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Sex Differences in Exercise-Induced Muscle Pain and Muscle Damage

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Abstract

There is uncertainty about sex differences in exercise-induced muscle pain and muscle damage due to several methodological weaknesses in the literature. This investigation tested the hypothesis that higher levels of exercise-induced muscle pain and muscle damage indicators would be found in women than men when several methodological improvements were executed in the same study. Participants ($N = 33$; 42% women) with an average age of 23 years ($SD = 2.82$) consented to participate. After a familiarization session, participants visited the laboratory before and across four days after eccentric exercise was completed to induce arm muscle pain and muscle damage. Our primary outcomes were arm pain ratings and pressure pain thresholds. However, we also measured the following indicators of muscle damage: arm girth; resting elbow extension; isometric elbow flexor strength; myoglobin (Mb); tumor necrosis factor (TNF α); interleukin 1 β (IL1 β); and total nitric oxide (NO). Temporary induction of muscle damage was indicated by changes in all outcome measures except TNF α , and IL1 β . In contrast to our hypotheses, women reported moderately lower and less frequent muscle pain than men. Also, women's arm girth and Mb levels increased moderately less than men's, but the differences were not significant. Few large sex differences were detected.

Keywords

delayed-onset muscle soreness; stretch injury

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Introduction

Recent review articles have stated that women generally report more frequent and higher pain than men.^{32,41} However, another review has advocated no clear and consistent pattern of sex differences in experimental pain is discernable.⁵¹ Regardless, authors typically agree the consistency of results varies depending upon methodological issues such as the type of pain.^{19,32,41} For example, although it has been advocated that there is strong and consistent support for women describing higher muscle pain from algescic intramuscular injections than men,^{19,51} numerous research groups recently debated sex differences in exercise-induced muscle pain and muscle damage.^{3,15,25,26,39,48,49,56,59,61,64,66,67,71} These authors sparred over the measures that should be analyzed and the discordance between the non-human animal and human animal literature, in which the former generally shows protective effects of estrogen and the latter generally shows no sex differences.

Exercise-induced pain, which is often measured as an indicator of muscle damage, is particularly important to consider for several reasons. Physical activity can acutely exacerbate clinical pain. For example, patients with osteoarthritis^{1,20} low back pain,^{53,69} chronic regional myalgia,⁵⁵ fibromyalgia syndrome,^{7,29,38,62,68} migraine,³⁶ neuropathic pain,^{23,24} neuromuscular disease,⁴⁷ and post-surgical pain⁴³ have reported acute exacerbations of pain with activity. In addition, pain from therapeutic exercise impairs adherence to the exercise in people with chronic pain.^{17,31,34,35,37,40,42,60,70}

One type of exercise-induced pain that is particularly intriguing to investigate is delayed-onset muscle pain. This type of exercise-induced muscle pain is best produced by unaccustomed lengthening muscle contractions, which are called eccentric contractions. Such contractions can be performed in a tightly controlled manner to temporarily produce endogenous, deep tissue pain and muscle damage. The pain peaks one to two days after the eccentric muscle contractions and it may last for up to 10 days,⁴ during which people perform self-care behaviors.¹⁰ Also, the delayed-onset muscle pain has been associated with allodynia,¹⁴ hyperalgesia,²¹ and enhanced temporal summation.^{2,44}

Current reviews of human studies of delayed-onset muscle pain do not support meaningful sex differences.^{9,25} For example, one review of six studies did not detect consistent sex differences in delayed-onset muscle pain²⁵ and another review of 13 studies concluded that evidence did not support sex differences in delayed-onset muscle pain.⁹ However, as noted previously, the topic is still debated because the literature has been limited by numerous methodological issues. For example, human studies of sex differences in exercise-induced muscle pain have been impaired by probable sex differences in the intensity of eccentric contractions applied to induce damage, weak pain or soreness measurement methodology, and lack of control of women's menstrual cycle phase.⁹

The objective of this research study was to advance our understanding of sex differences in endogenous muscle pain by testing the hypothesis that women would report greater exercise-induced muscle pain as well as other indicators of muscle damage than men when several methodological improvements were executed. One improvement was that the intensity of the eccentric muscle contractions for inducing the delayed-onset muscle pain was based on participants' eccentric strength in contrast to concentric strength (i.e., shortening muscle contractions), which is important because sex differences exist in the relationship between eccentric and concentric strength.⁵⁷ In addition, the eccentric contractions were completed while the female participants were in the follicular phase of their menstrual cycles. Another improvement was that multidimensional measures of muscle pain were collected with the exercised limb in different states along with several biomarkers of muscle damage. Furthermore, participants' diet and self-care behaviors were restricted

throughout the study. The incorporation of all these methodological improvements into a single study meaningfully advances the research on sex differences in experimental endogenous muscle pain.

Methods

Participants

Participants ($N = 33$; 42% women), who averaged 23 years of age ($SD = 2.82$) and were 84.8% Caucasian, were recruited by posting flyers around the community. They were screened for eligibility by telephone. Once present in the lab, participants provided written informed consent to participate in a six-session protocol that was approved by the University of Missouri's Health Science Institutional Review Board. They were financially compensated for their participation.

The restrictions for participation were the following: (a) had not engaged in upper body strength training on a regular basis (i.e., two times per week) for consecutive weeks within the previous six months, (b) were not currently experiencing arm pain, (c) had no history of upper arm injury within the previous six months, and (d) no chronic pain conditions. In addition, participants were screened for potential risk factors to the exercise protocol (e.g., excessive swelling, loss of range or motion, exertional rhabdomyolysis). Furthermore, participants were restricted from the following behaviors: smoking 3 hrs prior to a session, consuming any food or drink except water 8 hrs prior to a session, and performing self-care behaviors for musculoskeletal pain (e.g., taking analgesics) throughout the study period. Only two of the 14 women were consuming oral contraceptives.

Measures

Numeric muscle pain ratings—In order to evaluate the multidimensional nature of pain,⁵⁰ ratings of non-dominant arm pain intensity and pain unpleasantness were assessed before and after the eccentric exercise with 0–100 numeric scales. More specifically, these ratings were collected while the non-dominant arm was (1) stationary at approximately 90° of elbow flexion, (2) moving through active range of motion without applied load, and (3) completing a strength test, during which the elbow is held in one position (i.e., isometric strength). The anchors of the pain intensity rating scale were “no pain” and “most intense pain sensation imaginable.” The anchors of the pain unpleasantness rating scale were “no unpleasantness” and “most unpleasant imaginable.” Numeric pain scales have been found to be reliable and valid.²⁷

Pressure Pain Threshold—Pressure pain threshold was defined as the point at which a pressure stimulus first became painful. The pressure stimulus was applied at 25% of the distance from the cubital fossa to the greater tuberosity of the humerus while the non-dominant arm was stationary at approximately 90° of elbow flexion. Using a hand-held 10 kg dolorimeter with a 1 cm rubber tip (Pain Diagnostics Inc., Great Neck, NY), pressure was increased at a rate of about 1 kg/s until participants first reported feeling pain. The average of two repeated measurements was analyzed.

Biomarkers of Muscle Damage—Swelling of the non-dominant upper arm was measured by calculating the average girth at 5 cm and 10 cm proximal from the olecranon of the ulna with a Gulick tape measure (Creative Health Products, Inc., Plymouth, MI). Also, flexibility of the non-dominant elbow joint was measured using a standard 12" goniometer. In addition, the strength of the non-dominant elbow flexors was determined using the Biodex System 3 (Biodex Medical Systems, Inc., Shirley, NY) with the elbow held at 90° of elbow flexion.

Furthermore, several serum biomarkers of muscle damage^{45,46,72} (myoglobin (Mb), tumor necrosis factor (TNF α), interleukin 1 β (IL1 β), and total Nitric Oxide (NO)) were measured by enzyme linked immunosorbent assay (ELISA) using commercially available kits (Mb: BioCheck, Inc., Foster City, CA; TNF α and IL1 β : QuantiGlo, R&D Systems, Inc., Minneapolis, MN; NO: Assay Designs, Inc., Ann Arbor, MI). These biomarkers evaluate muscle injury (Mb), inflammation (TNF α and IL1 β), and free radical status (NO). They were included as multidimensional indicators of muscle damage.

Procedures

A familiarization session was held to determine isometric strength and to acclimate the participants to the sensory tests and girth and range of motion measures. After the familiarization session, participants visited the laboratory for five consecutive days. The first session was scheduled when women were in the follicular phase of their menstrual cycles, which was determined by counting the 4–10 days since women began menstrual bleeding.^{6,18,28}

At the beginning of the first session, participants were seated and asked to complete questionnaires regarding their adherence to the study restrictions. Next, non-dominant arm pain during rest and movement and pressure pain thresholds were collected. Then, after participants had been seated for a minimum of 15 min, 10 mL of blood was collected from venous access on the dominant arm. Subsequently, non-dominant upper arm girth and resting elbow extension were measured before participants were positioned in a muscle testing apparatus (Biodex System 3; Biodex Medical Systems, Shirley, NY). While seated in the muscle testing apparatus, the isometric strength test was completed and ratings of perceived exertion and pain during the test were collected.

Following the isometric strength test, an eccentric strength test was completed. Then, the participants performed 3 sets of 12 maximal eccentric contractions to induce temporary muscle damage. All of the eccentric contractions were completed at a velocity of 90°/s through the participants' active range of motion with a rest period of 60 s in between each set.

During the next hour, participants were instructed to continue their adherence to the pre-session restrictions, but they were allowed to leave the laboratory if they desired. After the 1-hr delay, arm pain, pressure pain thresholds, upper arm girth, resting extension, and 10 mL of blood were collected again in the same manner as before the eccentric exercise. Finally, the session was terminated and participants were reminded of the schedule and restrictions for the subsequent sessions, which included avoiding any self-care behaviors for musculoskeletal pain (e.g., ice or heat application, stretching, massage, etc.).

Participants returned to the laboratory at one, two, three, and four days after the eccentric exercise with all these follow-up sessions held either in the morning or afternoon hours in congruence with the first session. During the follow-up sessions, arm pain, pressure pain thresholds, upper arm girth, resting extension, and 10 mL of blood were collected again.

Data Analyses

As stated previously, our primary focus was sex differences in muscle pain. Sex differences in muscle pain ratings when the non-dominant arm was stationary, moving, and completing the strength test and pressure pain thresholds were tested by conducting repeated mixed-model analyses of variance (ANOVAs) with the factors of sex (men, women) and time (pre-eccentrics, 1-hr post-eccentrics, 1 day, 2 days, 3 days, 4 days). Secondary analyses with the same factors were also run on upper arm girth, elbow resting girth, isometric strength, Mb,

TNFA, IL1b, and NO. Significant 2-way interactions were followed up with independent t-tests for sex differences at each time point.

All analyses were conducted using SPSS software (SPSS, Inc., Chicago, IL) with Greenhouse-Geisser correction of degrees of freedom to adjust for violations of sphericity. Statistical significance was defined as $p < .05$ and the meaningfulness of results was determined by calculated effect sizes. Eta squared (η^2) values of .01, .06, and .14 are typically interpreted as thresholds for small, medium, and large effect sizes, respectively⁵

Results

Baseline Characteristics

The age, BMI, and exercise behavior of the men and women were similar. There were no significant sex differences in the intensity and unpleasantness of the recalled most painful physical event. In addition, with regard to arm muscle pain specifically, there were no significant sex differences in the frequency, intensity, and unpleasantness of recalled past pain and there were no significant sex differences in expectations of pain intensity, pain unpleasantness, frequency, interference, threat, and challenge. Also, the prevalence of previous arm muscle pain (78.9% of men and 64.3% of women; $p = .35$) and conceptualization of muscle pain from exercise as beneficial (57.9% of men and 50% of women; $p = .65$) were comparable for men and women. Thus, the women and men were similar in these baseline characteristics.

Eccentric Exercise

The average percentage of eccentric strength produced and range of motion during the eccentric exercise were comparable for both sexes. Average exertion during the eccentric exercise was moderately lower for women than men, but the ratings were not significantly different between the sexes.

Pain Ratings and Pressure Pain Thresholds

Arm pain ratings at rest, movement, and during the isometric contractions increased significantly across time supporting the induction of muscle damage. (See Table 1.) Women's pain intensity at rest and with movement tended to increase less across time than men's ($p = .05$, $\eta^2 = .10$ and $p = .05$, $\eta^2 = .10$) and women's pain unpleasantness with movement increased significantly less than men's ($p = .04$, $\eta^2 = .10$), but sex differences in pain unpleasantness at rest across time were not statistically significant ($p = .23$, $\eta^2 = .05$). Also, non-significant, but moderate sized sex differences in changes across time for ratings of pain intensity and unpleasantness during the maximal isometric strength tests indicated women's pain ratings increased less across time than men's with adjustment for force produced ($p = .11$, $\eta^2 = .08$ and $p = .14$, $\eta^2 = .07$) without adjustment ($p = .12$, $\eta^2 = .08$ and $p = .09$, $\eta^2 = .08$).

The main effects of time and sex by time interactions were most relevant to our hypotheses, but women also tended to generally have lower pain intensity ratings at rest ($p = .05$, $\eta^2 = .12$), which was largely driven by the post-eccentric measures. Also, women tended to generally have lower pain intensity ratings during the maximal isometric strength tests ($p = .06$, $\eta^2 = .13$), but again the main effect was largely driven by the post-eccentric measures and its magnitude decreased with adjustment for force produced ($p = .10$, $\eta^2 = .10$). All of the other main effects of sex also showed lower pain ratings by women, but none approached statistical significance (p 's = .07–.11, η^2 's = .08–.12). (See Figures 1, 2, and 3 and see Table 2 for sex by time interactions.)

Pressure pain thresholds decreased significantly across time (see Table 1), but sex differences in change across time were not statistically significant ($p = .30$, $\eta^2 = .04$). The main effects of sex were also not statistically significant ($p = .40$, $\eta^2 = .02$). (See Table 2 for sex by time interactions.)

Biomarkers of Muscle Damage

Upper arm girth increased significantly while arm extension and strength both decreased significantly across time. These main effects of time further support induction of muscle damage. (See Table 1.) Also, as expected simply due to sex, women had smaller upper arm girths ($p = .01$, $\eta^2 = .21$) and lower isometric strength ($p < .01$, $\eta^2 = .45$) than men. No significant sex differences in the increased arm girth across time were shown, but girth increased moderately less in women than men ($p = .09$, $\eta^2 = .08$). Also, no sex differences in the decreased arm extension or strength across time were found ($p = .37$, $\eta^2 = .03$ and $p = .14$, $\eta^2 = .06$). (See Table 2 for sex by time interactions.)

Regarding the serum markers, one male outlier was detected and removed from the Mb analyses because the z-score of his Mb level at baseline was greater than 3.29.⁶⁵ Both Mb and NO increased significantly across time supporting induction of muscle damage (see Table 1). No significant sex differences in the increased Mb across time were shown, but Mb increased moderately less in women than men ($p = .13$, $\eta^2 = .07$). Also, the levels of NO increased similarly across time in both sexes ($p = .47$, $\eta^2 = .03$). Neither TNFa nor IL1b changed significantly across time (see Table 1). No statistically significant main effects of sex were observed (p 's = .07–.98, η^2 's = <.01–.10). (See Table 2 for sex by time interactions.)

Discussion

Ratings of arm pain and pain responses to pressure increased significantly after a bout of eccentric exercise. Moreover, these sensory responses were accompanied by increased arm girth, Mb, and NO and decreased range of motion and strength. Thus, the data support successful induction of both muscle pain and muscle damage.

We hypothesized that women would report greater exercise-induced muscle pain than men in order to concur with a current generalization within the pain literature that women typically express greater and more frequent pain than men. Instead, women described moderately lower and less frequent muscle pain than men. These results corresponded with non-significant sex differences in changes in biomarkers of muscle damage. Effect sizes indicated that women's arm girth and levels of Mb increased moderately less than men's. Thus, the direction of results was consistent across outcome measures and they align with the non-human animal findings.⁶⁷

Numerous reviews of sex differences in experimental pain have stated that methodological differences among studies impair synthesis. In fact, methodological variations are evident even when just focusing on our own research group's investigations of sex differences in exercise-induced muscle pain. For example, this current study and two of our previous studies^{11,13} based the stimulus intensity on eccentric strength instead of concentric strength, which is important for ensuring similar eccentric exercise between the sexes.^{22,57} Also, this study and two others^{11,12} measured muscle pain during unloaded movement, but none of our other studies measured muscle pain during rest, movement, and strength testing as was done in this study. None of our previous studies restricted the menstrual cycle phase of the female participants or combined the multiple methodological strengths as was done in this study.

It is possible that control of women's menstrual cycle was the most important methodological change from our previous studies. Indeed, estrogen can have beneficial effects on the immune system and maintain the integrity of muscle cells during exercise.²⁵ Also, non-human animal studies have detected beneficial effects of estrogen on induced muscle damage.⁶⁷ In fact, a human study by Kerkick and colleagues³⁰ also controlled for menstrual cycle by restricting their female participants to the mid-luteal phase when estrogen levels resemble the late follicular phase and they detected lower soreness ratings in women than men. In addition, a recent investigation reported that hormone-replacement therapy in post-menopausal women decreased serum and muscle biopsy biomarkers of exercise-induced muscle damage.¹⁶ However, it is noteworthy that Kerkick and colleagues³⁰ did not detect sex differences in biomarkers of muscle damage such as lactate dehydrogenase and strength. Obviously, more research is needed on this topic with measurement of circulating hormones.

Regardless, all of our studies on sex differences in exercise-induced muscle pain have generally disagreed with a current generalization within the pain literature that women usually express greater and more frequent pain than men. It is possible that women did not report higher and more frequent delayed-onset muscle pain than men because the exercise-induced muscle pain model is accompanied by temporary tissue damage. Indeed, this study's detection of the development of pain, weakness, swelling, loss of flexibility and increased levels of Mb and NO supported induction of temporary muscle damage.⁷²

It is also possible that our results have been affected by a participation bias in that the untrained male and female participants, who were willing to complete a bout of exercise to induce muscle pain, may not have pain responses that generalize to typical participants in studies of commonly induced experimental pain. However, at baseline, the pressure pain thresholds of the women were lower than the men ($\eta^2 = .07$) as has been widely reported in the experimental pain literature.

Readers may wonder if sex differences in participants' daily physical activities outside of the lab may have influenced the results. Young adult men are generally more physically active than women.³³ However, women have more physically repetitive employment in uncomfortable environments, work more frequently and for longer durations with their arms elevated above their shoulders, and spend less time resting than men.^{8,63} Therefore, future studies should consider controlling or monitoring participants' physical activity while outside the laboratory.

Certainly, our methodology could be improved by restricting the entire duration of the study to a specific menstrual cycle phase while actually measuring hormone levels. Also, statistically significant interactions were detected for some of the moderate effects in this study ($\eta^2 = .10$), but our data suggests 45 men and 45 women would be needed for 80% power to test a sex by time interaction with an effect size of $\eta^2 = .06$.⁵ Considering that we had seven pain outcome measures, it is possible that some of the effects occurred by chance. However, the direction of results with lower responses in women than men was similar across outcome measures. Also, only two previous studies of sex differences in delayed-onset muscle pain had total sample sizes of 100⁵⁸ and 164⁵² and neither of these previous studies detected significant sex differences in muscle pain or soreness.

In summary, our research continues not to detect meaningfully higher and more frequent exercise-induced muscle pain in women than men, which is a generalization based on complex literature with diverse methods and results.¹⁹ Indeed, it appears that women may actually express moderately less exercise-induced muscle pain than men when a methodology such as we used here is employed. Such exercise-induced muscle pain is

important to evaluate because it is induced endogenous deep tissue pain associated with allodynia,¹⁴ hyperalgesia,²¹ and enhanced temporal summation^{2,44} for which people perform self-care behaviors.¹⁰ Thus, health care providers should be cautious about assuming higher and more frequent pain in women than men across all types of muscle pain. Also, despite a recent review's conclusion that sex differences research has had little clinical impact so far,⁴¹ subsequent evidence may accumulate to clarify the mechanisms of variability in sex differences across types of pain and support differential pain treatment between the sexes for particular types of muscle pain.

Future research on this topic might, as suggested by Phillips,⁴⁸ test women and men on hormone replacement therapy. In addition, studies could consider measuring a wider assortment of factors that are thought to influence sex differences in pain such as gender roles and emotions^{19,51,54} and using advanced techniques to measure upper extremity activity (e.g., accelerometers) and localized muscle damage (e.g., imaging studies).

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Perspective

Lower muscle pain among women than men was detected with corresponding, but non-significant sex differences in other muscle damage indicators. Methodological advances may have improved alignment of these results with the non-human animal findings. This line of research continues to show exceptions to the generalization that women experience greater pain than men.

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Figure 1.

Men's and women's ratings of arm muscle pain intensity (int) and unpleasantness (unp) at rest. Means and SEMs are displayed.

Figure 2.

Men's and women's ratings of arm muscle pain intensity (int) and unpleasantness (unp) during movement. Means and SEMs are displayed.

Figure 3.

Men's and women's ratings of arm muscle pain intensity (int) and unpleasantness (unp) during isometric strength testing. Means and SEMs are displayed.

Table 1

Changes in the dependent variables across time, which tested the effects of the eccentric muscle contractions regardless of sex (i.e., main effects of time).

Variable	df	F	p	η^2
Pain Intensity				
resting (0–100 scale)	5, 150	5.78	<.01	.16
moving (0–100 scale)	5, 150	24.01	<.001	.45
isometrics (0–100 scale) ^a	5, 135	2.54	.08	.09
Pain Unpleasantness				
resting (0–100 scale)	5, 150	3.92	.02	.12
moving (0–100 scale)	5, 150	22.31	<.001	.43
isometrics (0–100 scale) ^a	5, 135	3.92	.02	.13
Pressure pain thresholds (kg)	5, 150	10.59	<.001	.21
Upper arm girth (cm)	5, 140	11.78	<.001	.30
Resting Extension (°)	5, 145	9.34	<.001	.24
Isometric strength (Nm)	5, 140	13.06	<.001	.32
Mb (ng/mL)	5, 150	6.13	<.01	.17
TNF α (pg/mL)	5, 150	0.75	.40	.03
IL1b (pg/mL)	5, 150	0.25	.66	.08
NO (μ mole/L)	5, 150	4.27	<.01	.13

^aThese values are for the pain ratings during the isometric strength testing without correction for percentage of isometric strength produced.

Table 2

Comparison between sexes in the changes in the dependent variables across time (i.e., sex by time interactions).

Variable	df	F	p	η^2
Pain Intensity				
resting (0–100 scale)	5, 150	3.30	.05	.10
moving (0–100 scale)	5, 150	3.23	.05	.10
isometrics (0–100 scale) ^a	5, 135	2.22	.11	.08
Pain Unpleasantness				
resting (0–100 scale)	5, 150	1.50	.23	.05
moving (0–100 scale)	5, 150	3.26	.04	.10
isometrics (0–100 scale) ^a	5, 135	1.94	.14	.07
Pressure pain thresholds (kg)	5, 150	1.22	.30	.04
Upper arm girth (cm)	5, 140	2.56	.09	.08
Resting Extension (°)	5, 145	1.02	.37	.03
Isometric strength (Nm)	5, 140	1.32	.14	.06
Mb (ng/mL) ^b	5, 150	2.11	.15	.07
TNF α (pg/mL)	5, 150	0.82	.38	.03
IL1b (pg/mL)	5, 150	0.76	.41	.03
NO (μ mole/L)	5, 150	0.86	.47	.03

^aThese values are for the pain ratings during the isometric strength testing without correction for percentage of isometric strength produced.

^bThese values reflect the removal of one male outlier.