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ORIGINAL ARTICLE

The influence of estradiol on muscle damage and leg strength after intense eccentric exercise

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Abstract
Purpose To examine the influence of estradiol on muscle damage and leg strength after intense eccentric exercise.
Methods Eight men (MEN), eight normally menstruating women (WomenNM), and eight women using oral contraceptives (WomenOC) participated in this study. Subjects performed 240 maximal-effort bilateral eccentric contractions of the quadriceps muscle groups designed to elicit exercise-induced muscle damage (EiMD). Serum creatine kinase (CK), myoglobin (Mb), and fatty acid-binding protein (FABP) concentrations were measured before (pre-) EiMD, as well as 0, 6, 24, and 48 h post-EiMD. Peak isometric quadriceps torque (i.e., leg strength) was measured pre-EiMD, as well as 24 and 48 h post-EiMD.
Results The increases in CK, Mb, and FABP concentrations from pre- to post-EiMD were greater in MEN (10-fold, 15-fold, and fourfold, respectively) and WomenOC (sevenfold, 11-fold, and ninefold) compared with WomenNM (five-, six-, and threefold; $p < 0.05$). The decline in leg strength was about 10 % pre- to 24 h post-EiMD in all groups and decreased a further 10–15 % by 48 h post-EiMD in the MEN and WomenOC only.
Conclusion Our findings suggest an important role of estradiol in blunting the muscle damage response to intense eccentric exercise and preserving muscle function after EiMD.

Keywords Men and women · Exercise-induced muscle damage · Delayed-onset muscle soreness · Isometric resistance exercise · Oral contraception

Abbreviations

EiMD	Exercise-induced muscle damage
CK	Creatine kinase
Mb	Myoglobin
FABP	Fatty acid-binding protein
WomenNM	Normally menstruating women
WomenOC	Women taking the oral contraceptive pill

Introduction

Given the evidence suggesting that estradiol can be neuroprotective (Garcia-Segura et al. 2001), osteoprotective (Imai et al. 2010), and cardiovascular protective (Mendelsohn and Karas 1999), it is not surprising that sport and exercise scientists are interested in the role of estrogens in the muscle damage and repair response to exercise. In order to examine the role of estrogens in the muscle damage response to exercise, comparisons can be made between gender (Dannecker et al. 2012; Sewright et al. 2008; Stupka et al. 2000), and in women with varying estrogenic status: across the menstrual cycle (Kendall and Eston 2002), pre- and postmenopause (Roth et al. 2000; Buckley-Bleiler et al. 1989), as well as with and without the use of hormone replacement (Dieli-Conwright et al. 2009) or oral contraception (Carter et al. 2001; Kendall and Eston 2002;

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Roth et al. 2001; Savage and Clarkson 2002; Thompson et al. 1997). Many of these studies report no effect of estrogens on markers of EiMD (Dannecker et al. 2012; Kendall and Eston 2002; Savage and Clarkson 2002; Stupka et al. 2000; Thompson et al. 1997), while others demonstrate greater muscle damage after eccentric exercise in individuals deficient in estradiol (Dieli-Conwright et al. 2009; Roth et al. 2000, 2001). Thus, there remains uncertainty as to the influence of estradiol on EiMD.

In addition to the initial mechanically induced disruption of the muscle fibers that is associated with EiMD, a coordinated inflammatory response is initiated that can exacerbate muscle damage early in the repair phase (Clarkson and Tremblay 1988; Tidball 2005). Stupka et al. (2000) reported a lower number of inflammatory cells in women compared with men 48 h after EiMD and Savage and Clarkson (2002) demonstrated that leg strength took longer to recover after EiMD in women taking oral contraceptives when compared to normally menstruating women. Thus, it is suggested that lower estradiol concentrations may affect the recuperative capacity of the muscle, thereby delaying the recovery of strength in women taking oral contraceptives. Perhaps the most compelling evidence supporting the role of estradiol in EiMD and repair is in the assessment of muscle function determined via repeated measures of skeletal muscle strength (Pizza 2009; Sayers and Clarkson 2001; Warren et al. 1999). Therefore, the present study examined both early (i.e., serum myoglobin, Mb and fatty acid-binding protein, FABP) and late (i.e., serum creatine kinase, CK) markers of muscle damage as well as isometric quadriceps torque (i.e., leg strength) before, 24 and 48 h after EiMD to observe the recuperative capacity of men and women.

The blending of women on and off oral contraception in sex-comparison studies (Dannecker et al. 2012; Stupka et al. 2000), a lack of statistical power and/or substantial variability in blood data (Carter et al. 2001; Roth et al. 2001; Thompson et al. 1997) in studies of women with varying estrogenic status, makes it difficult to accurately determine the role of estradiol in EiMD. The purpose of the present study was to examine the role of gender and oral contraception in the response to muscle damage after intense eccentric exercise.

Methods

Subjects

Eight men (MEN), eight normally menstruating women (WomenNM), and eight women who were using oral contraceptives (WomenOC) volunteered to participate as subjects in this study. The subjects did not have any documented history, or clinical signs and symptoms of pulmonary, cardiovascular, or metabolic disorders. Subjects were habitually active, typically undertaking moderate-intensity endurance-based activities such as walking, jogging, and swimming (~2 to 3 days/week for 30 min). Volunteers were excluded from the study if they reported participating in any resistance exercise, or competitive sporting activities. This was established during the recruitment and screening process via questionnaire and interview. While we cannot ensure that every subject was naïve to eccentric activity, based on our questionnaire and interview, we are confident that the two groups were homogenous with respect to volume, intensity, and mode of exercise habits. Nonetheless, it should be noted that any previous exposure to heavy-intensity eccentric exercise might dampen the muscle damage attained during the present exercise protocol.

All normally menstruating women had regular menstrual cycles occurring every 28–30 days. Women using oral contraception had been using a combined monophasic oral contraceptive pill for at least 12 months and continued their oral contraceptive pill throughout the experimental period. All subjects had never knowingly been pregnant. It should be noted that subjects included in this study acted as subjects in the study by Joyce et al. (2014) and that data for both studies were collected based on subjects performing the EiMD protocol only once.

Experimental design

After pre-exercise health screening had been performed and written informed consent attained for each subject, a sample of blood was collected before the start of the experiment for all subjects that was during the follicular phase of the menstrual cycle for WomenNM (i.e., day 2–6), and during the withdrawal phase for WomenOC (i.e., day 2–6 of placebo pill ingestion) for the subsequent determination of serum 17β-estradiol concentration (Sullivan Nicolaides Pathology, Australia). Each subject completed a bilateral, lower limb eccentric resistance-exercise protocol designed to induce muscle damage of the quadriceps muscle groups (i.e., EiMD protocol). The EiMD protocol took place during the follicular phase of the menstrual cycle (i.e., day 2–6) for WomenNM, and during the withdrawal phase (i.e., day 2–6 of placebo pill ingestion) for WomenOC. Serum CK, Mb, and FABP concentrations were measured before (pre-) EiMD, as well as 0, 6, 24, and 48 h post-EiMD. Mb and FABP concentrations were determined in part, to provide early (i.e., 0–6 h post-exercise) evidence of muscle damage (Montgomery et al. 2008). Peak isometric quadriceps torque (i.e., leg strength) was measured pre-EiMD, as well as 24 and 48 h post-EiMD. The Griffith University Human Research Ethics Committee approved all procedures.

Assessment of leg strength

Peak isometric quadriceps torque (i.e., leg strength) was assessed for both legs using a Biodex dynamometer (Biodex Medical Systems, NY, USA) pre-, 24 h post-, and 48 h post-EiMD. Subjects were seated upright on the Biodex with their back supported and hips at 85º. The rotational axis of the dynamometer lever arm was aligned with the lateral femoral epicondyle and the resistance pad positioned on the tibia, proximal to the malleoli. Each subject's pelvis and thighs were strapped to the seat to avoid any extraneous movement during exercise and subjects were required to cross their arms over their chest. Before completing the strength tests, each subject performed a warm-up comprising ten submaximal contractions at an angular velocity of 30° s^{-1} through their entire range of movement. A 5-min rest period separated the warm-up and the experimental trials. The peak torque for each subject was measured at a knee-joint angle of 75° during three 5-s maximal-effort contractions separated by 60 s of passive rest. The right and left legs were tested in a randomized order determined by flipping a coin, and the highest peak torque recorded for each leg was averaged together and reported as leg strength.

Blood sampling and analyses

Venous blood samples (~12.5 mL) were collected directly into serum separator tubes (BD Diagnostics Systems, NJ, USA) 20 min before the commencement of the EiMD protocol (i.e., baseline) as well as 0, 6, 24, and 48 h after. Whole blood samples were stored on ice for ~30 min before centrifugation at 1600*g* for 10 min. Serum samples were stored frozen at −80 °C until analysis for Mb, CK, and FABP and were subjected to only one freeze–thaw cycle. All assays were performed on the Abbott Architect ci16200 (Abbott Diagnostics, IL, USA) using assays supplied by Abbott Diagnostics.

Eccentric resistance-exercise protocol (i.e., EiMD protocol)

Subjects were warmed up before the EiMD protocol and seated on the Biodex in the same position as the leg strength assessment. Range of movement was set to 60° (110°–50° of knee flexion) and repetitions were performed at an angular velocity of 30° s^{-1}. Knee flexion was chosen, as compared to a more traditional muscle damaging exercise protocol (e.g., elbow flexion), in order to assess a functionally relevant movement pattern. Each subject attempted to resist the downward force of the dynamometer arm by maximally contracting their quadriceps muscle group. The Biodex then moved the leg back to the starting position passively. The eccentric exercise bout was divided into 48 sets of 10 contractions. Subjects performed 6 sets of 10 maximal eccentric contractions on one leg, before completing 6 sets of 10 maximal eccentric contractions on the other leg. This cycle was repeated four times, completing a total of 24 sets for each leg. A 1-min rest interval was allowed between sets. The rest intervals between sets and switching of legs allowed subjects to better restore intramuscular ionic homeostasis so as to maintain the highest possible exercise intensity throughout the EiMD protocol. To ensure maximal effort, participants were verbally encouraged to resist the action of the dynamometer lever arm with maximal effort and visual feedback of the angular torque was provided throughout the EiMD protocol. The bilateral eccentric exercise model used in the present study was specific to leg cycling and, our previous research (Joyce et al. 2014) suggested that it promoted muscle fatigue and resulted in elevated CK levels.

Statistical analyses

All results are presented as group mean ± SD. Fully factorial ANOVA was used to make comparisons among groups (MEN, WomenNM, WomenOC) as well as before and repeatedly after the EiMD protocol. Where statistically significant F values were detected, least-squares difference post hoc tests and pairwise comparisons were performed. IBM SPSS Statistics (IBM Corporation, Version 22.0) was used for the data analyses, and significance was accepted at $p \leq 0.05$.

Results

Subject characteristics

The age of menarche was not different between WomenNM (14 ± 1 years) and WomenOC (13 ± 2 years; $p = 0.41$). Table 1 presents the subject characteristics and peak isometric quadriceps torque measures. The MEN were older, taller, and heavier than the women ($p > 0.05$), whereas there were no differences in age ($p = 0.15$), height ($p = 0.22$), or body mass ($p = 0.79$) between the two female groups. Compared with WomenNM, estradiol was lower in MEN ($p < 0.01$) and in WomenOC ($p < 0.01$).

Response to the EiMD protocol

Mean torque calculated for both legs across the 240 eccentric contractions was greater in MEN (203 ± 47 Nm) compared with WomenNM (142 ± 21 Nm, $p < 0.01$) and WomenOC (132 ± 13 Nm, $p < 0.01$), but there was no difference between the two female groups ($p = 0.26$). However, mean torque expressed relative to body mass were not different

Table 1 Subject characteristics and baselines measures of peak quadriceps torque

	MEN	WomenNM	WomenOC
Age (years)	25 ± 4*	22 ± 3	20 ± 2
Body mass (kg)	80.0 ± 5.6*	62.3 ± 6.3	59.4 ± 5.9
Height (cm)	180.7 ± 4.5*	168.6 ± 5.4	163.8 ± 5.4
Estradiol (pmol L^{-1})	87.8 ± 11.2*	132.3 ± 41.7	45.9 ± 22.8#
Isometric torque @ 75° (Nm)	192.7 ± 13.9*	101.2 ± 19.3	107.6 ± 10.4

Values presented are mean ± SD. All values for isometric torque were calculated as the average of the right and left legs

* Different from WomenNM and WomenOC, $p < 0.05$

Different from WomenNM, $p < 0.05$

between groups (MEN, 2.4 ± 0.5; WomenNM, 2.3 ± 0.3; WomenOC, 2.2 ± 0.4 Nm kg^{-1}, $p = 0.60$).

Figure 1 shows the change in torque (expressed relative to the torque recorded in Set 1 for each subject). The rate of decline in force was greater for MEN compared with both female groups ($p < 0.01$) with MEN reaching a force value of <65 % of the force achieved in Set 1 of the EiMD protocol. Conversely, women responded similarly ($p > 0.61$) and on average did not drop below 80 % of the force achieved in Set 1.

Figure 2 illustrates the CK, Mb, and FABP responses to EiMD. For clarity, only group differences are presented on the figure, whereas time effects are reported here only. Serum CK concentration measured pre-EiMD was not different between WomenNM and WomenOC ($p = 0.69$), whereas MEN had a higher concentration of CK pre-EiMD compared with both female groups ($p < 0.05$). The EiMD protocol resulted in an immediate increase in CK concentration ($p < 0.05$), and the group differences remained the same. A further increase in CK after 6 h was observed in all groups ($p < 0.05$); MEN reached a peak CK concentration that was higher than both female groups ($p < 0.05$); and WomenOC increased to a value greater than WomenNM ($p = 0.04$). CK concentration remained stable to 24 h post-EiMD in MEN ($p = 0.75$), but decreased in both female groups ($p > 0.05$). Nevertheless, CK concentration at 24 h post-EiMD remained higher in WomenOC compared with WomenNM ($p = 0.05$) and were still higher than pre-EiMD values in both groups ($p < 0.01$). CK concentration decreased in MEN after 48 h compared with 24 h post-EiMD ($p = 0.01$), but remained higher than their pre-EiMD values ($p < 0.01$) and higher than both female groups ($p < 0.05$). CK concentration in the female groups continued to decrease from 24 h post- to 48 h post-EiMD ($p < 0.01$), but remained higher than their pre-EiMD values ($p < 0.01$).

Serum Mb concentration was not different pre-EiMD among groups ($p > 0.05$). Although Mb increased in both the female groups ($p < 0.01$), the magnitude of change was greater in WomenOC ($p = 0.05$) and Mb measured in MEN increased ($p < 0.01$) to a greater extent than both female groups ($p < 0.01$) after EiMD. Mb remained stable in MEN 6 h post-EiMD ($p = 0.68$) and decreased in both WomenNM ($p < 0.01$) and WomenOC ($p < 0.01$) to values not different from each other ($p = 0.51$), but higher than their respective pre-EiMD concentrations ($p > 0.05$). MEN demonstrated a sharp decrease in Mb 24 h post-EiMD ($p < 0.01$) but did not return to pre-EiMD values until 48 h post-EiMD ($p = 0.21$). There was a further decrease in Mb concentration in both female groups from 6 to 24 h

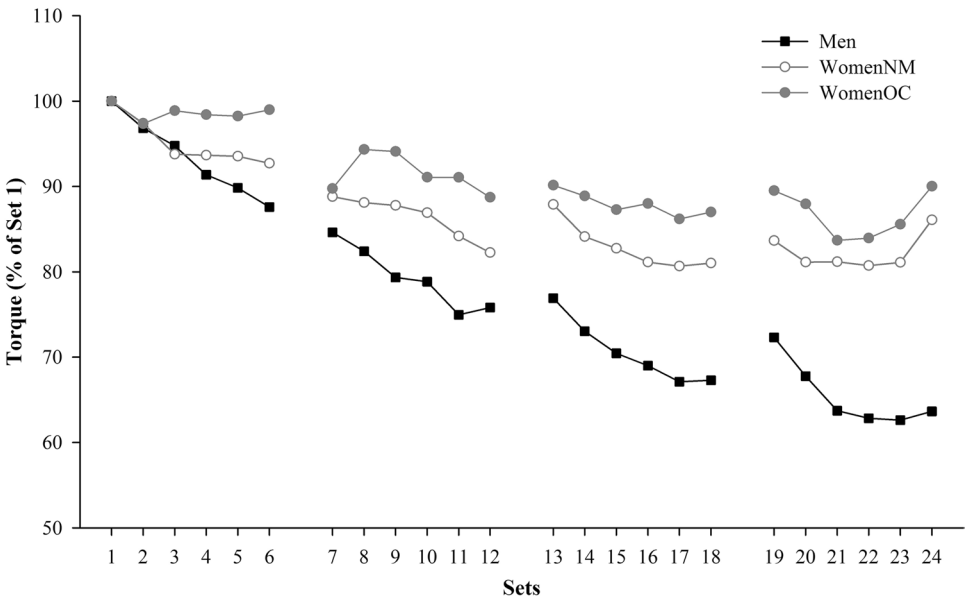

Fig. 1 Change in torque expressed relative to the torque recorded for Set 1 in MEN (*squares*), normally menstruating women (WomenNM; *open circles*), and women using oral contraceptives (WomenOC; *shaded circles*). *Each marker* represents the group mean for each set (i.e., 10 repetitions) using an average of the left and right leg values. *Error bars* have been omitted for clarity

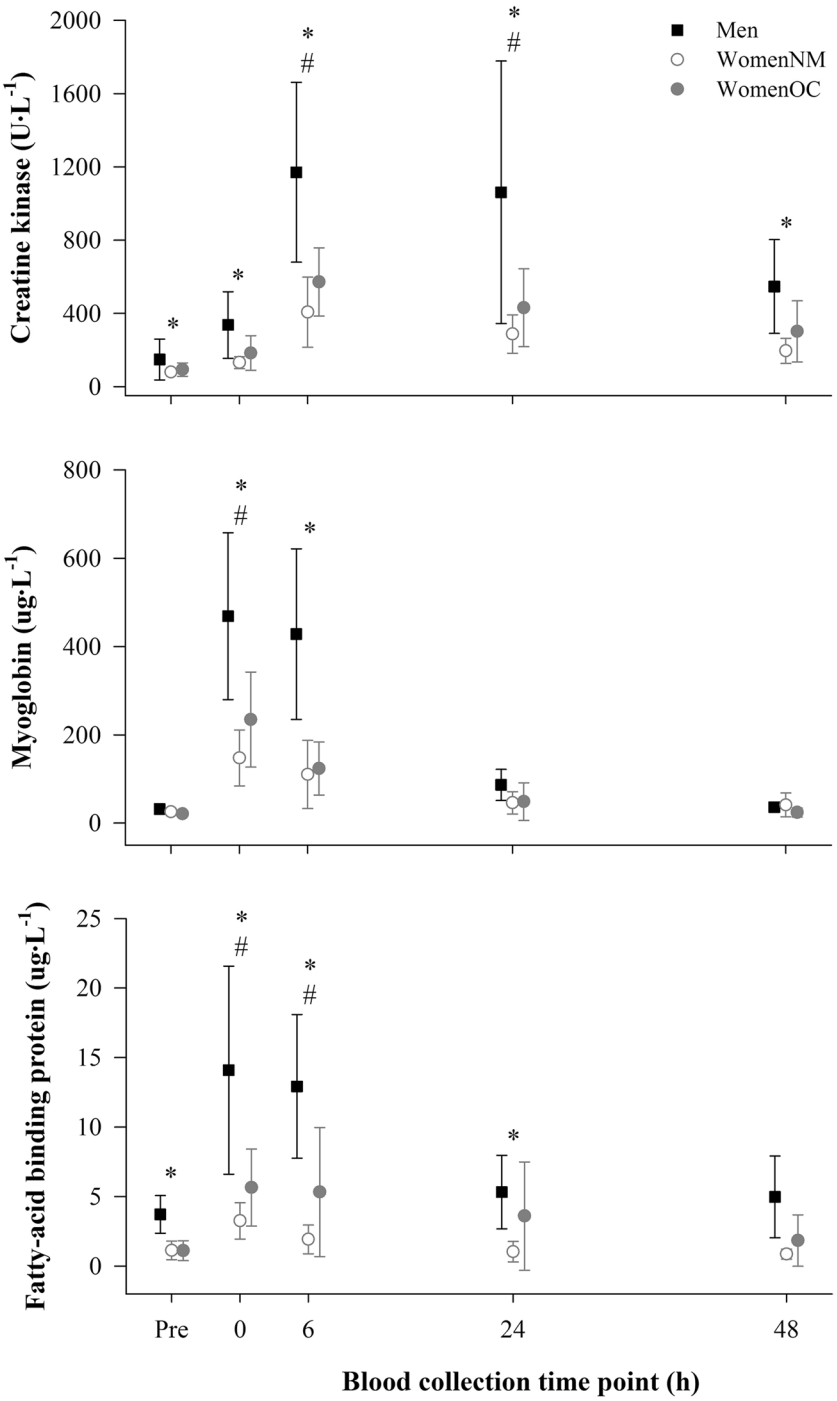

Fig. 2 Creatine kinase (CK; *upper panel*), myoglobin (*middle panel*), and fatty acid-binding protein concentrations (*lower panel*) measured pre-, as well as at 0, 6, 24, and 48 h post-exercise-induced muscle damage (EiMD) in MEN (*squares*), normally menstruating women (WomenNM; *open circles*), and women using oral contraceptives (WomenOC; *shaded circles*). Groups are offset at each sample point for clarity. Values presented are mean ± SD. *MEN different from WomenNM and WomenOC, #WomenNM different from WomenOC. Significance accepted at $p \leq 0.05$

post-EiMD ($p < 0.05$), where it remained constant in both groups at a level not different from pre-EiMD ($p > 0.01$).

FABP concentration was greater in MEN ($p < 0.01$) but not different between the two female groups ($p = 0.94$) pre-EiMD. FABP concentration increased in all groups immediately after EiMD ($p < 0.05$), with MEN displaying a greater increase than both female groups ($p < 0.05$) and WomenOC group displaying a greater increase than WomenNM ($p = 0.03$). FABP did not change in WomenOC after 6 h, whereas FABP concentration decreased in both the MEN ($p = 0.03$) and WomenNM ($p < 0.01$). All groups displayed decreases in FABP concentration at 24 h post-EiMD ($p < 0.05$) to values not different from pre-EiMD ($p > 0.05$). FABP concentrations at 48 h were not different from those measured at 24 h in all groups ($p > 0.05$).

Figure 3 shows peak isometric quadriceps torque (a measure of leg strength) achieved by each subject pre-, 24 h post-, and 48 h post-EiMD protocol, as well as the group

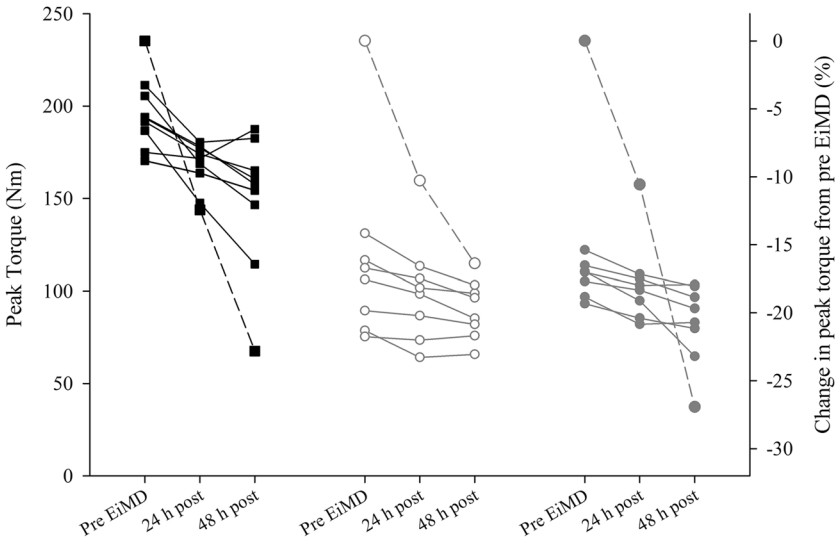

Fig. 3 Leg strength, determined by measuring peak isometric quadriceps torque in MEN (*squares*), normally menstruating women (WomenNM; *open circles*), and women using oral contraceptives (WomenOC; *shaded circles*) pre-, 24 h post-, and 48 h post-exercise-induced muscle damage (EiMD). The group mean relative (%) change in peak torque is shown (*dashed lines*) for each group from pre-EiMD after 24 h and 48 h

mean relative (percentage) change in peak torque (dashed lines) from pre-EiMD at 24 and 48 h post-EiMD. MEN attained higher peak torque pre-EiMD (191.1 ± 13.8 Nm) compared with both WomenNM (104.2 ± 20.8 Nm, $p < 0.01$) and WomenOC (106.0 ± 10.0 Nm, $p < 0.01$), whereas there was no difference between the two female groups ($p = 0.38$). MEN ($p < 0.01$) demonstrated a relative decrease in peak torque, as did WomenNM ($p = 0.01$) and WomenOC ($p < 0.01$), from pre-EiMD to 24 post-EiMD. Peak torque continued to decrease from 24 to 48 h post-EiMD in MEN (11 ± 13 %, $p < 0.01$) and WomenOC (16 ± 19 %, $p = 0.01$), but no further change was observed in WomenNM (5 ± 7 %, $p = 0.27$).

Discussion

When asked, more than 10 years ago, "Are women less susceptible to exercise-induced muscle damage?", Clarkson and Hubal (2001) responded "No." Ten years and several experiments later, we and others (Dannecker et al. 2012) are still pondering this question as there has been recent support for both answers: Yes (Sewright et al. 2008) and No (Fredsted et al. 2008; Miles et al. 2008). In the present study, we found greater concentrations of CK, and other indices of damage, measured in men compared with women after EiMD, thus reinforcing support for the affirmative.

Variances observed among studies might be due to inconsistencies in inducing muscle damage in all subjects (Fredsted et al. 2008; Thompson et al. 1997), the inclusion of women on oral contraception in the female group (Sewright et al. 2008; Dannecker et al. 2012; Stupka et al. 2000), as well as the inherent variability in (Clarkson and Hubal 2001; Carter et al. 2001; Sayers and Clarkson 2001), and ambiguity of (Warren et al. 2006) CK concentration as a marker of damage after EiMD. Furthermore, the comparison of responses to resistance-type exercise between men and women poses some difficultly as the maximal forces are significantly different. In the present study, the gender comparison is complicated by age and body mass differences at baseline. However, the body mass values of the three groups represent typical gender differences in healthy individuals and an attempt to control for body mass across gender may have introduced more complicated confounding variables such as training status. Indeed, the EiMD protocol in the present study was prescribed based on each individual's peak quadriceps strength and each individual acted as their own control by comparing pre- versus post-blood variables. In addition, although men were significantly older than the two female groups in the present study, one might argue that exposure to principle sex hormones is more important than chronological age. Perhaps future studies might consider reporting the onset of puberty as well as age.

The present study employed a maximal-intensity, high-volume eccentric exercise protocol, engaging a large muscle mass. This protocol was designed to promote extensive muscle damage and large increases in circulating CK, while imposing an equal relative mechanical load for men and women. Furthermore, the delineation of normally menstruating women from women on oral contraception permits the true comparison of EiMD between sexes (MEN v WomenNM) without the potential influence of exogenous synthetic hormones. We also measured Mb and FABP concentration after EiMD in order to substantiate earlier evidence of muscle damage (Montgomery et al. 2008; Sorichter et al. 1998). Both Mb and FABP concentrations were greater in MEN compared with WomenNM after EiMD in the present study. Thus, our study provides

strong evidence to suggest that women are less susceptible to EiMD when compared with men.

The role of estradiol in EiMD cannot be clearly explained from sex-comparison studies alone, given other inherent differences between men and women such as muscle mass, familiarity with maximal exercise (Esbjorsson-Liljedahl et al. 1996; Sewright et al. 2008), and resting concentrations of markers of muscle damage (Sorichter et al. 2001). In order to examine large, long-term differences in estradiol, without conceding confounding gender- or age-related differences, experiments comparing normally menstruating women and women on oral contraception have been performed (Thompson et al. 1997; Roth et al. 2001; Carter et al. 2001; Sewright et al. 2008; Savage and Clarkson 2002). Despite reporting mean peak CK concentrations 1.5- to 4.0-fold higher in women using oral contraception compared with normally menstruating women, Clarkson and colleagues routinely report no statistically significant effect of oral contraception on blood markers of EiMD (Thompson et al. 1997; Savage and Clarkson 2002; Sewright et al. 2008). In contrast, the results of the present study and those of Roth et al. (2001) demonstrate that women using oral contraception have higher serum CK concentration after EiMD than normally menstruating women. These findings are supported by the higher concentrations of Mb and FABP observed at 0 and 6 h after EiMD in WomenOC compared with WomenNM, suggesting greater muscle damage in women with lower circulating estradiol.

This is the first study to report CK, Mb, and FABP concentrations for MEN, normally menstruating women, and women on oral contraception after EiMD, concluding that there is a protective role of estradiol in EiMD. However, WomenOC demonstrated lower CK, Mb, and FABP concentrations after EiMD compared with MEN, suggesting that they are less susceptible to EiMD despite lower baseline estradiol concentrations. These findings raise doubt in the notion that estradiol is solely responsible for protection against muscle damage after EiMD. It is possible that previously mentioned differences between men and women are responsible for the observed difference in EiMD between MEN and WomenOC in the present study or that long-term exposure to estradiol in WomenOC before they commenced hormone therapy (i.e., menarche to ~17 years of age) provides residual protection against EiMD. Nonetheless, the relative increase in Mb (MEN, 92 ± 4; WomenOC, 91 ± 5 %) and FABP (MEN, 74 ± 13; WomenOC, 82 ± 15 %) was similar in MEN and WomenOC, whereas the relative increases in WomenNM were less (Mb, 83 ± 5; FABP, 64 ± 17 %) in the present study. Therefore, we suggest that normally menstruating women sustain less muscle damage compared with men and women using oral contraception due to sustained blood concentrations of estradiol.

A reduction in muscle function after EiMD may be the result of initial muscle damage and/or the resultant inflammation. Reduced muscle function is an important consideration for athletes competing on consecutive days during tournament events (Montgomery et al. 2008). Indeed, measurements of muscle strength after EiMD are regarded by some as the most relevant measurement to assess the role of gender and estrogenic status in the response to muscle damage after intense eccentric exercise (Stupka 2009; Warren 2009). Strength measured on the day after strenuous eccentric exercise does not typically reveal any gender- or estradiol-related differences in the degradation of muscle function with EiMD (Savage and Clarkson 2002; Sayers and Clarkson 2001; Sewright et al. 2008). However, there is mounting evidence to suggest that the absence of estradiol results in a prolonged recovery in strength from EiMD (Sayers and Clarkson 2001; Savage and Clarkson 2002). Savage and Clarkson (2002) illustrated group differences in maximal isometric force 48 and 72 h after eccentric exercise of the elbow flexors, concluding that women taking oral contraceptives have prolonged recovery in strength after EiMD when compared to normally menstruating women. In accordance with these findings, the present study observed a similar loss (~10 %) of peak isometric quadriceps torque (i.e., leg strength) 24 h post-EiMD in all groups; however, both the MEN and WomenOC continued to demonstrate significant losses in leg strength to 48 h post-EiMD, with no further loss of leg strength in WomenNM. These findings suggest that the protective effects of estradiol are blunted in women using oral contraception (by replacement with exogenous synthetic estrogen), who consequently display an attenuated rate of recovery from EiMD that is similar to men. Conversely, elevated concentrations of estradiol appear to preserve muscle function after the initial mechanical damage insult by potentially attenuating the secondary phase of muscle damage resulting from a localized inflammatory response (Savage and Clarkson 2002). Although it is recognized that the inflammatory response can be difficult to interpret after EiMD due to its complex and potentially ambiguous nature (Chaffin et al. 2011; Pizza 2009), the measurement of IL-6 and TNF in the present study may have provided further insight into EiMD between genders and among women. Finally, in addition to its protective role, animal studies provide some evidence to suggest that estradiol might augment the regenerative process including satellite cell activation and proliferation (see Enns and Tiidus 2010). Thus, the faster restoration of muscle strength after EiMD in normally menstruating women compared with men and women using oral contraception might be due to enhanced muscle repair in the presence of estradiol concentrations.

Our findings support the notion of an important protective role of estradiol in the muscle damage response to

intense eccentric exercise, and the preservation of muscle function after EiMD in the presence of estradiol. Nevertheless, the mechanisms by which estradiol reduces mechanically induced muscle damage, modulates muscle damage from post-injury inflammatory processes, and/or augments muscle repair remain speculative.

References

Buckley-Bleiler R, Maughan R, Clarkson P, Bleiler T, Whiting P (1989) Serum creatine kinase activity after isometric exercise in premenopausal and postmenopausal women. Exp Aging Res 15:195–198

Carter A, Dobridge J, Hackney A (2001) Influence of estrogen on markers of muscle tissue damage following eccentric exercise. Hum Physiol 27:626–630

Chaffin M, Berg K, Meendering J, Llewellyn T, French J, Davis J (2011) Interleukin-6 and delayed onset muscle soreness do not vary during the menstrual cycle. Res Quart Exerc Sport 82:693–701

Clarkson P, Hubal M (2001) Are women less susceptible to exercise-induced muscle damage? Curr Opin Clin Nutr 4:527–531

Clarkson P, Tremblay I (1988) Exercise-induced muscle damage, repair, and adaptation in humans. J Appl Physiol 65:1–6

Dannecker E, Liu Y, Rector S, Thomas T, Fillingim R, Robinson M (2012) Sex differences in exercise-induced muscle pain and muscle damage. J Pain 13:1242–1249

Dieli-Conwright C, Spektor T, Rice J, Schroeder E (2009) Hormone therapy attenuates exercise-induced skeletal muscle damage in postmenopausal women. J Appl Phsyiol 107:853–858

Enns D, Tiidus P (2010) The influence of estrogen on skeletal muscle: sex matters. Sports Med 40:41–58

Esbjorsson-Liljedahl M, Holm I, Sylven C, Jansson E (1996) Different responses of skeletal muscle following sprint training in men and women. Eur J Appl Physiol 74:375–383

Fredsted A, Clausen T, Overgaard K (2008) Effects of step exercise on muscle damage and muscle Ca^{2+} content in men and women. J Strength Cond Res 22:1136–1146

Garcia-Segura L, Azcoitia I, DonCarlos L (2001) Neuroprotection by estradiol. Prog Neurobiol 63:29–60

Imai Y, Kondoh S, Kouzmenko A, Kato S (2010) Mini review: osteoprotective action of estrogens is mediated by osteoclastic estrogen receptor-alpha. Mol Endocrinol 24:877–885

Joyce S, Sabapathy S, Bulmer A, Minahan C (2014) The effect of prior eccentric exercise on heavy-intensity cycling: the role of gender and oral contraceptives. Eur J Appl Physiol 114:995–1003

Kendall B, Eston R (2002) The effect of menstrual cycle status and oral contraceptive use on exercise-induced muscle damage. J Sports Sci 20:53–54

Mendelsohn M, Karas R (1999) The protective effects of estrogen on the cardiovascular system. N Engl J Med 340:1801–1811

Miles M, Andring J, Pearson S, Gordon L, Kasper C, Depner C, Kidd J (2008) Diurnal variation, response to eccentric exercise, and association of inflammatory mediators with muscle damage variables. J Appl Physiol 104:451–458

Montgomery P, Pyne D, Cox G, Hopkins W, Minahan C, Hunt P (2008) Muscle damage, inflammation and recovery interventions during a 3-day basketball tournament. Eur J Sport Sci 8:241–250

Pizza F (2009) Comments on point: counterpoint: estrogen and sex do/do not influence post-exercise indexes of muscle damage, inflammation, and repair. J Appl Physiol 106:1016

Roth S, Martel G, Ivey F, Lemmer J, Metter E, Hurley B, Rogers M (2000) High-volume, heavy-resistance strength training and muscle damage in young and older women. J Appl Physiol 88:1112–1118

Roth S, Gajdosik R, Ruby B (2001) Effects of circulating estradiol on exercise-induced creatine kinase activity. JEPonline 4:10–17

Savage K, Clarkson P (2002) Oral contraceptive use and exercise-induced muscle damage and recovery. Contraception 66:67–71

Sayers S, Clarkson P (2001) Force recovery after eccentric exercise. Eur J Appl Physiol 84:122–126

Sewright K, Hubal M, Kearns A, Holbrook M, Clarkson P (2008) Sex differences in response to maximal eccentric exercise. Med Sci Sports Exerc 40:242–251

Sorichter S, Mair J, Koller A, Pelsers M, Puschendorf B, Glatz J (1998) Early assessment of exercise induced skeletal muscle injury using plasma fatty acid binding protein. Br J Sports Med 32:121–124

Sorichter S, Mair J, Koller A, Calzolari C, Huonker M, Pau B, Puschendorf B (2001) Release of muscle proteins after downhill running in male and female subjects. Scand J Med Sci Sports 11:28–32

Stupka N (2009) Comments on point: counterpoint: estrogen and sex do/do not influence post-exercise indexes of muscle damage, inflammation, and repair. J Appl Physiol 106:1017–1018

Stupka N, Lowther S, Chorneyko K, Bourgeois JM, Hogben C, Tarnopolsky MA (2000) Gender differences in muscle inflammation after eccentric exercise. J Appl Physiol 89:2325–2332

Thompson H, Hyatt J, De Souza M, Clarkson P (1997) The effects of oral contraceptives on delayed onset muscle soreness following exercise. Contraception 56:59–65

Tidball J (2005) Inflammatory processes in muscle injury and repair. Am J Physiol Regul Integr Comp Physiol 288:R345–R353

Warren G (2009) Comments on point: counterpoint: estrogen and sex do/do not influence post-exercise indexes of muscle damage, inflammation, and repair. J Appl Physiol 106:1018

Warren G, Lowe D, Amstrong R (1999) Measurement tools used in the study of eccentric contraction-induced injury. Sport Med 27:43–59

Warren G, O'Farrell L, Rogers K, Billings K, Sayers S, Clarkson P (2006) CK-MM auto-antibodies: prevalence, immune complexes, and effect on CK clearance. Muscle Nerve 34:335–346