Unlike in ovariectomized immature rats, where estrogen appears to diminish muscle IGF-1 levels (87), HT in postmenopausal females will enhance serum levels of IGF-1, as well as muscle gene expression of IGF-1 splice variants (IGF-1Ea, IGF-1Ec) and IGF-1 receptor expression (1). This has been speculated to occur, in part, as a consequence of the HT-induced attenuation of postexercise systemic and muscle levels of IL-6 (1, 10). It has been suggested that IL-6 may act as a negative regulator of IGF-1 production and may also indirectly diminish muscle IGF-1 sensitivity (1). ERβ agonists have also been demonstrated to enhance muscle IGF-1 expression in rodents and to consequently enhance muscle hypertrophy in male rats, thereby highlighting the possible role of muscle estrogen receptors in inducing these effects (89). Hence, it is possible that the maintenance of muscle mass by HT in postmenopausal women may, in part, be acting via enhanced IGF-1-related signaling. However, enhancement of exercise-induced muscle hypertrophy by HT in postmenopausal women may require additional or alternate explanations.

Estrogen supplementation in ovariectomized rats will also enhance postexercise satellite cell activation and proliferation in muscle (15, 16). Although significant muscle hypertrophy can occur without satellite cell proliferation in mice (44), satellite cells can still be factors in muscle hypertrophy and repair in normal circumstances (29). Both muscle ERs α and β have been reported to be involved in conveying the estrogen signal to augment postexercise muscle satellite cell activation and proliferation (16, 82, 89). Although macrophage infiltration of skeletal muscle is an important factor in muscle satellite cell activation (29), estrogen-induced activation of muscle satellite cells will occur despite the attenuating effects that estrogen has on muscle ED1+ and ED2+ macrophage infiltration in injured or atrophied skeletal muscle (17, 32, 45). It is possible that estrogen may act to enhance muscle satellite cell activation via other signaling mechanisms, such as the PI3K/Akt pathway (16), since this pathway is known to be activated by estrogen and is involved in protective and regenerative signaling in various other tissues in addition to skeletal muscle (36, 99).

A gene expression analysis of the monozygotic postmenopausal twins discordant for HT use also highlights possible mechanisms by which estrogen may act to enhance muscle hypertrophy (61). In particular, this study reported enhanced expression of genes associated with regulation of muscle collagen matrix and microtubule network integrity correlating with enhanced muscle strength and size in the twins using HT (61). These findings suggested the existence of a level of gene expression control, which is responsive to estrogen presence and which may also influence factors associated with the maintenance of muscle size and integrity (61). As will be noted later, the enhancement of muscle matrix generation is an important factor supporting enhancement of muscle hypertrophy.

The preponderance of recent evidence highlights the important effects of estrogen and HT on maintenance and regeneration of skeletal muscle mass, which has implications for the health of estrogen-deficient and aging females. Regular resistance exercise is also an effective mechanism for maintenance and enhancement of muscle mass in postmenopausal females (25). However, the potential accentuating effects of estrogen and HT on exercise-induced muscle mass gains and maintenance in aging females requires further research. In addition, the importance of HT in delaying muscle mass loss and frailty in nonexercising postmenopausal females and the potential for HT to enhance recovery from immobilization-induced muscle atrophy in this population also needs further research verification.

Estrogen HT and Muscle Strength

It appears likely that HT will enhance maintenance and exercise-induced hypertrophy of muscle mass in postmenopausal females. However, another important effect that estrogen appears to have on skeletal muscle is its ability to enhance muscle strength and force production through mechanisms beyond those of increased contractile proteins and muscle mass alone. Determining the underlying mechanisms by which estrogens and HT affect intrinsic contractile function, through activation of ERs or by ER-independent modes, is a growing area of research. The focus here will be on strength, as it is a major contractile outcome of skeletal muscle and vitally important for aged individuals in terms of functional status and mortality (31).

Most human studies of estrogenic effects on skeletal muscle strength have been conducted on postmenopausal women, and not all have shown beneficial influences of HT on strength. To address the inconsistent reports, Greising et al. (24) conducted a systematic review and meta-analysis of the research literature for studies in which strength was compared between postmenopausal women on an estrogen-based HT and those not on HT. When data from nearly 10,000 postmenopausal women were combined, the overall result was that strength was significantly greater in women on HT. The impact was small, with an effect size of 0.23, equating to women on HT being ~5% stronger. Effect sizes tended to be greater (~0.45) when only randomized, controlled trials were considered or when strength was normalized for muscle size, indicating that estrogens have a positive and meaningful impact on muscle strength. The benefit of estrogen on strength is corroborated by positive correlations between serum estrogen levels in premenopausal and postmenopausal women and their quadriceps femoris muscle strength (55). Interestingly, while strength was significantly correlated to serum estrogen, it was not correlated to the concentration of estrogen in the quadriceps muscle. Further understanding of the mechanisms underlying estrogen and HT effects on muscle contractile function will also need to include the importance of local, i.e., skeletal muscle production of estrogen (55).

A series of papers from The Finnish Twin Cohort Study (some of which were noted earlier) describe elegant studies conducted on postmenopausal monozygotic female twin pairs who were discordant for HT. Data supporting the premise that
HT beneficially affects muscle contractile function include the following. Co-twins on HT had significantly better mobility and lower-body power (60), greater involuntary (but not voluntary) plantar flexor strength (20), and improved single-fiber contractile function (57) relative to sisters not on HT. In the study by Qaisar et al (57), specific force (maximal force normalized to fiber cross-sectional area) was ~25% greater in type I and type IIa fibers from co-twins on HT compared with those not on HT. The greater specific force by fibers that had been chronically exposed to estrogens was driven by better intrinsic force-generating capacity because there was no significant difference in fiber cross-sectional areas between muscles from HT and non-HT twins. Furthermore, among the type IIa fibers, active stiffness was higher in the HT group, indicating that estrogens impact cross-bridge function (57), and thus qualitatively affect muscle force generation.

The majority of evidence from human studies indicating that estrogens beneficially affect strength comes from studies on aged women. Complementing and extending those results are data from female rodents in which estrogens are manipulated by ovariectomy. Data on estrogenic benefits to muscle strength in rodent models were also synthesized by meta-analysis, and effect sizes were found to be particularly large in mice and when strength was normalized for muscle size (0.88 to 0.66, respectively) (24). Furthermore, estrogen was identified as the key ovarian hormone responsible for the effects on strength because ovarioctomized mice replaced with estrogen were protected. Similar to the positive correlations between serum estrogen and strength in aged women, plasma estrogen levels have been positively correlated with maximal isometric tetanic force of mouse soleus muscle (49). A potentially confounding effect of ovariectomy in rodents is that estrogen deficiency causes reduced cage and wheel-running activities (18, 23). In mice, estrogenic effects on muscle force generation are independent of mouse activities and muscle use (23). In rats, ovariectomy-induced physical inactivity has some effects on soleus muscle characteristics, although force generation was not reported (21), and, therefore, this potentially confounding effect should be taken into consideration when using rat models.

Four lines of evidence indicate that one of the ways estrogen impacts strength is by affecting the quality of muscle, most likely by influencing contractile protein function. First, results of both human and rodent studies that were summarized above show that estrogenic effects on muscle strength are greater when force generation is normalized to muscle size. This indicates that the intrinsic quality of muscle is better when chronically exposed to estrogen. Second, contractile proteins are directly implicated by measurements of force on permeabilized muscle fibers because in this preparation, contraction is initiated by adding exogenous calcium, completely bypassing neural and excitation-contraction-coupling processes. Beneficial estrogenic effects on force generation by permeabilized fibers have been demonstrated in both human and rodent studies (50, 56, 90), although an earlier study on fibers from postmenopausal women did not find an effect of HT (92). Third, stiffness measured during contraction (active stiffness) is an indication of myosin cross bridges that are strongly bound to actin, and stiffness is greater in muscle fibers from ovarioctomized mice treated with estrogen and postmenopausal women on HT, compared with estrogen-deficient counterparts (23, 40, 57). Fourth, electron paramagnetic resonance spectroscopy paired with site-directed spin labeling of the myosin head directly showed that the fraction of myosin cross bridges strongly bound to actin and generating force was greater in muscle fibers from estrogen-replete compared with estrogen-deficient mice (49). Collectively, these data provide evidence that force generation at the molecular level, i.e., myosin-actin interactions, is affected by estrogen status.

How estrogen affects contractile proteins is not known and could be mediated by classical ER mechanisms or by ER-independent mechanisms. A conceivable non-ER mechanism involving estrogen’s antioxidant capacity, whereby the presence of estrogen helps to maintain the balance of oxidative stress in muscle (40). Maintenance of oxidative stress is important because myosin structure and function are susceptible to oxidation (56), and differential posttranslational modifications of this key contractile protein have been identified in biopsies from postmenopausal twins discordant for HT (57). Oxidation status of contractile proteins could also be modulated by estrogen through ER mechanisms because ERs regulate antioxidant gene expression in skeletal muscle (3), as well as nonmuscle tissues. Posttranslational modifications of contractile proteins besides those related to oxidative stress can be induced by estrogen and may influence contractility, as was recently reported in cardiac muscle (35). Related signaling pathways regulated by estrogen have been identified in skeletal muscle with downstream consequences likely impacting contractile function (1, 96).

**Estrogen HT and Collagen Formation and Repair**

Integral to muscle function and hypertrophy are noncontractile components of muscle, such as collagen, and there is accumulating evidence that muscle collagen is affected by estrogens. It was recently shown that postmenopausal women on HT tended to have lower rates of muscle collagen synthesis in a quadriiceps muscle during rest compared with those not on HT (28). This estrogenic inhibitory effect on collagen has also been demonstrated in a rat ovariectomy model (46) and a mouse model of muscle disease (14). In each of these rodent studies, an estrogen compound (17β-estradiol and tamoxifen, respectively) was used as a treatment modality that suppressed unwanted accumulation of collagen in muscle. In other words, fibrosis was blunted with an estrogen therapy. Excessive intramuscular collagen likely has deleterious consequences on muscle contractile functions, such as passive muscle stiffness (the resistance of inactive muscle to lengthening), which has been shown to increase with estrogen deficiency (50), and potentially contributes to the overall decline in muscle quality with aging (28). However, the balance between unwanted excessive muscle collagen and healthy levels of muscle collagen is important to consider, and there appears to be a critical interaction with physical activity. For example, following exercise, muscle collagen synthesis was enhanced in postmenopausal women on HT, which was interpreted as a positive factor for exercise-induced muscle remodeling and hypertrophy (53). As previously noted, gene expression profiling studies show that estrogens improve the overall regulation of muscle’s extracellular matrix in addition to intracellular components (1, 61), and these types of studies will continue to assist in unraveling estrogens’ impact on overall muscle quality.
Tendon collagen is also important for muscle contractile function in regard to transmitting force from muscle to its adjoining bone. Studies of tendon structure and function comparing sexes or postmenopausal women on and not on HT have suggested that relatively high levels of estrogens may not be conducive to good tendon health. Finni et al. (19) studied the Achilles tendons of postmenopausal monozygotic twins discordant for HT and found that among all twin pairs, tendon thickness and cross-sectional area did not differ between HT users and nonusers. However, when only physically active twins were considered, although numbers were small, co-twins on HT had significantly smaller Achilles tendon cross-sectional area than their sisters. These results indicate that the combination of physical activity and estrogen may be related to smaller tendon size. This effect of estrogen on tendons may or may not be mediated by the hormone’s influence on collagen synthesis. Hansen et al. (26) showed that postmenopausal women on HT had greater rates of tendon collagen synthesis at rest and during exercise, relative to their estrogen-deficient counterparts, but that the change in synthesis from rest to exercise was lower with HT. Young women chronically exposed to estrogens via oral contraceptives had lower rates of collagen synthesis in tendon and muscle connective tissue compared with age-matched women not on oral contraceptives (27). These chronically estrogen-exposed women also did not have an increase in collagen synthesis in response to exercise, whereas the untreated, control young women had an increased rate of muscle collagen synthesis after exercise.

The interactive effects of estrogens and exercise on muscle and tendon collagen and how those relationships change with estrogen deficiency, aging, and HT are important to understand in regard to overall musculoskeletal health. More research needs to be done in this area.

Collectively, the preceding sections have noted a number of estrogen- and HT-related influences and mechanisms that affect skeletal muscle and muscle collagen dynamics that are not yet fully understood and that future research directions could pursue. These are summarized in Table 2.

### Table 2. Some suggested future research directions in estrogen and HT effects on skeletal muscle and connective tissue

<table>
<thead>
<tr>
<th>HT/Estrogen Effects</th>
<th>Research Direction</th>
</tr>
</thead>
</table>
| Estrogen, HT, and muscle hypertrophy and repair | • Confirmation of estrogen and HT influences on signaling pathways related to inducing muscle hypertrophy and repair  
• Definition of interactive effects of estrogen and HT and resistance exercise on degree of muscle hypertrophic responses  
• Role of estrogen receptors and signalling in muscle satellite cell activation and proliferation in response to unaccustomed exercise  
• Potential short-term effect of estrogen or HT on the acquisition and maintenance of muscle mass and strength, for the recovery of atrophic muscle. |
| Estrogen, HT, and muscle strength | • Mechanisms by which estrogen and HT affect contractile proteins for enhance strength development  
• Role of estrogen receptors in enhanced muscle strength consequent to estrogen and HT exposure |
| Estrogen, HT, and muscle collagen and tendon modifications | • Mechanisms and signaling pathways by which estrogen and HT influence muscle collagen matrix remodeling at rest and in response to immobilization and training  
• Interactive effects and mechanisms of estrogen and HT or estrogen deficiency on tendon collagen at rest or in response to exercise |
| Resolve the questions related to timing and duration of HT | • Duration of optimal postmenopausal HT for overall health and muscle function |

### Estrogen, HT, and Women’s Health

The potential muscle mass and strength benefits of HT for older women could not be realized if there were significant threats to overall health in starting or continuing with HT. Indeed, the use of HT and its health effects in postmenopausal women have been controversial. However, recent evidence suggests that earlier findings of risk may have been premature.

There is strong epidemiological and observational evidence that in premenopausal women, estrogen is beneficial in reducing heart disease risk and overall mortality relative to men of the same age (36). It has been suggested that in addition to its potential protective effects as an antioxidant and membrane stabilizer, estrogen will also act to significantly lower circulating low-density lipoprotein and enhance high-density lipoprotein levels (36). However, when and under what circumstances estrogen, particularly in the form of HT, in older women might subsequently act to increase or decrease the overall risk of mortality and disease have been controversial. The form of estrogen in HT (e.g., Premarin, synthetic 17β-estradiol), its combination or separation from progesterone, and its form of delivery (e.g., transdermal patch, oral intake) may also influence the health effects of heart rate (HR) (36); however, an in-depth discussion of these issues is beyond the scope of this review.

The Women’s Health Initiative (WHI) was a large multicenter clinical trial that examined the effects of HT on women’s health (2). It was prematurely halted in 2002 (estrogen and progesterone arm) and 2004 (estrogen only arm) because higher than acceptable hazard ratios for stroke and blood clots developed. Women in the WHI who were taking estrogen also had significantly more strokes and heart attacks than women taking placebo therapy. These findings contributed to a significant decline in HT use by women and the number of prescriptions for HT provided by physicians to their patients in subsequent years (30).

These findings and their influence on the subsequent reduction in HT use by postmenopausal women due to health concerns may, in retrospect, have been unwarranted and per-
happened even counterproductive to the overall health of postmenopausal women. A major criticism of the WHI study design was that postmenopausal women in the study were substantially older than women at menopausal onset and with the study design, many had, therefore, delayed the initiation of HT for many years subsequent to menopausal onset (average age of women in WHI was 63 years) (30). Subsequent reanalysis of the WHI data on women between the ages of 50 and 59 years revealed that those who used HT had a 30% lower overall risk of dying than nonusers and the risks for coronary heart disease, pulmonary embolism, and heart attack were also significantly less compared with age-matched, nonusers (37). Conversely, women who had delayed starting HT for up to 20 yr postmenopause had a 28% higher risk of heart attack. These and other reevaluations of the WHI data suggested a timing effect of HT, where women who started HT at the time of menopause were afforded significant protection from cardiovascular related events, while women who started HT some years after the onset of menopause and had consequently undergone further aging-related tissue and gene expression changes no longer benefited from HR (36). Indeed, while estrogen has been shown to ameliorate inflammatory response in numerous tissues, including skeletal and cardiac muscle and neural and hepatic tissues (36, 79, 83, 99), a delay of several years for introduction of HT may actually upregulate inflammatory related gene expression, and this may consequently contribute to some of the reported negative health effects of beginning HT use well after the onset of menopause (37).

A number of additional studies since the WHI have further supported the hypothesis that beginning HR proximal to menopausal onset is a critical factor in maintaining hormonal efficacy in reducing cardiovascular disease and overall mortality in women. Manson et al. (42) studied 1,064 women in the 50–59-yr-old age range (perimenopausal), who received either Premarin or placebo for an average of 7.5 yr. These investigators performed CT scans and found 30–40% less plaque in coronary arteries of women taking Premarin relative to those taking placebo, which is consistent with the epidemiological findings. Two meta-analyses of all clinical trials performed, also indicated that women who initiated hormone therapy at younger ages (35–50), clearly had less heart disease than women who began taking estrogen many years beyond menopause (30, 63).

A recent 10-yr Danish randomized control trial involving over 1,000 recently postmenopausal women (aged 45–58 at the start of the trial) added further support for these findings. The women in the HT group were provided synthetic 17β-estradiol and norethisterone acetate. Women taking HT had significantly reduced overall mortality and cardiovascular events relative to nonusers over the 10-yr trial without any increased risk in overall cancer, breast cancer, thrombosis, or stroke (66). These findings strongly support the contention that there is a “window of opportunity” within which HT is cardioprotective and reduces mortality. A very recent comprehensive review of the literature also concluded that HT is generally safe and beneficial for women under 60 yr of age (62).

It is possible that such a “window of opportunity” relative to timing or delay of the introduction of HT following menopause may also exist for its positive effects on skeletal muscle mass and strength. Further research is required to provide answers to this possibility.

In addition to these cardioprotective and mortality-reducing benefits, HT also has numerous other potential health-related benefits, particularly for postmenopausal females. These include its well-documented benefits for bone health and bone density maintenance (80, 98), as well as amelioration of abdominal obesity, improved insulin sensitivity, and enhanced neuroprotection, cognitive function, and maintenance of mitochondrial and metabolic function (11, 22, 33, 70, 79, 88). Although these benefits of HT and estrogen can potentially be seen in all postmenopausal women, regular exercise can also positively influence most of these factors. However, whether HT in combination with exercise will lead to further additive benefits for postmenopausal women requires more research (77).

Not all postmenopausal women may derive health benefits from HT even if started proximal to menopause. Evidence from LaCroix et al. (37) also suggests that postmenopausal women with preexisting heart disease may experience a worsening of their condition with HT as either estrogen with progesterone or estrogen alone. The use of HT for chronic disease reduction in women over 70 yr old is also contra-indicated by current literature, as there are increased risks of cardiovascular incidents and breast cancer in this population (62).

Summary and Conclusions

There is a growing body of evidence describing the beneficial effects and mechanisms behind estrogen and HT effects on muscle mass, strength, and related muscle connective tissue. These enhancing effects of estrogen on skeletal muscle can have important implications for offsetting or delaying age-related loss of muscle mass and function, particularly in postmenopausal women. The benefits of HT effects may also be seen in enhanced recovery from muscle atrophy or damage. These benefits combined with other health-related benefits of reduced cardiovascular risk and mortality, improved metabolic and cognitive functions, and better bone health cumulate to strengthen the case for a more widespread and prolonged use of HT in women beginning at the onset of menopause (62). The effects of HT may complement or replace some of the benefits derived from exercise as far as helping to maintain or increase muscle mass, improve postatrophy muscle recovery, and enhance muscle strength in an aging female population, which may otherwise be at greater risk of frailty. As there is a general lack of regular exercise among postmenopausal women, HT may be an important factor in maintaining muscle and overall health at least for the first years following menopause. More research is still needed to fully document the potential muscle-related benefits of estrogen and HT and their mechanisms of action. In light of the growing evidence for lack of health risks and the potential muscular and other health benefits of HT use in the years immediately following menopause, it is tempting to suggest that a more widespread use of HT in postmenopausal women will result in net health and functional benefits in this population.

REFERENCES

Estrogen Skeletal Muscle and Health • Tiidus PM et al.


