Sex-based differences following eccentric exercise-induced muscle damage.

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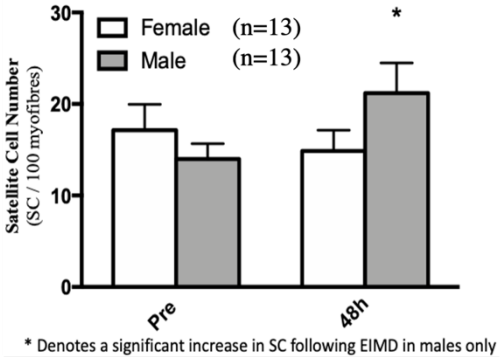
Muscle health is dependent on the ability to repair and remodel in response to exercise-induced muscle damage. With a damaging stimulus such as resistance exercise, ultrastructural damage occurs in the muscle causing inflammation, swelling, and the activation of muscle stem cells, or *satellite cells* (SC). [1, 2] SC are essential for muscle regeneration after damaging exercise with early indications suggesting a blunted response in females. The discovery that females incur less ultrastructural damage and inflammation compared to males points to sex hormone effects on muscle homeostasis. [3]

Recent work from our lab shows that the muscle SC response to exercise is blunted in females (**Figure 1**), hypothesized to be the result of estrogen regulation in the muscle. Estrogen protects muscle through its indirect antioxidant capacity, alleviating inflammation and preserving cell membrane integrity.[4] Thus, it is an intriguing factor that may not only attenuate muscle damage but enhance repair.

Figure 1. Satellite Cell Expansion 48h Following EIMD



PURPOSE: The primary objective of my research was to comprehensively characterize the muscle damage and subsequent SC response to eccentric exercise-induced damage, particularly focusing on variations observed among individuals with different hormonal profiles. By thoroughly investigating the extent and nature of muscle damage incurred post-exercise, we aimed to gain insight into the mechanisms underlying muscle repair and regeneration.

Additionally, we sought to explore potential correlations between circulating levels of sex hormones and the observed differences in muscular damage and the SC response. This allowed us to elucidate the role of sex hormones in modulating the response to exercise-induced muscle damage, potentially uncovering novel pathways and mechanisms involved in muscle adaptation.

METHODS: Thirty young recreationally active males and females (21 ± 3 years [mean ± SD]) underwent 300 (30 sets x 10 reps) maximal eccentric leg extension contractions on an isokinetic dynamometer (Biodex), and measures were collected prior to and at six time points after exercise (**Figure 2**). Skeletal muscle biopsies from the *vastus lateralis* were collected for measures of muscle protein synthesis (MPS; with deuterated water; D_2O), transmission electron microscopy (TEM), immunohistochemistry, western blotting, and RT-PCR. Blood draws were performed to determine concentrations of 17β-estradiol, progesterone, creatine kinase (CK), and inflammatory markers TNF-a. IL-6, IL-1b, and IFN-y. Ultrasound sonography was used to determine muscle thickness, pennation angle, and echo intensity. Measures of strength (F_{peak}) as well as subjective measures of pain and soreness (via visual analog scale and algometry) were also collected.

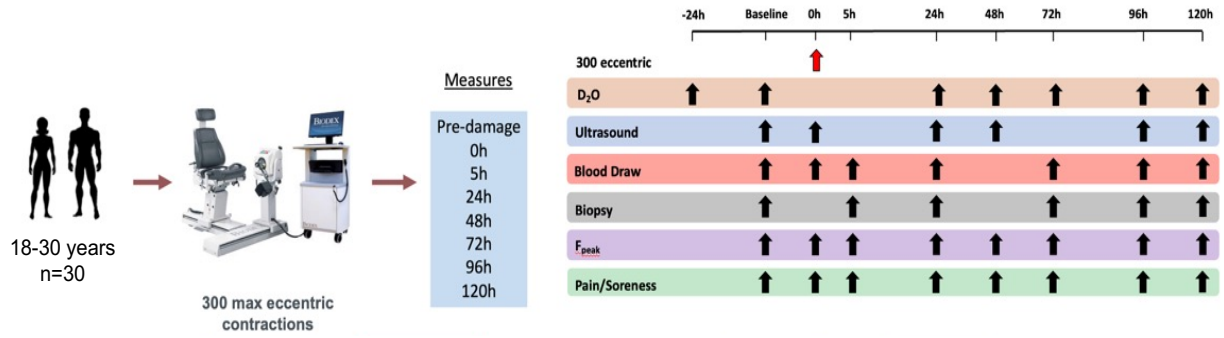


Figure 2. Experimental Design

RESULTS: MPS (myofibrillar fractional synthetic rate) increased with no differences between sexes ($p>0.05$). TEM analyses revealed that males and females were not different in the amount of damage categorized as "mild" post-exercise, but females were found to have significantly more "severe" damage than males 5h and 48h post-exercise. SC content in type II fibers peaked at 72h in males (10.1 ± 3.0 Pax7+ cells/100 fibers; $p<0.05$), but the same expansion was not observed in females.

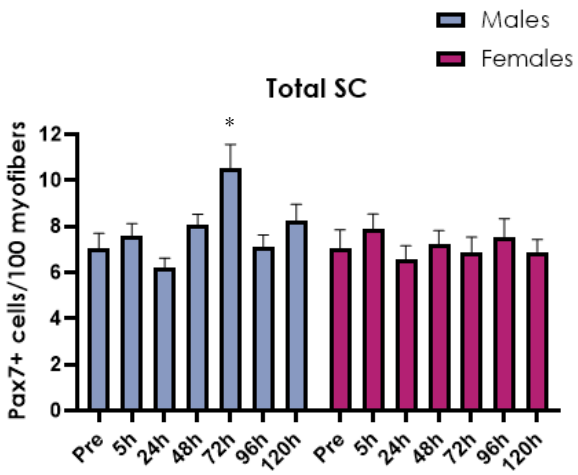


Figure 3. Satellite cell (Pax7+) content in males (blue) and females (red) over the course of 120h. * denotes significance from baseline.

We observed an interaction in the CK response demonstrating a peak at 24h (M: 536 ± 109 U/L, F: 415 ± 79 U/L); this remained elevated in males over 120h while females returned to baseline ($p<0.05$). IL-6 and TNF-a exhibited changes over time but were not different between males and females ($p>0.05$), along with IFN-y and IL-1b.

An interaction was detected for muscle thickness, peaking at 48h in males (2.90 ± 0.35 cm) while females peaked at 72h (2.47 ± 0.25 cm). Echo intensity and pennation angle did not change significantly over time in either sex. Strength decreased significantly in both groups but was restored to baseline in males at 5h while females recovered at 120h. No measures were associated with changes in circulating levels of 17β-estradiol or progesterone.

CONCLUSION: A sexual dimorphism in the response to damaging exercise was evident between males and females, particularly as it pertains to the severity of ultrastructural damage (via TEM), SC expansion (via immunohistochemistry), CK levels (via serum analysis), and muscle thickness (via ultrasound sonography). These differences were not associated with circulating 17β-estradiol or progesterone.

References

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