Point: Counterpoint: Estrogen and sex do/do not influence post-exercise indexes of muscle damage, inflammation, and repair

POINT: ESTROGEN AND SEX DO INFLUENCE POST-EXERCISE INDEXES OF MUSCLE DAMAGE, INFLAMMATION, AND REPAIR

Estrogen and sex influences due to difference in estrogen exposure have been consistently reported to attenuate damage and/or inflammation and to accentuate repair in a variety of tissues and organs (4, 13, 22). Consistent with these findings, rodent models have provided compelling evidence of the efficacy of estrogen in decreasing indexes of post-exercise damage and inflammation in skeletal muscle (10, 29). In addition, we recently demonstrated tantalizing indications of the potential for estrogen to accentuate factors involved in muscle repair (5, 6, 28). Although less consistent than the findings in rodents, human studies focusing on sex differences have also provided some evidence for positive estrogenic influences of skeletal muscle damage and repair (18, 23). This article will present an overview of the evidence for estrogen to 1) ameliorate indexes of post-exercise muscle damage, 2) diminish post-exercise muscle inflammatory responses, and 3) accentuate factors related to muscle repair, as well as the possible mechanisms by which estrogen may act.

Estrogen diminishes indexes of post-exercise muscle damage. Several lines of evidence, primarily from animal studies, indicate that exposure to estrogen will diminish indexes of muscle damage. In one of the few studies to directly examine histological evidence of muscle damage, Komulainen et al. (10) reported that for up to 96 h post-downhill running male rats exhibited earlier and greater indexes of damage to muscle structural proteins and more muscle fiber swelling than female rats. They also noted significantly elevated levels of β-glucuronidase (β-glu) activity in the muscles of male relative to female rats. β-glu is a lysosomal enzyme activated in response to muscle disruption and considered to be a quantitative indicator of muscle damage (17). Our laboratory has also reported that ovariectomized female rats with estrogen replacement have significantly diminished elevations in muscle β-glu activities following downhill running relative to sham-supplemented animals (5, 6). Since skeletal muscle possesses both α- and β-estrogen receptors (9), we tested the hypothesis that estrogen influence on post-exercise muscle damage may manifest through receptor-mediated mechanisms. Using the pure estrogen receptor blocker ICI-182,780, we recently demonstrated the ability of estrogen to attenuate exercise-induced muscle damage, as quantified by reduced muscle β-glu activation is not receptor mediated and may instead be related to other characteristics of estrogen as discussed below (6).

Although not a specific indicator of structural muscle damage, serum creatine kinase (CK) levels have been used as reliable semi-quantitative indicators specifically of sarcolemma membrane disruption (7). As noted by Clarkson and Sayers (3) pioneering studies by Amelink and colleagues in the 1980s conclusively established that estrogen will attenuate post-damage muscle CK release in male and ovariectomized female rats. The most compelling of these studies avoided possible in vivo confounds by demonstrating that isolated muscle from exercised male rats with prior estrogen exposure released CK into the surrounding medium significantly slower than untreated male rats (1). Studies examining sex differences in humans have also reported higher post-exercise serum CK levels in men relative to women as well as a greater preponderance of high post-exercise CK responders in men (18, 23).

Estrogen attenuates inflammation-related muscle leukocyte infiltration and damage. The potential for estrogen to stabilize muscle membranes and diminish sarcolemma disruption may be a mechanism by which estrogen acts to reduce exercise-induced muscle damage and inflammatory responses (27). We have proposed that estrogen may act both as an antioxidant against exercise-induced membrane phospholipid peroxidation and as a cholesterol-like influence on membrane fluidity and stability (26, 27).

Findings from our laboratory have consistently demonstrated an estrogen-induced attenuation of post-damage, inflammation-related neutrophil infiltration of red and white skeletal muscles in male as well as ovariectomized female rats (6, 16, 29). We suggested that the potential of estrogen to preserve sarcolemma stability following damaging exercise may help maintain muscle calcium homeostasis (27), which may, as we have demonstrated, result in attenuation of post-exercise muscle calpain activation (29). Both reductions in muscle sarcolemma disruption and attenuation of calpain activation could contribute to the ability of estrogen to attenuate post-exercise neutrophil infiltration in both red and white skeletal muscle of rats (27). In further support of this theory, we recently demonstrated, with the use of an estrogen receptor blocker, that the ability of estrogen to diminish post-exercise muscle neutrophil infiltration is not estrogen receptor mediated and have suggested that this ability is instead mediated via direct estrogen action on muscle membranes (6).

Neutrophils, while important in initiating tissue repair, are also responsible for significant post-exercise, inflammation-related muscle structural and oxidative damage (14). The attenuation of post-exercise neutrophil infiltration into skeletal muscle by estrogen may thus also be a factor in reducing post-exercise muscle damage progression. Indeed, several studies have reported reduced indexes of oxidative damage in muscles of estrogen supplemented versus unsupplemented ovariectomized female rats following exercise or ischemia-induced disruption (13, 24).

Estrogen can enhance potential for skeletal muscle repair. Estrogen can also attenuate post-exercise macrophage infiltration of skeletal muscle (6, 11). Macrophage infiltration of skeletal muscle as well as muscle damage itself are both important for initiating post-damage muscle regeneration and satellite cell activation (25, 30). Hence it is possible that by delaying or diminishing post-exercise macrophage infiltration or reducing damage in skeletal muscle, estrogen may diminish muscle repair-related responses such as satellite cell activation (5, 6). Despite this possibility we recently showed that estrogen supplementation will actually enhance activation and proliferation of satellite cells in muscles following downhill running in male and ovariectomized female rats (5, 6, 28).
Although the mechanisms by which estrogen can enhance post-damage muscle satellite cell responses are not yet understood, we demonstrated that by blocking muscle estrogen receptors we can completely block post-exercise muscle satellite cell activation and proliferation (Fig. 1) (6). We speculated that estrogen receptor-mediated phosphatidylinositol 3-kinase/protein kinase B (Akt) pathway, which stimulates muscle growth and protein synthesis (20), or the estrogen-receptor induced induction of myoblast c-fos and egr-1 genes (8) may be involved in these effects. Alternatively, estrogen has also been shown to upregulate nitric oxide synthase (NOS) activity and nitric oxide (NO) levels in epithelial cells (4) and to influence epithelial inflammation via NO-mediated mechanisms (15). Since NO is also a critical regulator of muscle satellite cell activation and proliferation (2), it is possible that estrogen may also act via muscle estrogen receptors to alter muscle NOS activity and NO levels and hence influence satellite cell responses to muscle damage (5, 6).

**Application to human muscle damage and repair.** The influence of estrogen on muscle damage, inflammation, and repair may have its greatest relevance with post-menopausal women, as older women tend to suffer greater declines, impairments in muscle repair, and rates of sarcopenia than older men (19, 21). Fortunately, studies have found that strength training significantly increases satellite cell numbers in skeletal muscles of all individuals, especially those of older women (16). Furthermore, estrogen has been shown to enhance muscle recovery following periods of disuse atrophy (12). Thus research examining countermeasures to protect skeletal muscle from the loss of estrogen-related protection in older women would be particularly relevant to preserving their health, strength, and functional abilities.

**REFERENCES**


**Fig. 1.** Effects of estrogen supplementation and ICI-182,780 administration on numbers of fibers positive for Pax7 (A), MyoD (B), and BrdU (C) satellite cell markers in rat soleus muscle 24 and 72 h following downhill running. Values are means ± SE. *P < 0.05 compared with treatment-matched control group. 
*a*P < 0.05 compared with treatment matched estrogen group. 
*P < 0.05 compared with treatment-matched sham and estrogen groups (6).


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COUNTERPOINT: ESTROGEN AND SEX DO NOT SIGNIFICANTLY INFLUENCE POST-EXERCISE INDEXES OF MUSCLE DAMAGE, INFLAMMATION, AND REPAIR

Exercise-induced muscle damage (EIMD) occurs following strenuous, novel exercise and is assessed directly via tissue analysis and characterized indirectly by muscle dysfunction, inflammation, delayed onset muscle soreness, and increased levels of muscle proteins [e.g., creatine kinase (CK), myoglobin] in circulation. Repair typically takes place during the 7–14 days following the initial exercise bout.

There has been much debate over the past 20 years concerning the existence of sex differences in EIMD and repair, primarily focused on the assumption that estrogen levels affect skeletal muscle’s response to damaging exercise (14, 28). Potential mechanisms by which estrogen levels could affect the EIMD response include estrogen’s antioxidant properties and its potential to stabilize the membrane of the skeletal muscle cells during exercise. Either or both of these mechanisms would serve to protect females from EIMD and promote repair when compared with males.

Indeed, animal studies have often demonstrated attenuated EIMD susceptibility in female or estradiol-supplemented animals, based largely on decreased levels of CK in the blood (1, 3). Animal studies (23) have also reported attenuations in the inflammatory process due to sex or estrogen status. However, other animal studies (17, 28) that used contractile deficits as the primary muscle damage marker have not found similar effects. In fact, Warren et al. (29) found that estradiol-supplemented ovariectomized mice demonstrated significantly greater contractile losses as compared to non-supplemented mice.

In contrast to animal studies, the majority of human studies have reported similar responses for various EIMD markers when comparing men and women or groups with different estrogen levels (reviewed in Refs. 6–8).

Direct muscle damage assessment. Two studies to date addressed the effect of sex on skeletal muscle ultrastructural properties following eccentric exercise in humans. Stupka et al. (24) found no differences between men (n = 8) and women (n = 8) in focal and extensive damage areas following unilateral eccentric leg exercise. A follow-up study (25) detected no difference in sex on the amount of Z-line streaming after a first bout of eccentric exercise. Although it may be beneficial to examine larger cohorts of men and women for direct markers of muscle damage in the future (given the variability associated with the biopsy method), these two studies indicate that ultrastructural changes in skeletal muscle following eccentric exercise are unaffected by sex.

Muscle function. Several studies (4, 18, 20, 25) reported no sex differences in maximal isometric strength loss immediately following repetitive maximal eccentric contractions, while one study found that women demonstrate greater relative strength loss immediately after exercise (~57.8% in women vs. ~50.4% loss in men) (21). In a recent study (13), we found that patterns of relative isometric and eccentric torque losses during 50 maximal eccentric actions of the arm were remarkably similar between men (n = 22) and women (n = 24). We also found similar decrements in other contractile properties (i.e., work, rate of force production, and half-relaxation time) throughout the exercise. Adding to this, several studies that examined women of different estrogenic status (e.g., pre- vs. postmenopausal or oral contraceptive users vs. nonusers) also demonstrated similar strength changes after both isometric (5) and eccentric (19, 26) exercise. Together, these data suggest that relative muscle fatigue during and immediately after exercise are unaffected by sex or estrogen levels.

Studies that have examined recovery of strength following damaging exercise largely found no differences between men and women (20, 26). Some studies reported differences in contractile characteristics during recovery (4, 15), but these differences were based on statistical analysis of the change in absolute levels over time. Given the large baseline differences...