Gender differences in muscle inflammation after eccentric exercise

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Stupka, N., S. Lowther, K. Chorneyko, J. M. Bourgeois, C. Hogben, and M. A. Tarnopolsky. Gender differences in muscle inflammation after eccentric exercise. J Appl Physiol 89: 2325–2332, 2000.—Unaccustomed exercise is followed by delayed-onset muscle soreness and morphological changes in skeletal muscle. Animal studies have demonstrated that women have an attenuated response to muscle damage. We studied the effect of eccentric exercise in untrained male ($n = 8$) and female ($n = 8$) subjects using a unilateral exercise design [exercise (Ex) and control (Con) legs]. Plasma granulocyte counts [before (Pre) and 48 h after exercise (+48h)] and creatine kinase activity [Pre, 24 h after exercise (+24h), +48h, and 6 days after exercise (+6d)] were determined before (Pre) and after (+24h, +48h, +6d) exercise, with biopsies taken from the vastus lateralis of each leg at +48h for determination of muscle damage and/or inflammation. Plasma granulocyte counts increased for men and decreased for women at +48h ($P < 0.05$), and creatine kinase activity increased for both genders at +48h and +6d ($P < 0.01$). There were significantly greater areas of both focal ($P < 0.001$) and extensive ($P < 0.01$) damage in the Ex vs. Con leg for both genders, which was assessed by using toluidine blue staining. The number of leukocyte common antigen-positive cells/mm$^2$ tissue increased with exercise ($P < 0.05$), and men tended to show more in their Ex vs. Con leg compared with women ($P = 0.052$). Men had a greater total (Ex and Con legs) number of bcl-2-positive cells/mm$^2$ tissue vs. women ($P < 0.05$). Atrophic fibers with homogeneous bcl-2-positive staining were seen only in men ($n = 3$). We conclude that muscle damage is similar between genders, yet the inflammatory response is attenuated in women vs. men. Finally, exercise may stimulate the expression of proteins involved in apoptosis in skeletal muscle.

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duced NADP oxidase system and by releasing proteolytic enzymes from their granules. This response is not very specific and may damage neighboring healthy cells. Whereas neutrophil infiltration into skeletal muscle has been studied in men (13) and animal models of both sexes (33), we are aware of only one report using human female subjects (20). With the use of $^{99m}$Tc-white blood cell scanning, an increase in inflammation was observed in women after eccentric exercise (20). Gender comparative studies using direct histological indexes of inflammation have not yet been completed in humans.

For some time, it was believed that differentiated skeletal muscle only underwent necrosis in response to injury (1). However, the finding of apoptotic nuclei and regulatory proteins of apoptosis in skeletal muscle suggests otherwise (7). The antiapoptosis oncoprotein bcl-2 is localized to intracellular sites of oxygen free-radical generation and is thought to have potent antioxidant effects (15). With the use of immunohistochemical techniques and/or Western blotting, bcl-2 has been detected in skeletal muscle isolated from patients with spinal muscular atrophy, peripheral neuropathy (36), and Duchenne muscular dystrophy (30), and in mdx (dystrophin-deficient) mice (29, 31, 38). Others have observed an increase in apoptotic nuclei in normal and mdx mice after the mice performed a night of treadmill running (29, 31). It is not known whether eccentric exercise can stimulate the expression of regulatory proteins, such as bcl-2, or lead to apoptosis in the skeletal muscle of healthy humans.

Because of the paucity of data with respect to gender differences in muscle damage, we proposed to assess changes in several direct and indirect indexes of muscle damage (plasma CK activity, Z-disk disruption, and inflammatory cell infiltration) after acute eccentric exercise in men and women. We hypothesized that women would show an attenuated response to the exercise-induced increases in the aforementioned indexes of muscle damage compared with men. Furthermore, we studied the expression of oncoprotein bcl-2 in human skeletal muscle in response to eccentric exercise-induced muscle damage. To our knowledge, there have not been any reports of the presence of bcl-2 protein in human skeletal muscle after exercise.

MATERIALS AND METHODS

Subjects

Eight healthy, nonsmoking male and eight healthy, nonsmoking female university students volunteered to participate in this study and gave informed, written consent. The study was approved by the McMaster University Human Ethics committee. None of the subjects was engaged in lower body resistance training, and all were involved in some form of moderate cardiovascular training (2–4 times/wk; 30–60 min/session). All of the female subjects were oral contraceptive (OC) users and were tested in the mid-to-late follicular phase of their cycle. Although women taking OCs may have lower serum $17\beta$-estradiol concentrations compared with non-OC users, the use of OCs does not alter indexes of muscle damage after an eccentric stepping protocol (37). Furthermore, the women in the present study still had estradiol concentrations that were several times higher than those of the men (see RESULTS).

Testing Protocol

Before starting the study, subjects were asked to keep 4-day diet records (3 weekdays and 1 weekend day). Subjects were asked to refrain from consuming alcohol on the days that they were recording their diets. The records were analyzed by using computer software (Nutritionist IV, San Bruno, CA). We also completed bioelectric impedance (RJL Systems) measurements in each subject to estimate the percent body fat and fat-free mass (FFM).

On the exercise day, subjects did not consume caffeine after breakfast. They drank 235 ml of defined formula diet (Boost, Mead-Johnson) 2 h before their scheduled exercise bout. Given the observed irregularity in the timing of the dietary intake among the subjects, we provided them with the defined formula diet to ensure that all were in the fed state before the exercise bout. The exercise bout and all subsequent follow-up testing took place in the late afternoon between 1600 and 1900.

The exercised (Ex) and control (Con) legs were randomized in each subject. The eccentric exercise protocol began with the determination of the subject’s concentric, unilateral 1 repetition maximum (RM) for the leg press and leg extension. The concentric 1 RM was determined by having the subjects perform one repetition at each successive load using a weight-training machine (Universal Gym). The load was increased in 1- to 5-kg increments with a 30-s break between each attempt. Each subject was required to be able to lift his or her maximum load in a smooth, controlled motion (16).

The eccentric workload was calculated to be 120% of the concentric 1 RM. The subjects performed three sets of eccentric, unilateral leg press, with 12 repetitions/set, and nine sets of eccentric, unilateral leg extensions, again with 12 repetitions/set. There was a 1-min rest after every set, except after every third set there was a 3-min rest. All of the subjects completed each repetition of every set. They were verbally encouraged to maintain the eccentric contraction for $\sim 3$ s. The absolute and relative (per kg FFM) peak strength for each exercise is presented in Table 1.

Blood samples were collected before (Pre) and 24 h (+24h), 48 h (+48h), and 6 days (+6d) after the eccentric exercise protocol. Blood was collected in untreated tubes for CK analysis at all four times and in EDTA-treated tubes for preexercise estradiol concentration and for complete blood cell count.

<table>
<thead>
<tr>
<th>Table 1. Subject descriptive characteristics</th>
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<tr>
<td><strong>Age, yr</strong></td>
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<td>Age, yr</td>
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<td>Height, cm</td>
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<td>Body fat, %</td>
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<td>FFM</td>
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<td>Knee extension (absolute), kg</td>
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<td>Knee extension (per kg FFM), kg</td>
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<td>Leg press (per kg FFM), kg</td>
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Values are means ± SD; $n = 8$ men and $n = 8$ women. FFM, fat-free mass. Subjects were matched for age; however, the men were $^a$heavier and $^†$leaner ($P < 0.05$). Men had significantly higher peak strength for both the knee extenders and leg press when expressed as an absolute value ($P < 0.01$); however, when expressed relative to FFM, there were no gender differences in relative strength.
counts (CBC) Pre and +48h. The plasma or serum was stored at −20°C (<1 mo) until the time of analysis.

The vastus lateralis of the Ex and Con legs was biopsied at +48h. Biopsies from the vastus lateralis have been used previously to assess muscle damage after eccentric leg-extension exercise (8, 16, 21). The biopsy was divided into two pieces. Muscle allotted for immunohistochemical analysis was frozen in isopentane cooled with liquid nitrogen after being placed on a block with embedding medium (optimum cutting temperature compound) and stored in a −50°C freezer. A second small piece (~2 mm³) was immediately placed into chilled (4°C) 2% glutaraldehyde solution buffered with 0.1% sodium cacodylate.

**Analyses**

**CBC.** Fresh, whole blood samples collected in EDTA tubes were analyzed at the McMaster University Medical Center hematology laboratory for CBC.

**CK.** Serum was assayed spectrophotometrically (wavelength = 6340 nm) for CK by using a commercially available kit (no. DG147-UV, Sigma Diagnostics, Columbus, OH). The intra- and interassay coefficient of variation was <10%.

**Plasma estradiol concentration.** Plasma estradiol concentration was assayed by using a commercial radioimmunoassay kit (no. TKE25, Coat-A-Count).

**Toluidine blue-stained microscopy.** The glutaraldehyde-fixed muscle was postfixed in 1% osmium tetroxide, dehydrated in graded alcohol, and embedded in plastic resin (Spurr’s). Longitudinal, semithin sections (~1 μm in thickness) were cut with a glass knife and stained with toluidine blue for light microscopic evaluation. An average of 61 fibers (range 13–100) per sample were counted. Focal damage encompassed no more than two adjacent Z disks, and extensive damage encompassed more than two adjacent Z disks (23). We confirmed that the areas reported as Z-disk streaming by toluidine blue did represent Z-disk streaming by cutting ultrathin sections from the same blocks, staining them with uranyl acetate and lead acetate, and examining them using a JEOL 1200 EX transmission electron microscope (n = 3 blocks). Results are expressed as the number of focal or extensive areas of Z-disk streaming per fiber. Samples were blindly assessed by a pathologist with specialized training in electron microscopy (K. Chorneyko). The entire data set was analyzed and then reanalyzed blindly 10 days later to determine test-retest reliability. This demonstrated a Pearson r value of 0.987 (2.1% difference between trials) for the focal damage and 0.997 (1.1% difference between trials) for the extensive damage. An example of a muscle fiber stained with toluidine blue is provided in Fig. 1.

**Immunohistochemistry.** Frozen muscle was serially cross-sectioned to 7-μm thickness on a cryostat. A negative control serial section was included in all analyses. The slides were dried overnight and then fixed in cold acetone (~20°C in cryostat) for 15 min. The slides were blocked with 1% goat serum for 15 min. The primary antibody was diluted 1:50 in goat serum on the positive slide and allowed to incubate overnight. To the negative slide only goat serum was added. The secondary goat anti-mouse antibody (no. 95–6543-B, Zymed, San Francisco, CA) incubation lasted 15 min. Peroxidase was then added to the slides for 15 min, and the AEC kit (no. 00–2007, Zymed) was used for color development. The primary antibodies used were monoclonal mouse anti-human bcl-2 (no. M0887, Dako Diagnostics) and monoclonal mouse anti-human leukocyte common antigen (LCA) (no. M0701, Dako Diagnostics).

The number of LCA and bcl-2-positive cells was counted in the total cross-sectional area and expressed as number of positive cell/mm² of muscle. The slides were counted by three independent and blinded individuals and then averaged. Final cell counts for each sample slide were accepted when all of the evaluators had values within two cells of each other; otherwise the slide was recounted. Test-retest correlation r values for the bcl-2-positive slides were 0.96, and between-observer r values were 0.89. For the LCA cells, the test-retest correlation r values were 0.98, and the between-observer r values were 0.97. Examples of the bcl-2 and LCA-positive inflammatory cells and a muscle fiber staining homogeneously for bcl-2 are presented in Fig. 2.

**Statistics**

Diet records and subject descriptive data were analyzed by using an independent-group t-test. The CK, ultrastructural damage, and cellular infiltration data were analyzed by using

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**Fig. 1.** Toluidine blue stained muscle fiber showing extensive (arrows) Z-disk streaming.
ANOVA with factors of time (3 levels) or Ex or Con leg (2 levels) and gender (2 levels). Significant results were further analyzed by using the Newman-Keuls post hoc test (Statistica, Statsoft, Tulsa, OK). The level of significance was $P < 0.05$. All data in texts and Tables 1–3 are presented as means ± SD.

RESULTS

Subject Characteristics

See Table 1 for subject age, height, weight, and body composition. Men were leaner and weighed more than the women ($P < 0.05$).

Plasma Estradiol Concentrations

Women had significantly higher plasma estradiol concentration compared with men ($60.25 ± 10.78$ vs. $7.55 ± 8.03$ pg/ml; $P < 0.01$). Seven of the women used triphasic OC, and one used a monophasic OC. The daily dose of ethinyl estradiol ingested during the follicular phase was $0.0300–0.0400$ mg (average $0.0333 ± 0.0035$ mg).

Diet Records: Antioxidant Intake

The absolute energy and antioxidant (vitamin C, vitamin E) intake was significantly lower for women.
than men ($P < 0.01$; Table 2). When expressed per kilogram of body weight, only energy intake was significantly different between the men and women ($P < 0.05$; Table 2).

**CBC**

There was no difference in baseline circulating granulocyte concentrations. At $+48h$ the granulocyte concentrations increased for men (Pre = $4.31 \pm 1.18$ vs. $+48h = 5.33 \pm 1.14 \times 10^9/l$) and did not change for women (Pre = $4.13 \pm 1.17$ vs. $+48h = 3.29 \pm 1.79 \times 10^9/l$) ($P < 0.05$ for interaction; gender $\times$ time).

**CK**

For serum CK activity, there was a main effect for time ($P < 0.01$). CK activity increased significantly over baseline at $+48h$ and $+6d$; the $+48h$ and $+6d$ plasma CK values were statistically not different from each other. An overall trend toward a gender difference was noted, with women having lower values compared with men [not significant (NS), $P = 0.14$, 2-tailed test; Fig. 3]. Sample size calculations ($\alpha = 0.05$; $\beta = 0.20$) revealed that the present study was underpowered by three subjects per group with respect to CK analysis (main effect).

**Toluidine Blue Sections**

There was no difference in the amount of focal or extensive damage between men and women. There was significantly more focal and extensive damage in the Ex leg than in the Con leg ($P < 0.05$; Fig. 4).

**Immunohistochemistry**

Bcl-2-positive inflammatory cells and fibers. There was a main effect for gender, with men having a greater total number of bcl-2-positive inflammatory cells/mm$^2$ of tissue than women ($P < 0.05$). There was no main effect for exercise (Table 3). Atrophic muscle fibers that stained intensely and uniformly for bcl-2 were seen in three men in the Ex leg (Fig. 2). These

Table 2. Absolute and relative daily energy and vitamin C and vitamin E intake

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<tr>
<th></th>
<th>Women</th>
<th>Men</th>
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<tr>
<td></td>
<td>Absolute* (per kg body weight)</td>
<td>Relative* (per kg body weight)</td>
</tr>
<tr>
<td>Dietary intake, cal</td>
<td>1,437 ± 257</td>
<td>23.0 ± 5.5†</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>121.3 ± 94.1</td>
<td>1.9 ± 1.6</td>
</tr>
<tr>
<td>Vitamin E, mg</td>
<td>5.2 ± 2.2</td>
<td>0.08 ± 0.04</td>
</tr>
<tr>
<td>a-Tocopherol, mg</td>
<td>2.0 ± 0.9</td>
<td>0.03 ± 0.05</td>
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<tr>
<td></td>
<td>2,571 ± 332</td>
<td>34.9 ± 5.2†</td>
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<tr>
<td></td>
<td>203.5 ± 129.0</td>
<td>2.8 ± 1.8</td>
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<tr>
<td></td>
<td>8.5 ± 3.6</td>
<td>0.12 ± 0.06</td>
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<tr>
<td></td>
<td>3.3 ± 1.2</td>
<td>0.44 ± 0.95</td>
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Values are means ± SD; $n = 8$ men and $n = 8$ women. *Average daily caloric, vitamin C, total vitamin E, and a-tocopherol intake was significantly greater in men than in women ($P < 0.05$). †Relative energy intake was greater in men compared with women ($P < 0.05$).
fibers were seen in one of ~250 fibers in two of the men and in two of ~200 fibers in the other men. LCA-positive inflammatory cells. Exercise significantly increased the number of LCA-positive cells/mm² of tissue ($P < 0.05$). There was a very strong trend ($P = 0.052$) for an interaction between gender and exercise, with the number of LCA-positive cells/mm² of tissue tending to be greater in the Ex vs. Con leg of men compared with women (Table 3). A sample size calculation revealed that the addition of one more subject per group would have yielded a significant difference between the genders in LCA-positive cells.

**DISCUSSION**

Muscle damage in response to strenuous exercise has been well documented in humans and animal models. Exercise-induced muscle damage is characterized by delayed-onset muscle soreness, a decrease in force generation, increased plasma CK activity, myofibrillar disruptions (i.e., Z-disk streaming), and inflammatory cell infiltration. Sex differences in exercise-induced muscle damage have been reported in the animal literature (9). We found that eccentric exercise resulted in an increase in the number of areas with focal and extensive myofibrillar damage and that this was similar in men and women. Despite similar myofibrillar disruption, men showed a higher number of bcl-2-positive inflammatory cells in muscle compared with women ($P < 0.05$), and the number of LCA-positive inflammatory cells tended ($P = 0.052$) to increase more after exercise in men compared with women.

Plasma CK activity increased significantly over baseline values by +48h and remained elevated at +6d. There was a trend for women to show an attenuated rise in plasma CK activity compared with men (NS, $P = 0.14$). Achieving statistical significance for an interaction of gender with time when measuring plasma CK activity is difficult, because of high inter-subject variability in CK response. The high inter-subject variance in the CK response may be related to the variability in exercise-induced muscle damage (27) and/or differences in membrane permeability. We noted great inter-subject variability in the extent of focal and extensive Z-disk streaming. However, with the use of histological techniques, a significant relationship between CK response and the extent of muscle damage was not demonstrated in this study or in the literature, suggesting that, although morphologically there is a similar amount of damage, it does not directly correlate with CK release into the plasma (42).

Plasma CK activity at rest and during training has been reported to be lower in women compared with men (34). However, others have not found this gender difference after an acute bout of exercise (10). The present findings suggest the potential for a gender-specific response; however, further work to delineate the mechanism(s) is required. Animal data have shown that the female sex hormone 17β-estradiol attenuates plasma CK activity rise after a 2-h treadmill run in male rodents (5). An attenuation of exercise-induced CK rise in women may be related to the antioxidant properties of 17β-estradiol (35). One study did find that both plasma CK activity and plasma malondialdehyde (a marker of lipid peroxidation) concentrations were lower in exercising female compared with male rowers (11). Furthermore, gender differences in dietary antioxidant intake cannot explain gender differences in any indicator of damage reported, for the women had a lower absolute and similar relative (per kg body weight) intake of major antioxidant vitamins.

It could be argued that women do not work as hard as men and, consequently, will have less total myofibrillar derangement. However, men and women experienced a similar increase ($P < 0.05$) in focal and extensive Z-disk streaming in the Ex leg. If this is a true reflection of damage, these results indicate that women were as susceptible to Z-disk streaming as men when they exercise at the same relative intensity (i.e., expressed relative to each individual’s 1 RM/kg FFM). These results support direct electron micrographic measurements of increased Z-disk streaming demonstrated immediately after and 48 h after eccentric exercise (14). Others found that the extent of discontinuous dystrophin and desmin staining and alterations in actin and fibronectin staining were greater in male vs. female rodents after a bout of downhill running (17). This latter study measured cytoskeletal proteins by immunohistochemistry, which may not directly correlate with Z-disk streaming per se (17). Furthermore, the downhill-running protocol used in rodent studies (17) elicits a combined eccentric and aerobic stress, which together may be more damaging to the cytoskeleton.

Exercise-induced muscle damage stimulates an acute-phase inflammatory response, which includes infiltration of skeletal muscle by neutrophils and macrophages (13). Overall, there was significantly less cellular infiltrate in women than men. The total number (Ex and Con leg) of bcl-2-positive cells/mm² of tissue was greater in men than women, and the number of LCA-positive cells/mm² of tissue was greater in the Ex vs. Con leg of men compared with women ($P = 0.052$). These findings support previous work done in rodents, where female or estradiol-supplemented male rats had fewer myofibers invaded by acid phosphatase-positive leukocytes (33), less focal inflammation, less fiber ne-

Table 3. Number of bcl-2- and LCA-positive cells/mm² of tissue

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Leg Condition</th>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td>Bcl-2</td>
<td>Con</td>
<td>0.08 ± 0.12</td>
<td>1.26 ± 2.19^*</td>
</tr>
<tr>
<td></td>
<td>Ex</td>
<td>0.27 ± 0.41</td>
<td>1.18 ± 0.90^*</td>
</tr>
<tr>
<td>LCA</td>
<td>Con</td>
<td>0.41 ± 0.40</td>
<td>1.10 ± 1.60</td>
</tr>
<tr>
<td></td>
<td>Ex †</td>
<td>0.74 ± 0.59</td>
<td>2.70 ± 2.18‡</td>
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</table>

Values are means ± SD; $n = 8$ men and $n = 8$ women. LCA, leukocyte common antigen; Con, control; Ex, exercise. †Total number of bcl-2-positive cells/mm² of tissue was greater in men than in women ($P < 0.05$). ‡Increase in LCA-positive cells tended to be greater in men than in women (interaction, $P = 0.052$).
Muscle damage after eccentric exercise

crosis, lower β-glucoronidase (17), and myeloperoxidase activity (41). The increase in LCA- and not bcl-2-positive cells in the Ex leg appears to be discordant; however, the LCA stain will stain T and B cells strongly and macrophages and neutrophils weakly and variably, whereas the bcl-2 stains only those cells expressing the bcl-2 protein. Given that leukocytes are removed from skeletal muscle by apoptosis and not via reentry into the plasma (39), the bcl-2 stain provides an index of leukocytes expressing bcl-2 and not total leukocytes. The higher concentrations in men at rest and postexercise may imply a higher overall turnover of inflammatory cells in skeletal muscle compared with that in women. Given the lack of specificity in the LCA stain, it will be important for future studies to examine specific antigenic determinants for the subpopulations of leukocytes.

The concentration of circulating granulocytes increased only in men +48h, as previously reported in the literature (13). There was no change in women, which is similar to previously reported results (24). Exercise increases IL-1β and IL-6 cytokine expression in men, and these mediate changes in circulating granulocyte populations (6). There are gender differences in cytokine concentrations at rest (19), and such differences may be observed postexercise. Future studies need to look at gender differences in exercise-induced alterations in cytokines and adhesion molecules to better understand lymphocyte trafficking.

In three of the male subjects, atrophic muscle fibers were identified in the postexercise sample, which stained intensely for bcl-2 oncoprotein. This is the first report to demonstrate an increase in bcl-2 in the skeletal muscle of healthy individuals in response to a physical stressor. Bcl-2 has been detected in differentiated muscle fibers in spinal muscular atrophy and Duchenne muscular dystrophy patients, which lends credibility to the hypothesis that skeletal muscle can express proteins involved in apoptosis and, therefore, may be capable of undergoing programmed cell death (31, 36). Future studies will be required to determine whether physiological stressors can alter the expression of other proteins involved in apoptosis (i.e., Bax, Apaf-1, bcl-x, and caspase-3). In addition, it will be important to examine further the observation that the bcl-2-positive cells were only seen in some of the male subjects. Although the relatively small sample size is an issue, this could yield important information on gender-related responses to muscle damage.

These results show that gender differences in the response to eccentric exercise-induced muscle damage are not due to differences in sarcomere damage but are due to the subsequent inflammatory response. Women showed less muscle inflammation compared with men despite the same amount of Z-disk streaming. The mediating role of estradiol in the etiology of exercise-induced muscle damage needs to be investigated further in humans. Finally, a novel finding of the present study was that human skeletal muscle can express a protein involved in apoptosis (bcl-2) after an exercise stimulus.

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REFERENCES


