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

TO THE EDITOR: Interpretations on the effect of estrogen/sex should be based on direct measures of muscle injury and subsequent repair/regeneration (i.e., improvements in muscle structure and function after injurious exercise). The inclusion of indexes of the inflammatory response (e.g., accumulation of neutrophils and/or macrophages) and inflammation (e.g., edema) into the discussion seems to make interpretations ambiguous (2, 6). We reported that neutrophils and/or macrophages can accumulate in rodent skeletal muscle in the absence of histological and functional signs of injury after either passive stretching, isometric contractions, or concentric contractions (4, 5). These findings support our belief that neutrophil and/or macrophage accumulation in skeletal muscle after exercise should not be used as markers of muscle injury nor repair/regeneration. As mentioned by Tiidus and Enns (6), neutrophils may exacerbate contraction-induced injury, whereas, macrophages appear to aid muscle repair/regeneration. Recent evidence in rodents, however, indicates that neutrophils and/or macrophages also contribute to skeletal muscle hypertrophy (1, 3). Thus neutrophil and/or macrophage accumulation in skeletal muscle is not contingent on the presence of an injury nor does their function in skeletal muscle after exercise appear to be restricted to events that follow an injury. Commonly used measures of edema (e.g., arm circumference, arm volume, and gapping between myofibers) tend to show a high degree of intersubject variability, have a low degree of sensitivity, and have a poor temporal resolution to histological and functional signs of injury and thus, they have limited value when interpreting the influence of estrogen/sex on muscle injury and repair/regeneration.

REFERENCES


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OF RODENTS AND (WOMEN) TO THE EDITOR: Upon reviewing the two posted studies (3, 8) and others by these and other authors (5–7), I am struck by the failure of these studies to correct for plasma volume shifts for the blood chemistry parameters. Prior work with resistance training has clearly shown substantial plasma volume changes (PVΔ) in the order of 13.3%, 14.3%, and 10.1% respectively (1, 2, 4). Failure of these studies to correct for these fluids shifts while indicating an awareness of these shifts, referred to in the posted papers as swelling of the tissues, makes data interpretation spurious and debates superfluous.

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OF RODENTS AND HUMANS

TO THE EDITOR: Reading the Point:Counterpoint exchange of Tiidus and Enns vs. Hubal and Clarkson (5) is reminiscent of the title of John Steinbeck’s 1937 novella Of Mice and Men; however, an appropriate renaming to this exchange should perhaps be Of Rodents and Humans? Much of the work cited by Tiidus and Enns as evidence in favor of estrogen as a “protective agent” against lengthening contraction-induced muscle damage comes from rodents (4, 6). Clarkson and Hubal argue that when this estrogenic protection is tested in humans the results are far more equivocal (2, 3). There are a number of other instances in physiological research where animal and human data do not line up, so is this simply a case where rodents and humans are different? Tiidus and Enns argue that a valid approach would be to study women during the menopause since the withdrawal of estrogen during that time would provide a model of estrogen withdrawal in humans (5). However, hormonal changes during the menopause are gradual, often take years, and involve hormones other than estrogen. It might be more valid to study women who had surgical ovariectomy pre- and postsurgery? Alternatively, women on hormone replacement therapy postmenopause would also be of interest to study compared with those that are not. In addition, there is at least one report of oral contraceptive use influencing creatine kinase release (1). An intriguing possibility would also be to assess men who are receiving a sex change, a procedure that involves extensive and often high-dose estrogen therapy.

REFERENCES


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TO THE EDITOR: Muscle weakness following menopause (3) and the deleterious effects of ovariectomy on strength (2) and muscle mass recovery following unloading (4) in rodents, as well as the positive effects of estrogen supplementation, provide compelling support for its role in muscle health and function. If estrogen and sex do influence muscle damage, inflammation, and repair, then this has implications for training adaptations in women and maintaining muscle mass and strength postmenopause. While increased estrogen levels may be associated with lower serum CK activity postexercise, this not a consistent finding (1) and CK is a poor marker of muscle damage. Function is a better indicator of damage, which should be assessed routinely postexercise and during recovery. Unlike CK, most human studies report no sex differences in force deficit and recovery following strenuous exercise (1), which fits well with our observation that posteccentric leg exercise the extent of Z-disk streaming was similar in young, healthy men and women (5). Furthermore, in ovariectomized mice, estrogen supplementation did not protect EDL muscles from eccentric contraction-induced injury in vitro (2). Estrogen may not protect muscle from injury per se, but it may regulate the repair process by modulating the inflammatory response, satellite cell dynamics or muscle protein synthesis (4, 6). To assess this, careful time course studies are needed, as it is difficult to draw conclusions about the effects of estrogen on dynamic processes such as inflammation and satellite cell activation, proliferation, and/or differentiation based on a single time point.

REFERENCES

TO THE EDITOR: Current literature on the influence of estrogens on human skeletal muscle shows conflicting results as also shown by the discussion regarding the influence of sex and estrogen on post-exercise muscle damage, inflammation, and repair (2, 4). The discrepancies between the results of different studies are at least partly explained by different study designs and indirect measures used. Studies comparing men and women are confounded by a number of sex-related parameters and those comparing pre- and postmenopausal women by the aging associated wide ranging effects on the whole neuromuscular system, endocrinology, and immunology in general (3, 5). When investigating the role of estrogens on skeletal muscle in humans, comparisons should be made between groups of people with same sex and mean age but with notable and consistent difference in circulating estrogen levels. This can be achieved, e.g., by comparing postmenopausal women on estrogen replacement therapy (ERT) with those without therapy or by randomized controlled trials including ERT as a treatment.

Experimental animal studies enable the use of sophisticated study designs (1) and representative muscle-specific biological markers (6). These studies show that indicators of post-exercise muscle damage and repair are affected by estrogen in either estrogen receptor dependent (satellite cell activation) or non-dependent manner (β-glucuronidase activity, number of leucocytes) (1). In conclusion, we believe that estrogens have influence on skeletal muscle damage, inflammation, and regeneration/repair after exercise. More studies of good quality are, however, needed to demonstrate the significance of the adaptive/protective effect of estrogens in muscles among women.

REFERENCES


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ESTROGEN AND SEX DO NOT INFLUENCE PRIMARY MUSCLE DAMAGE AND DO INFLUENCE SECONDARY MUSCLE DAMAGE

TO THE EDITOR: Evidence presented in the Point:Counterpoint argument regarding the influence of sex and estrogen on muscle damage, inflammation, and repair (2, 5) suggests that sex and estrogen do not influence primary muscle damage and do influence secondary muscle damage. According to Faulkner et al. (1), primary damage consists of focal disruptions to sarcomere architecture caused by mechanical forces, and secondary muscle damage consists of damage extension in prep-
HORMONAL IRRITATIONS?

TO THE EDITOR: Epidemiological data provide evidence that premenopausal females are protected from various diseases, i.e., high arterial blood pressure (1) or sleep apnea (7). This may also confer a positive effect of sex on the human muscles regarding injury or damage. Tiidus and Enns (8) provide fascinating data on this note in animal studies; however, so far, these findings could not be clearly attributed to human studies as described by Hubal and Clarkson (3).

All authors discussed the diverse findings of sex differences in CK levels. However, there are several observations on the variability of CK activity after comparable, histologically quantified exercise-induced muscle damage in humans (2) and animals (4), which preclude a simple interpretation of increased CK activity, especially with regard to the magnitude of injury. These limitations could be reduced by using more specific parameters for future studies, such as skeletal troponin I (6). A study by our group did not provide any difference in muscle injury between males and females after downhill running (5).

Appreciating the findings of Tiidus and Enns of estrogen effects on muscle membrane stability and fiber regeneration, a provocative assumption may be postulated: the lacking difference of indicators of muscle injury in men and women might be attributed to recurrent hormonal effects, equalizing differences between both sexes, which might become apparent in the absence of estrogen in women. However, the modifiable factors such as pre- and post-exercise levels or nutrition may outweigh the single effect of estrogen on the muscle cell in humans.

REFERENCES


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SEX DIFFERENCES DO EXIST IN HIGH RESPONDERS TO ECCENTRIC EXERCISE

TO THE EDITOR: Tiidus and Enns (6) and Hubal and Clarkson (2) present an intriguing Point:Counterpoint regarding the effect of estrogen on post-exercise muscle damage in animals and humans, respectively. The argument against sex differences in muscle damage after eccentric exercise (2), however, is confounded by differences reported among men and women who exhibit extreme responses to eccentric exercise (1). In our first report on this topic, we detailed six “high responders” who exhibited combinations of prolonged strength loss, profound swelling, elevated creatine kinase activity, and extreme soreness after eccentric exercise, all of whom were men (5). In a second report on prolonged strength loss after eccentric exercise (3), we found that although a greater number of women had large strength losses immediately postexercise, they demonstrated a faster recovery compared with men, possibly from an estrogen-related attenuation of secondary damage from inflammation. Moreover, the most prolonged strength losses reported in this study (47, 61, and 89 days) were observed in men (3). In a final study on profound swelling after eccentric exercise, 3 of 4 high responders described were men (4). Raw data from these studies indicate a 3% incidence of prolonged strength loss and/or profound swelling in men [6 of 204 (5); 5 of 153 (4)] and less than a 1% incidence in women.
Although difficult to study because of the sample sizes required, future research could examine older men and post-menopausal women “high responders” to determine whether sex differences persist in the absence of estrogen.

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A MATTER OF MODEL

TO THE EDITOR: On the basis of the plethora of studies cited in the Point:Counterpoint of estrogen/sex’s influence on muscle damage and repair, one would have to agree that the evidence supports that estrogen and/or sex have an effect in rodents but not in humans in this regard (1, 3). The use of rodent models has several advantages over studies on humans, least of which are controlling potential confounding effects and subject variability. Controlling variability factors in human studies is admittedly difficult but ideally could be controlled by using a within subjects design. For example, Tiidus and Enns’ suggestion of comparing pre-versus post-menopausal women may be better controlled by using a within-subjects design. This would mean studying middle-aged women before they start menopause and again soon after menopause, about 10 years later, an age similar to those used by Sipila et al.(2).

Clearly results from rodent studies and human studies seem to lead to very different conclusions regarding estrogen and sex’s influences on exercise and muscle damage. Although rodent studies are generally a useful model for human disease and conditions and have been used as such for human muscle damage and recovery, if the results are not in line with studies in humans, the utility of such a model is circumspect. The real question therefore should not be why estrogen’s positive effects are not seen in human studies, but rather, is there a better experimental model for estrogen/sex influence on EIMD and recovery in humans?

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