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Pregnancy Represses Induction of Efflux Transporters in Livers of Type I Diabetic Mice

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Post-Menopausal Effects of Resistance Training on Muscle Damage and Mitochondria

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Abstract

The purpose of this study was to measure the effects of a 12 month, progressive resistance training intervention on muscle morphology and strength gains in postmenopausal women. Skeletal muscle biopsies were obtained from the vastus lateralis of five (N=5) independent community dwelling women, (mean age: 75.6 ± 4.28 yrs; mean height: 163 ± 5.34 cm; mean weight: 72 ± 17.5 kg) before, six months and 12 months after progressive resistance training. Muscle strength (1-RM) was measured at the same time points. After six months of training morphological analysis revealed evidence of increased proteolysis and tissue repair, and rudimentary fiber development. The percent of Z bands with mild Z band disruption increased from 43.9% at baseline to 66.7% after six months of training ($p < 0.01$). Mitochondrial volume also increased (% of mitochondria = 0.86% at baseline, 1.19% at six months and 1.04% at 12 months, $p<0.05$) and there was a shift to larger sized mitochondria. The training did not result in statistically significant increases in muscle leg strength ($p<0.18$). It appears that mild Z band disruption acts as a precursor for increased protein synthesis and stimulates an increase in mitochondrial mass. Therefore, while a progressive resistance training program in this population did not increase muscle strength, it did demonstrate clinical applications that lend support to the importance of resistance training in older adults.

Keywords

aging; exercise training; strength; muscle adaptation

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INTRODUCTION

There are many conspicuous effects of aging on skeletal muscle including a reduction in cross-sectional fiber area and an associated myofilament thinning (30). Fiber changes are accompanied by an infiltration of both fat and connective tissue and are attributed, at least in part, to decreases in estrogen production (19). Skeletal muscle also functions as a transmission site for oxidative stress through inflammatory cytokines that serve as mediators of muscle wasting (22).

Various pathological conditions increase the risk of metabolic dysregulation. Exercise has been found to attenuate metabolic abnormalities via improvements in muscle tissue mass and mitochondrial bioenergetics. Moderate endurance exercise and progressive resistance training, have been shown to be beneficial in patients with various pathologies (3, 14, 21).

During menopause, endurance and resistance exercise have been shown to be effective in improving mitochondrial bioenergetics, metabolic dysregulation, and lean body mass (5). Mitochondrial bioenergetic effects include enhanced fat oxidation, accelerated turnover of stored triglycerides, improvements in insulin sensitivity and increased protein synthesis (16, 29). Resistance training has been shown to increase mass and strength in frail elders (6). It has been demonstrated that resistance training induces fiber damage accompanied by increases in strength, suggesting that muscle damage is a prerequisite to increasing strength in muscle of older adults and the frail elderly (25). There are no studies examining the long-term effects of moderate resistance training on skeletal muscle morphology in postmenopausal women. The aim of this study was to measure the effects of a 12 month, progressive resistance training intervention on muscle strength and morphology in postmenopausal women. We hypothesized that markers of fiber disarray and Z-band disruption would increase due to a training-induced increase in muscle repair. Similarly, we anticipated that long-term training would result in increased muscle strength and a shift toward larger mitochondria.

METHODS

Experimental Approach to the Problem

Post-menopausal women were recruited to participate in this study. Physiological measures of cardiovascular health, muscle strength, and vastus lateralis muscle biopsies were taken baseline and after six and 12 months of participating in a progressive resistance training program. Histological analysis was performed on muscle biopsy samples to determine the effects of the progressive resistance training program on skeletal muscle remodeling and adaptation.

Subjects

Five (N=5) independent community dwelling women, (mean age: 75.6 ± 4.28 yrs; height: 163 ± 5.34 cm; weight: 72 ± 17.5 kg) participated in this study. Subjects taking any medications thought to interfere with exercise adaptation were excluded from this study (e.g. statins, diuretics). Skeletal muscle biopsies were taken from the vastus lateralis at baseline and after six and 12 months of participating in a progressive resistance training program. Resistance training was performed at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRC) at Tufts University, Boston, Massachusetts. Subjects were supervised during resistance training sessions. The study was performed in accordance with the Tufts University Human Investigation Review Committee. All subjects gave written informed consent prior to participation.

Physiologic Measures

VO_2 peak was measured on a motorized treadmill (Woodway, Waukesha, WI) by a graded exercise tolerance test with continuous analysis of expired gases using a face mask (Hans Rudolph, Kansas City, MO). Expired gases were analyzed by a Beckman LB-2 CO_2 analyzer (Sensormedics, Schiller Park, IL) and an Applied Electrochemistry S-3A O_2 analyzer (Applied Electrochemistry, Inc., Sunnyvale, CA). Analyzers were interfaced with a Zenith-PC minicomputer programmed for a 0.5-minute output of minute ventilation, CO_2 production, VO_2 peak, and respiratory exchange ratio.

The treadmill speed was 0.1–3.0 mph, based on the habitual gait speed of each participant. The test was set initially at 80% of habitual gait speed, and then adjusted as needed. The first two minutes of the test were performed at 0% grade and the grade was increased by 2% every minute until the subject reached maximal effort. The highest oxygen consumption value during maximal effort was recorded as VO_2 peak.

Dynamic strength was measured as the bilateral one repetition maximum (1-RM) obtained on the chest press, leg press, upper back, and hip abduction computer-interfaced pneumatic resistance machines (Keiser Sports Health Equipment Inc., Fresno, CA). The 1-RM was defined as the maximum load that could be moved one time only throughout the full range of motion using proper form. Beginning with minimal resistance, each new weight was lifted once until no more resistance could be applied. Incremental resistance was tailored for the subject to achieve the 1-RM in approximately 8 to 10 lifts. Baseline 1RM testing was repeated once by the same tester within the first week of the initial test. The best of the two baseline measures was used as the 1-RM.

Exercise training intervention

Training involved three, one hour sessions each week for 12 months. Exercise began with five minutes of static stretching followed by 15 minutes on a NuStep (Ann Abor, MI) or Stairmaster (Vancouver, WA), at 60 ± 5% of maximum heart rate reserve or at a rating of perceived exertion of 8 – 9 (20-point Borg scale). Following a brief walk and rehydration, the women engaged the first set of eight repetitions at 85% of 1-RM using Keiser equipment (Keiser Sports Health Equipment Inc., Fresno, CA). Exercises included chest press, leg press, upper back, and hip abduction. These muscle groups were chosen because of their importance in functional activities. Subjects rested for one minute between resistance exercises. A new baseline was established every two weeks using the results of the 1-RM strength test.

Muscle Biopsies

A muscle biopsy was taken from the lateral portion of the vastus lateralis (~ 20 cm above the knee) at baseline and after six and 12 months of training. Prior to the biopsy, the site was treated with 3–5cc of 1% lidocaine. A six mm incision was made in the skin and fascia to expose the muscle. A 5 mm biopsy needle (Popper and Sons, New Hyde Park, NY) was inserted into the incision and advanced through the fascia into the muscle with the cutting window closed. With suction applied, the cutting window was opened and closed three times, resulting in a sample of ~ 75 mg. Samples were cleared of blood and connective tissue and stored at −80 °C. Microscopy samples were fixed in 1% glutaraldehyde, 4% paraformaldehyde and embedded in LR white resin.

Muscle examination

Vastus lateralis biopsies embedded in LR white resin were sectioned longitudinally on an ultramicrotome, stained, and analyzed. A Phillips EM301 transmission electron microscope (Hillsboro, OR) interfaced with a computer equipped with an image-grabbing board (Data

Translation, Marlboro, MA) was used. NIH Image software captured, stored, and calculated mitochondrial area. An investigator, blind to the condition and time point of each sample, analyzed ten fibers per subject using a 256 isotropic semicircular test point system. These fibers were used for stereological measurements of the percent of Z bands that were disrupted (%ZBD) (7).

Muscle fibers were also studied for degree of Z band disruption using the quantitative Z band disruption scale of Friden (9, 10). Each disrupted Z band was scored from "0" to "4"; with "0" being no damage and "4" being the most extensive. Mitochondrial size distributions were calculated using mitochondrial area with each mitochondrion being placed into a size category: Size 1 ($0.010u^2$– $0.030u^2$), Size 2 ($0.031\ u^2$– $0.051\ u^2$), Size 3 ($0.052\ u^2$– $0.072\ u^2$) and Size 4 ($0.073\ u^2$– $0.093\ u^2$). Area measurements were taken for ~500 mitochondria (mean = 506; range = 364 – 697) at baseline, six and 12 months using established procedures (24, 25).

Statistical Analysis

Group means and standard deviations were determined for the morphometric measures and the statistics used included a repeated measures ANOVA and Pearson-Product Moment correlations. $P < 0.05$ was considered significant.

RESULTS

Patients

Peak oxygen consumption at baseline was 19.1 ± 1.89 ml/kg/min and remained within 1.4 ml/kg/min of baseline at six and 12 months. The training did not result in statistically significant increases in muscle leg strength ($p<0.18$, Figure 1).

Muscle Examination

Light microscopy of the baseline samples revealed fiber angulation suggestive of fiber atrophy. The presence of intrafasicular wedging, nuclear chains, satellite cell formation, and rudimentary fiber development was apparent after six and 12 months of training. Electron microscopy showed Z band disruption, fiber atrophy, sarcolemmal blebbing, retraction and separation from the endomysium, myoblast formation, aggregates of subsarcolemmal mitochondria, and alterations in the extracellular matrix. The electron micrographs in Figure 2 are skeletal muscle biopsies taken from the same subject at baseline, six, and 12 months of resistance training. Mild Z band disruption (Z) can be seen at six months. Figure 3 illustrates the percent of Z bands disrupted (%ZBD), a positive indicator of muscle overload (8). The magnitude of Z band disruption after six months of training was significant ($p< 0.05$) and was categorized as mild (Figure 3; mean score = 0.899; modified Friden scale).

Mean mitochondrial volume density increased 28% after six months of training (Figure 4). When size distribution was used to classify mitochondria, increases in mitochondrial density were accompanied by an increase in larger sized mitochondria and a decrease in smaller sized mitochondria (Figure 5).

DISCUSSION

Sarcopenia is associated with atrophy, metabolic dysregulation (5) and a loss of strength and cross sectional area (4, 11, 13). These changes are due in part to fiber atrophy, a loss of fast twitch fibers, and increased muscle fat infiltration. Clinical studies of independently living postmenopausal women report that one-third are overweight (19). These increases in whole-body fat mass are accompanied by decrements in physical activity, physical performance,

and a higher frequency of disability. Exercise training can serve as a countermeasure to these physiological changes. Properly prescribed exercise can result in increased muscle strength, mass and bone density and reduced incidence of falls and fractures in postmenopausal women (26). We sought to determine the level of exercise needed to induce morphological changes that would render muscle metabolically fit while at the same time minimizing risk of injury due to excessive muscle damage and increasing strength gains.

Prior to training, we documented myofibrillar areas with sarcomeres in register despite scattered focal areas of fiber atrophy (characterized by mild Z band disruption). These may be morphological characteristics of the skeletal muscle of sedentary postmenopausal women. At six and 12 months of resistance training, more extensive areas of fiber atrophy and Z band disruption became evident. Roth et al. (23) quantified Z band damage in trained and control legs of young (20–30 years old) and older men (65 – 75 years old) after 9 weeks of heavy resistance strength training using isokinetic loading. They reported increases in muscle damage from 0–3% at baseline and 7 and 6% of the fibers in the treated vastus lateralis following training in the young and older men, respectively, with no differences between the old and young subjects. The authors note that the specificity of the workload must be considered, citing an earlier study by Manfredi et al. (20) that demonstrated greater damage in older adults when eccentric loads designed to create muscle damage was employed. The postmenopausal women who participated in this study experienced widespread, but mild, Z band disruption. These changes are suggestive of muscle tissue remodeling.

Although leg strength increased in all subjects, mean increases were not statistically significant (Figure 1). Indeed, in light of the small sample size, there is the potential that this is a type II error. However, based on the modest strength gains in each subject that appear to consistently level off after six months, it is possible that morphological changes are necessary for strength changes to occur in this aged population. These changes take place over a much slower time course than neurological changes that contribute to strength gains during the first few months of training. For example, sarcomere disruption observed at six months may indicate that Z band disruption is a morphological feature and a prerequisite to tissue remodeling. The relationship between muscle function and morphological change is supported by data from a previous study in which 10 weeks of resistance training in older adults (>70 years) was accompanied by an increase in leg strength and percent Z bands damaged (25).

Alternatively, the possibility exists that our strength training intervention was not rigorous enough for this population to experience strength gains. The machine-based exercises may not have provided an adequate stimulus for skeletal muscle adaptation. Similarly, participants only completed one bout of exercise for each muscle group. Additional sets of 8–10 repetitions may have promoted increased strength gains in this population. This is important to consider in the design of future studies.

This research group has previously shown evidence of a relationship between muscle function and morphological change. In a case-study using immunogold staining of quadriceps muscle IGF-1 receptors in elderly subjects, we determined that there was an increased receptor density with resistance training and these receptor changes were in concert with a heightened Z band disruption and appearance of central nuclei (27). This study also provided evidence that muscle remodeling due to exercise can reverse the down regulation of the IGF-1 system and that this may be an important mechanism for muscle anabolism in the older adult.

Microscopic analysis revealed satellite cell formation, nuclear chains and fiber atrophy with myoblast development, aggregates of subsarcolemmal mitochondria and the maintenance of mitochondrial integrity at six and 12 months of training. In a similar study, Roth et al. (23) examined skeletal muscle satellite cell morphology in young and older men and women before and after heavy resistance strength training and reported greater satellite cells in the vastus lateralis of older men and women. Johnston et al. (17) suggest that the popular mitochondrial theory of aging that hypothesizes that the path leading to cell senescence includes damage to mitochondria can be counterbalanced in part with resistance training. Balakrishnan et al. (1) also used resistance training as a countermeasure toward increasing mitochondrial biogenesis. These data suggest that resistance training is effective in enhancing mitochondrial mass in older adults and is an important area for further investigation.

We found increases in mitochondrial density and mitochondrial size after six months of resistance training, an important countermeasure in view of previous studies of middle-aged and older adults reporting signs of atrophy associated with smaller mitochondrial size and a trend toward mitochondrial degeneration (2). Others indicate that mitochondrial ultrastructural integrity can be maintained with aging and that this is a favorable adaptation to exercise (15). Increases in skeletal muscle mitochondrial mass have been reported to accompany enhanced aerobic capacity (12, 18). Our laboratory found several weeks of combined resistance and aerobic exercise increased muscle mitochondrial area and the percentage of larger sized mitochondria in heart failure patients (24). Others reported an increase in mitochondrial sizes in type I and II fibers in young women after 18 weeks of resistance training (28). Importantly, this increase in mitochondrial mass per unit of muscle fiber provides the tissue with an environment that is conducive toward enhanced fatty acid oxidation and glucose flux (5, 28).

Results of this study indicate a long-term resistance training program has distinct advantages for older women. It provides positive changes that can retard the development of sarcopenia. The specific morphological changes become evident after six months of resistance training and they appear to be a prerequisite to muscle strength increases. Although no measurements of substrate oxidation were taken, an enhancement of mitochondrial mass and muscle strength implies improvements in bioenergetic mitochondrial capacity in the postmenopausal muscle.

PRACTICAL APPLICATIONS

This paper provides morphological data to support what is occurring within skeletal muscle tissue in older adults who participate in a progressive resistance training program.

These data are important as if one were to only focus on strength gains, progressive resistance training does not appear to be beneficial in older adults (based on a lack of significance in leg strength over the 12 month intervention). However, morphological data indicate that the muscle is undergoing favorable metabolic and structural adaptations that are essential in increasing muscle mass, overall physical function, and possibly, oxidative capacity. Therefore, while a progressive resistance training program in this population did not demonstrate statistically significant increases in muscle strength, it did demonstrate clinical applications that lend support to the importance of resistance training in older adults.

Acknowledgments

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Abbreviations

IGF	insulin growth factor
vol%ZBD	volume % Z-band disruption
ZBD	% disrupted Z bands relative to total Z bands

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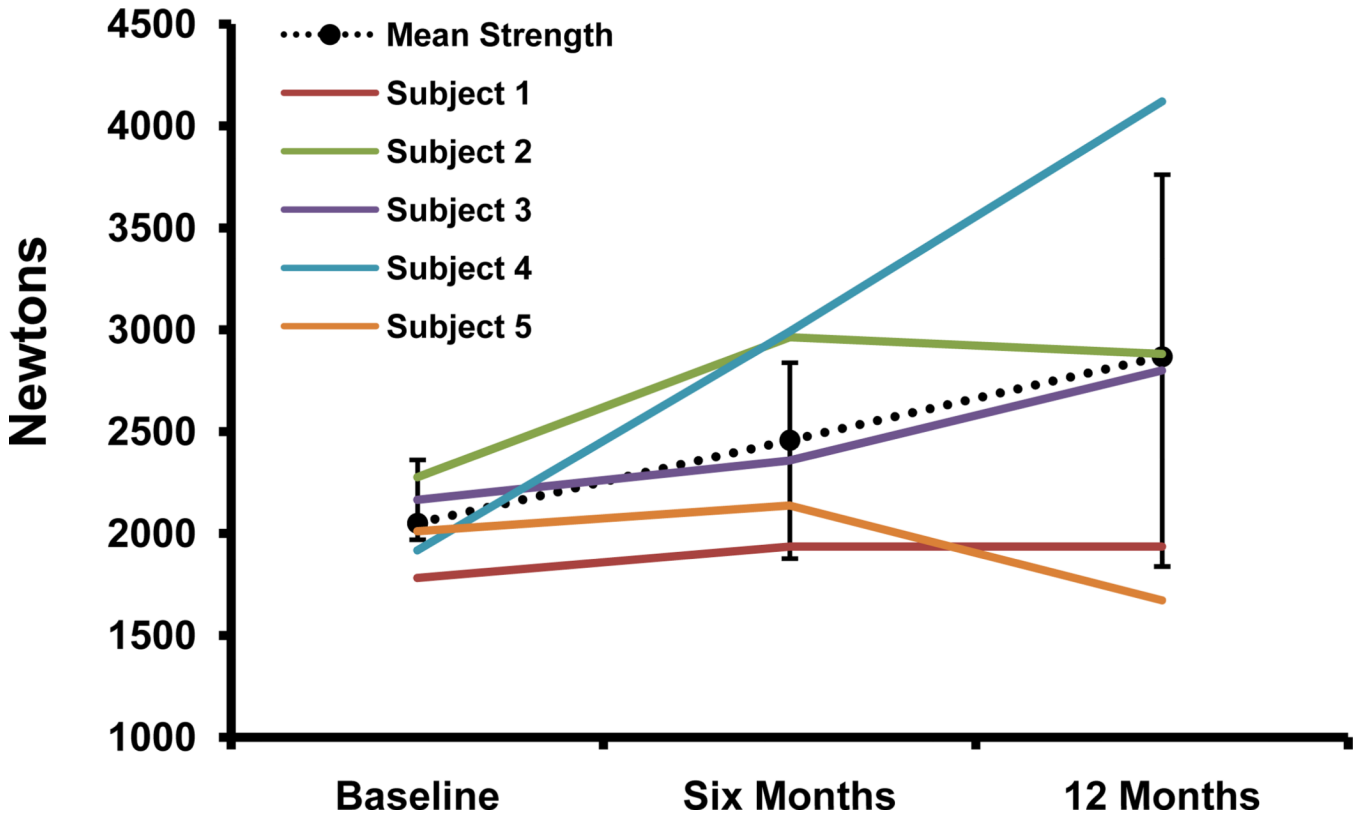

Figure 1.
Leg strength of the vastus lateralis at baseline and six and 12 months into the progressive resistance training. Solid lines illustrate individual subject strength scores (in Newtons). The dashed line represents mean strength data ± SD.

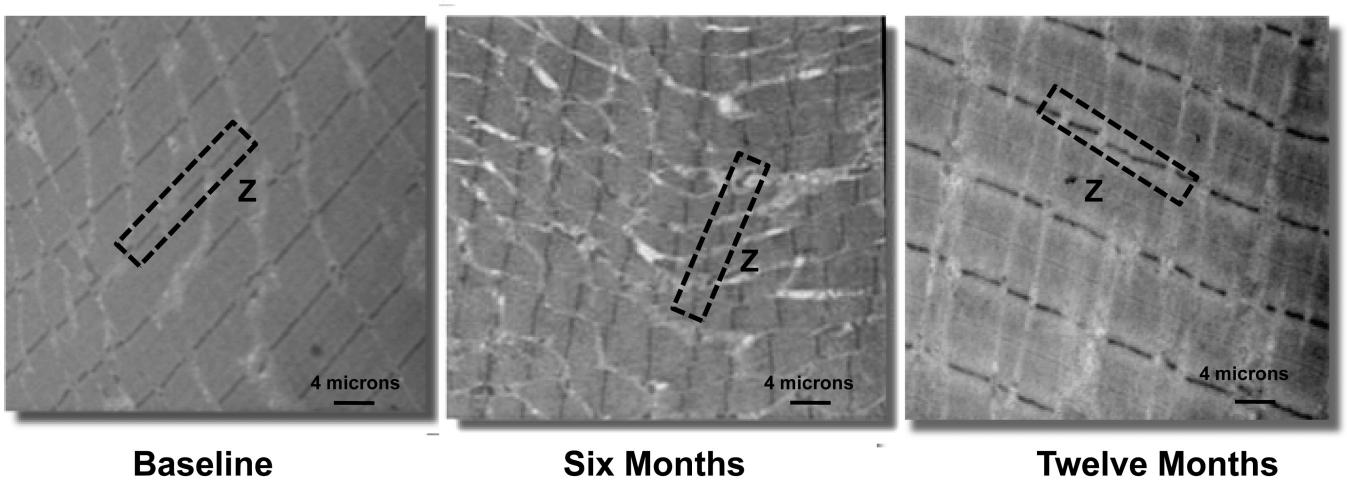

Figure 2.
Electron Micrograph (EM) of skeletal muscle biopsies taken from the same subject at baseline and six and 12 months into the progressive resistance training. Note the greater degree of Z band disruption after six months of exercise training.

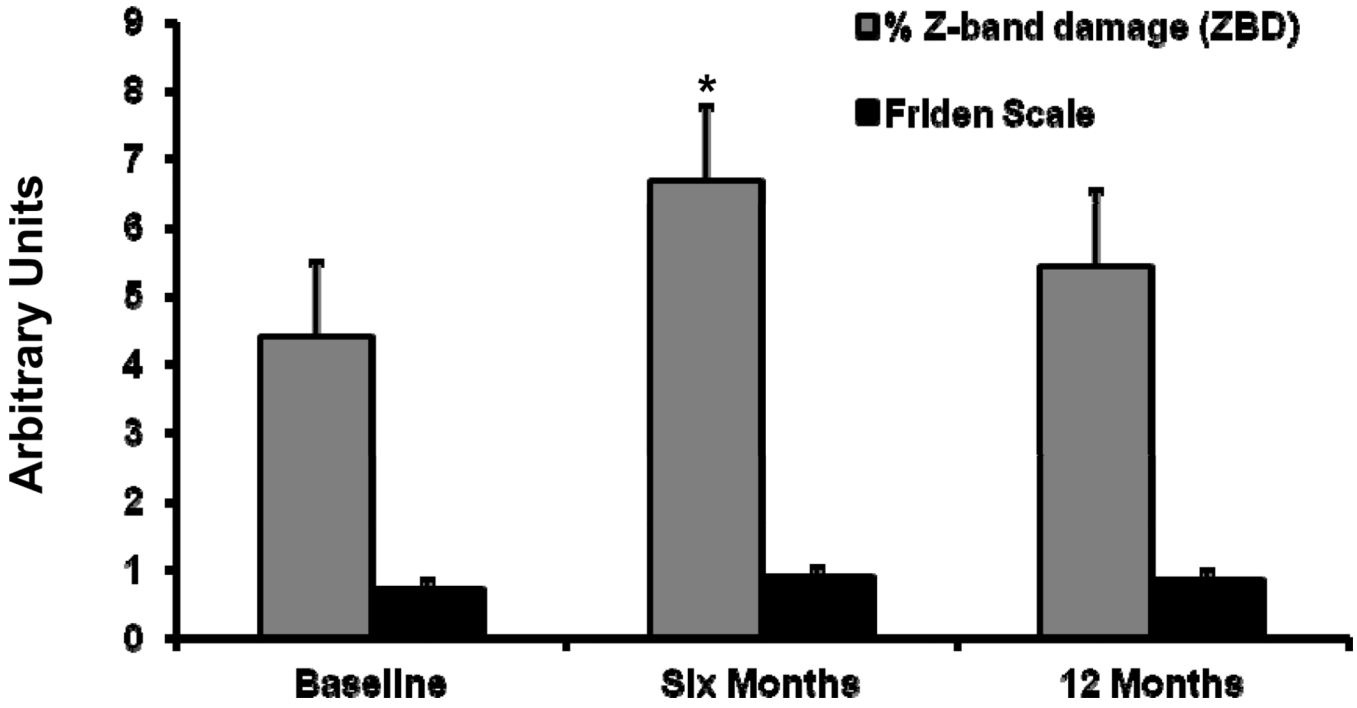

Figure 3.
Effect of training on markers of muscle Z band disruption (ZBD = Volume percent Z-band disruption [$1 \times 10^{-}$]). Z band disruption significantly increased at six months ($p < 0.05$). Volume percent data are means ± SD. * = $p<0.05$

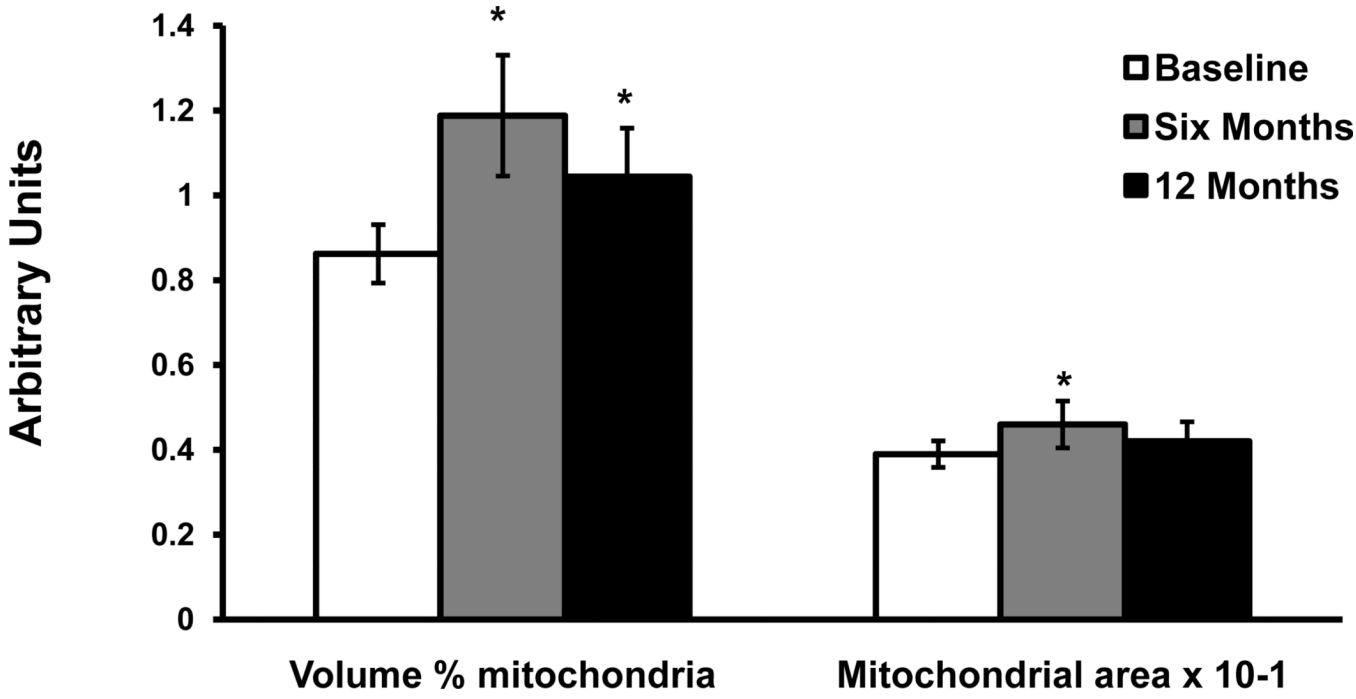

Figure 4.
Effect of exercise on mitochondrial volume density and area ($u^2 \times 10^{-1}$). Data are means ± SD. * = $p<0.05$

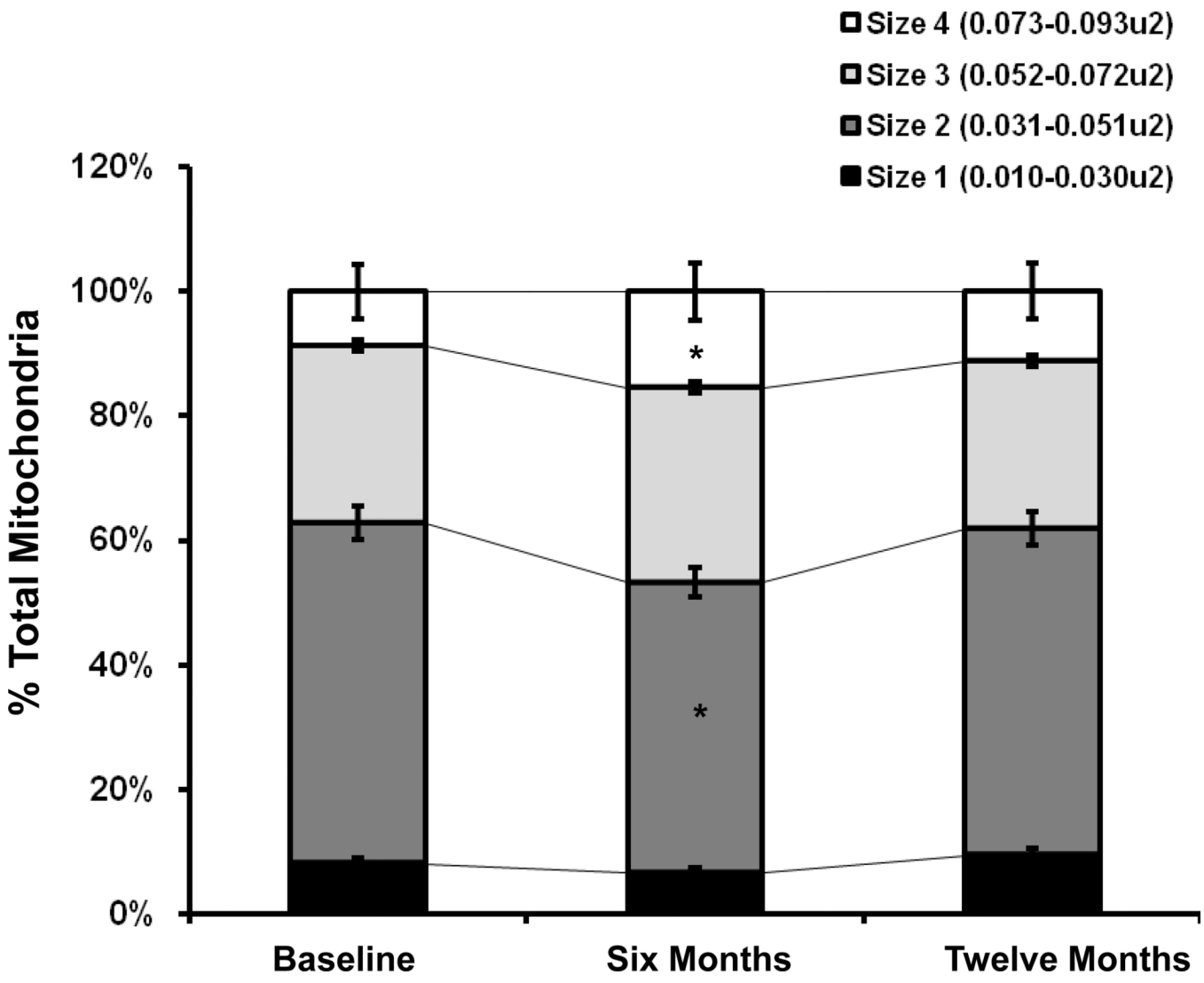

Figure 5.
Mitochondrial area size distributions at baseline, six and twelve months following training. At six months of training there was a significant increase in the percent of size 4 mitochondria ($p < 0.01$) and a significant decrease in the percent of size 2 mitochondria ($p < 0.05$) compared to baseline. Data are means ±SD. * = $p<0.05$