


There has been much debate over the past 20 years concerning the existence of sex differences in EIMD and repair. Predicated 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 effect of 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
between men and women, it is important to account for these differences (or a surrogate such as lean body mass) in the analyses. For example, Machintyre et al. (15) reported differences in concentric and eccentric torque recovery following 300 eccentric actions of the quadriceps. However, these differences were no longer significant when strength was normalized to body weight. Furthermore, although the recent Sewright et al. (21) paper demonstrated an acute difference in maximal isometric strength immediately postexercise, the overall strength loss/recovery pattern (to 10 days postexercise) was not significantly different between men and women. Studies examining strength recovery in relation to estrogenic status have demonstrated mixed results, with two reporting no group differences in strength recovery in the 5 days following exercise (5, 26) and one study suggesting a delay in recovery for oral contraceptive users (19).

**Muscle enzyme activity in blood.** Women have lower resting CK levels than men (2), but consistent differences in the CK response to exercise have not been reported. Following downhill running, Sorichter et al. (22) found no sex differences in several different muscle proteins in the blood, including CK, myoglobin, myosin heavy chain fragments, and troponin I. Eton et al. (12) also found no sex differences in CK following downhill running. After eccentric arm exercise, Sewright (21) found that women experienced a lower CK but not myoglobin elevations, while Stupka demonstrated lower CK values in women both before and after eccentric leg exercise (25).

Studies of CK response to exercise in relation to estrogen levels in different groups of women have largely demonstrated no differences between groups (5, 16, 19, 26). Furthermore, while Arnett et al. (2) found an increased CK response in menarchal women vs. pre- or post-menarchal women following eccentric hamstring exercise, this effect was lost when the analysis was covaried for lean body mass.

**Pain/soreness and inflammation.** Studies assessing pain or delayed onset muscle soreness measures typically have not found sex differences (10, 18, 21) or significant associations with estrogen (5, 19). One study that did report a difference in soreness patterns following eccentric exercise (15) looked only at soreness patterns over the first 24 h postexercise, while soreness levels typically peak several days following exercise.

While overall inflammation (as assessed by swelling or circumference measures) has not typically demonstrated estrogenic effects (19, 26), alterations of certain components of the inflammatory process have been reported to be different between men and women, but these results have been inconsistent. Machintyre et al. (15) reported higher numbers of neutrophils in women 2 h postexercise, while Stupka (24) demonstrated an exercise-induced rise in circulating granulocytes only in men. In a follow up study, Stupka (25) reported no sex difference in neutrophil and macrophage numbers following a single bout of exercise, while women demonstrated a rise in neutrophil concentration following a repeated bout of exercise.

**Variability.** While studies suggested that the average EIMD response may be similar between men and women, some data suggest differences in the variability of responses. For example, Sayers et al. (20) found that women had a greater incidence of profound postexercise strength loss (>70%), while Sewright et al. (21) found that men had greater variability in CK levels. These findings may be in part due to interactions of sex or estrogen with genetic variability effects. Studies have reported associations between genetic mutations and variability in EIMD markers (9, 11), and a subset of these associations were sex dependent. Genetic variability interactions might also explain, in part, apparent species differences in EIMD studies.

**Conclusion.** The majority of data from human studies have indicated that sex and estrogen levels do not significantly affect exercise-induced muscle damage, as measured directly (i.e., ultrastructural damage) or as indicated by functional losses, muscle protein levels in the blood, pain or soreness.

REFERENCES


Monica J. Hubal1
Priscilla M. Clarkson2
1Research Center for Genetic Medicine
Children’s National Medical Center
Washington, DC

e-mail: mhubal@cmmcresearch.org

2Department of Kinesiology
Totman Building
University of Massachusetts
Amherst, Massachusetts

REBUTTAL FROM TIIDUS AND ENNS

Drs. Hubal and Clarkson agree that while animal studies generally support positive effects of estrogen on muscle damage, inflammation, and repair, studies examining sex differences in humans have more varied results (4). Since estrogen has also been clearly demonstrated to have protective and regenerative effects on a variety of other tissues in humans and animals (1, 3, 6, 8), the real issue is not if estrogen can positively influence muscle damage and repair, but why this has not been clearly demonstrated in humans.

There are several potential reasons for this. Most human studies involving muscle damage have focused only on sex differences, which can be confounded by other sex-based variables beyond differences in estrogen levels. Also, since previous training and length of exposure to various estrogen levels may affect membrane stability and numbers of estrogen receptors on muscle (2, 10), looking for differences in female responses only over the course of a brief estrous cycle may be spurious. Unlike animal studies, no human studies have examined controlled variations in estrogen levels alone (9). A more ecologically valid human model to demonstrate the positive effects of estrogen on muscle damage and repair is the pre-versus post-menopausal woman. Studies have suggested that older females suffer greater strength declines and muscle damage with aging than men or younger women, respectively (5, 7).

Other factors confounding human results include the degree of muscle damage induced by exercise. It may be better to investigate damage and recovery rates in younger and older women following exercise-related muscle sprains or contusions where protective and recovery effects of estrogen may be more evident. It is also more difficult to detect diffuse muscle damage from small biopsy samples of mixed fiber type in humans relative to examining entire muscles from animals. Much of the human data is also based on changes in blood creatine kinase (CK) levels, which, due to its high variability, may be responsible for some of these inherent inconsistencies.

Due to less control over variables, and potentially less sensitive methods of measurement, it can be more difficult to detect protective and regenerative estrogen effects on muscle in humans than in animals. This does not mean that these effects do not exist or that they are not physiologically important. It does suggest that we have not yet conducted the most appropriately controlled experiments using the most relevant populations and measures necessary to unequivocally demonstrate the importance of estrogen in positively influencing muscle damage and repair.

REFERENCES


REBUTTAL FROM HUBAL AND CLARKSON

Drs. Tiidus and Enns make a compelling case that estrogen and sex significantly influence some markers of exercise-induced muscle damage (EIMD) in animal models, specifically muscle enzyme efflux and inflammatory markers. However, central to our case in arguing against significant estrogen and sex differences on EIMD are the lack of differences in other muscle damage markers (specifically muscle function) and the lack of substantiation of the inflammatory marker differences in human studies. The exception to this is findings of sex differences in creatine kinase (CK) levels, which may or may not be attributable to estrogen levels.

The preponderance of human studies of eccentric exercise effects shows no sex difference in soreness development and strength loss/recovery. In fact, our recent study (3) found that