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Gender Differences in Resistance-Training-Induced Myofiber Hypertrophy Among Older Adults

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We tested the hypothesis that older men (n = 9, 69 ± 2 years) would experience greater resistance-training-induced myofiber hypertrophy than older women (n = 5, 66 ± 1 years) following knee extensor training 3 days per week at 65–80% of one-repetition maximum for 26 weeks. Vastus lateralis biopsies were analyzed for myofiber areas, myosin heavy chain isoform distribution, and levels of mRNA for insulin-like growth factor 1 (IGF-1), IGFR1, and myogenin. Gender × Training interactions ($p < .05$) indicate greater myofiber hypertrophy for all three primary fiber types (I, IIa, IIx) and enhanced one-repetition maximum strength gain in men compared with women ($p < .05$). Covarying for serum IGF-1, dehydroepiandrosterone sulfate, or each muscle mRNA did not negate these interactions. In both genders, type IIx myofiber area distribution and myosin heavy chain type IIx distribution decreased with a concomitant increase in type IIa myofiber area distribution ($p < .05$). In summary, gender differences in load-induced myofiber hypertrophy among older adults cannot be explained by levels of circulating IGF-1 or dehydroepiandrosterone sulfate, or by expression of the myogenic transcripts examined.

PARTIAL reversal of age-associated sarcopenia with progressive resistance training (PRT) has been demonstrated in several recent investigations (1–4). Marked gains in strength (5,6), myofiber cross-sectional area (CSA) (7–9), whole muscle area (10,11), rates of muscle protein synthesis (12), and functional abilities (6,13) have been noted after PRT programs varying in duration from 8 to 52 weeks. These data provide encouraging evidence that older individuals, including the oldest old (14,15), are physiologically capable of adapting to mechanical overload with the same relative vigor as younger subjects. To date, however, comparisons of gender-specific adaptations to PRT in the older population have been extremely limited (16–18). In these investigations, greater absolute (17) and both absolute and relative (16) increases in knee extensor muscle volume (determined by magnetic resonance imaging) have been reported in men compared with women after 9 weeks of PRT.

In their studies of single myofiber contractile function before and after 12 weeks of PRT, Trappe and associates (18) found greater improvements in shortening velocity and absolute power production for both myosin heavy chain (MHC) type I (MHCI) and MHC type IIa (MHCIIa) myofibers in older men compared with older women. No significant gender differences in myofiber hypertrophy were found; however, when genders were analyzed separately (18,19), MHCIIa myofiber diameter significantly increased (13%) in men but not in women. MHCI fiber diameter increased similarly in both genders. Results of studies performed singularly with older men or women suggest a gender difference in the hypertrophic response. For example, hypertrophy of types I and II myofibers has been demonstrated in older men after just 9 weeks (27%) (7) of PRT, with greater increases after 12 weeks (I = 34%, II = 28%) (20) and 15 weeks (I = 38%, II = 52%) (21). In contrast, older women may be more resistant to myofiber hypertrophy in response to PRT. Type II CSA has been shown to increase 20% after 12 weeks of PRT in older women with no change in type I fiber size (22), whereas a full year of PRT has resulted in only modest increases in type I CSA (10–28%) and no significant changes in type II CSA (23). Only Hakkinen and colleagues (24) have found hypertrophy in all three primary myofiber types (22–36%) following 21 weeks of PRT in older women (there were no men). This study differed from the others in that the resistance training program was periodized across 21 weeks with higher volume loading during the final 8 weeks. Whether this influenced the results is not known.

If gender influences the hypertrophic response to PRT among older adults, determining its etiology would be difficult because the multifactorial mechanisms of load-induced myofiber hypertrophy are not fully understood. At least one factor that appears to play an important role is load-sensitive insulin-like growth factor 1 (IGF-1), which is upregulated in overloaded muscles and is associated with an increased expression of myogenic regulatory factors (MRFs) such as myogenin (25). We recently reported increased IGF-1 mRNA expression following a single resistance exercise bout in young adults (26). The family of MRFs including myogenin, MyoD, Myf-5, and MRF4

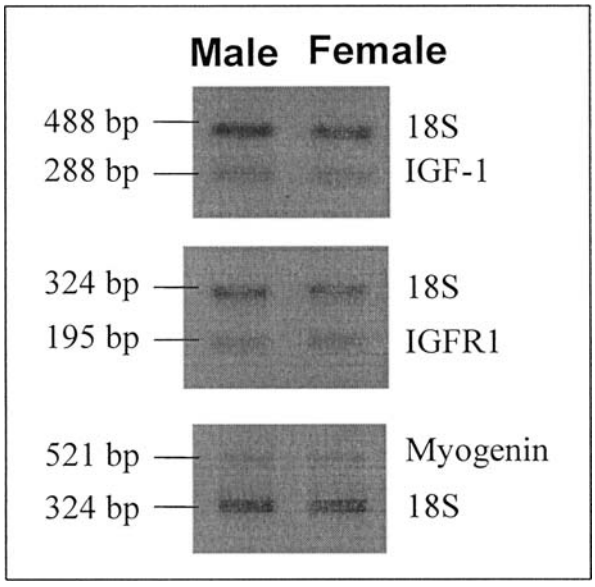

Figure 1. Polymerase chain reaction products from male and female pre-training samples separated on a 2% agarose gel by electrophoresis and stained with ethidium bromide. Product size in base pairs (bp) is shown to the left. Laser scanning densitometry revealed no gender or training effects. IGF-1 = insulin-like growth factor 1; IGFR1 = IGF receptor type 1.

are muscle-specific transcription factors that control muscle cell differentiation and regulate the expression of several muscle genes. The MRFs are therefore important during myofiber development and during satellite cell-mediated growth, repair, and regeneration in developed muscle. Myogenin appears to be preferentially expressed in type I myofibers, whereas MyoD is mainly expressed in type II myofibers (27–29). Enhanced myogenin expression has recently been shown during resistance-training-induced myofiber hypertrophy in young adults (30). Upon stimulation by loading (31) or myotoxicity (32), the expected increase in myogenin expression is blunted or delayed in older muscles compared with younger muscles. On the basis of these data, any possible gender differences in PRT-induced hypertrophy among older adults may perhaps be associated with gender differences in muscle IGF-1 or myogenin expression.

Evidence indicates that declining muscle mass with age is associated with declining levels of circulating hormones (33,34), including testosterone, IGF-1, and dehydroepiandrosterone sulfate (DHEA-S). Whether endogenous levels of circulating hormones play an important role in load-induced hypertrophy of localized muscles remains questionable. Limited evidence, however, indicates testosterone levels are related to the magnitude of PRT-induced hypertrophy (24) and strength gain (5,35). Low levels of testosterone (as found in hypogonadal men and in women) may therefore impede PRT-induced hypertrophy and strength gain. Testosterone treatment in untrained hypogonadal men has been shown to increase muscle protein synthesis and muscle IGF-1 mRNA expression (36), suggesting that circulating testosterone modulates muscle growth by means of activation of locally-expressed growth factors. Transgenic mice that overexpress IGF-1 in muscle have been shown to be partially protected against age-related atrophy (37). If muscle IGF-1 mRNA expression is influenced by testosterone, one might expect higher levels of IGF-1 expression in men than in women consequent to the approximately 35- to 40-fold gender difference in total testosterone concentration.

Decreased distribution of MHC type IIx (MHCIIx) is a common finding following resistance training (38,39) and has been reported recently in older adults (40). This shift is typically coupled with a concomitant increase in primarily MHCIIa distribution with little to no change in MHCI. Although data are limited, gender does not appear to substantially influence the MHC shift (38,40). For example, Sharman and colleagues (40) found similar decreases in MHCIIx after 24 weeks of PRT in older men (12% to 4%) and older women (17% to 7%).

The purposes of this study were thus to test the influence of gender in older adults on PRT-induced changes in myofiber size and MHC distribution. We hypothesized that older men would experience greater absolute myofiber hypertrophy (CSA in square micrometers), whereas relative myofiber hypertrophy (percent change) and MHC shifts would be similar in older men and women following PRT. Contrary to this hypothesis, our results indicate substantial gender differences in both the absolute and relative hypertrophic response. We therefore covaried for circulating IGF-1, DHEA-S, and mRNA levels of muscle IGF-1, IGFR1, and myogenin to determine if these circulating anabolic factors or muscle myogenic factors could account for the gender differences in myofiber growth. In the present study, they do not.

Methods

Subjects

Nine men and 5 women, 61 to 77 years old, participated in a 26-week PRT program. These 14 subjects represent the subset of participants from a larger study (41) who consented to muscle biopsy. All subjects passed a medical screening exam, including a diagnostic stress test. Subjects were free of any musculoskeletal or other disorders that might have affected their ability to complete training and testing for the study. All subjects were nonsmokers and weight stable (defined as within 1% body weight during the 4 weeks prior to training). None of the subjects had resistance training experience. All of the women were postmenopausal, and 2 of 5 women were on estrogen replacement therapy. None of the subjects were being treated with exogenous testosterone. Institutional Review Board-approved informed consent was obtained prior to participation in the study. Subjects were evaluated before and after the training period.

Progressive Resistance Training

Subjects exercised 3 times per week for 26 weeks. Each session was supervised by exercise physiology laboratory personnel, and average adherence rate of the subjects was over 90%. The whole body training program has been described in detail elsewhere (41). Each exercise session

began with a 5-minute warm-up on either a bicycle ergometer or treadmill at a low intensity, followed by static stretches. For the knee extensors, two resistance exercises were performed—knee extensions and leg presses or squats. Other exercises included elbow flexion, elbow extension, wide grip pull-down, seated row, chest press, overhead press, back extension, bent knee sit-up, and knee flexion. With the exception of sit-ups (two sets of 15–25 repetitions), subjects completed two sets of each exercise with 2-minute rest periods between sets and a target of 10 repetitions. Resistance was increased when subjects completed two sets of 10 repetitions at 80% of the most recent one-repetition maximum (1RM). Although all subjects performed knee extensions, men and women were randomly assigned to perform the squat or leg press such that no gender bias occurred. In this subset of 14 participants, 8 of the subjects (5 men and 3 women) performed squats and 6 of the subjects (4 men and 2 women) performed leg presses. After two familiarization sessions, subjects were tested for knee extension, squat, and leg press 1RM by using methods we have previously described (41). 1RM testing was repeated every 25 days throughout training, and the results were used in combination with daily training logs to incorporate progression in the program.

Body Composition

Total body fat mass and fat-free mass were determined by densitometry, using air displacement plethysmography (Bod Pod version 1.69, Life Measurement Instruments, Concord, CA) to estimate body density as we have previously described (41). Each subject wore the same fitted swimwear for body volume measurements before and after training. The methods used have been detailed previously and validated in our laboratory against hydrostatic weighing, dual-energy x-ray absorptiometry, and the four-compartment model (41–43).

Muscle Biopsy Procedure

Samples were removed under local anesthetic (1% lidocaine) from m. vastus lateralis of the left leg by percutaneous needle biopsy, using a 5-mm Bergstrom biopsy needle under suction as previously described (44). The posttraining biopsy was taken approximately 2 cm proximal to the pretraining incision site. Samples for histochemistry were mounted on cork with Tissue-Tek O.C.T. mounting medium (Miles Inc., Elkhart, IN), oriented cross-sectionally with a dissecting microscope, and quickly frozen in liquid-nitrogen-cooled isopentane. A portion of each sample was snap frozen in liquid nitrogen (used for mRNA analysis). All samples were stored at −80°C until analysis.

The muscle biopsy procedure was added to the menu of tests for a larger study (41) as the project began. As a result, subjects consented to muscle biopsy as a voluntary additional procedure yielding a subset of participants. Because of scheduling difficulties with numerous required tests after training, biopsies after training were collected an average of 4 days after the final training bout but the precise time point was not consistent (range 2–7 days). Although this variability should not have affected myofiber size measurements, we certainly recognize the limitation this poses on interpreting our posttraining muscle gene expression results.

Table 1. Descriptive Characteristics and Changes in Body Composition

	Men (n = 9)		Women (n = 5)	
Characteristic	Pretraining	Posttraining	Pretraining	Posttraining
Age (y)	68.7 ± 1.6		66.2 ± 1.4	
Height (cm)*	177.9 ± 2.0		165.6 ± 1.5	
Weight (kg)	76.5 ± 4.1	77.0 ± 4.3	69.4 ± 5.7	68.8 ± 5.5
FFM (kg)*,†	58.3 ± 2.4	60.9 ± 2.4	39.8 ± 1.0	41.5 ± 0.8
% Body fat*,†	23.3 ± 1.9	20.4 ± 2.1	40.9 ± 5.3	37.8 ± 5.7

Notes: Values are mean ± *SE*; FFM = fat-free mass.
*Main gender effect, $p < .05$; †main training effect, $p < .05$.

Myofiber Histochemistry

Pretraining and posttraining samples within subjects were analyzed concurrently to standardize staining conditions. Muscle blocks were sectioned (10 μm) in a cryostat microtome cooled to −22°C. Myofibers were classified as type I, IIa, or IIx by metachromatic dye–adenosine triphosphatase histochemistry, using methods described previously (45), and they were modified in our laboratory (46). Metachromasia was revealed by 0.1% Toluidine Blue after acid preincubation (pH 4.4) and incubation in 0.15% adenosine triphosphate disodium salt (pH 9.4). Type I myofibers stained dark turquoise blue, whereas type II myofibers spanned a color spectrum from pale (type IIa) to violet (type IIx). Microscope (Olympus BX-40, Melville, NY) views were captured by a color digital video camera (Olympus DP-11). Myofiber CSA and area distribution by type were determined by using Mocha (Jandel Scientific, San Rafael, CA) image analysis software, as we have detailed elsewhere (47).

MHC Distribution

To determine the distribution of MHC isoforms (I, IIa, IIx), 10 microtome sections (20 μm) were homogenized and the myofibrillar protein fraction was isolated and assayed for total protein as we have previously described (48). Two micrograms of myofibrillar protein (0.2 μg/μl) were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE; 4% stacking, and 8% separating gels with a 50:1 acrylamide:bis ratio) by using a minigel system (BioRad MiniProtean III, Hercules, CA). Run conditions were 150 V for 20 hours. Following SDS-PAGE and Coomassie blue staining, MHC isoforms were identified according to their apparent molecular masses (migration rate: I > IIa > IIx) and analyzed by densitometry. We have previously confirmed band order by Western analysis (48). Pretraining and posttraining samples within subjects were run in adjacent lanes to standardize run conditions.

mRNA Analyses

Tissue samples were analyzed for IGF-1, IGFR1, and myogenin mRNAs. Total RNA was extracted from frozen muscle samples by using the TRI Reagent (Molecular Research Center, Cincinnati, OH) according to the company's

Table 2. Myofiber Size and MHC Distribution

Parameter	Men		Women	
	Pretraining	Posttraining	Pretraining	Posttraining
Type I CSA (μm^2)*,†,‡	4901 ± 362	6320 ± 359	3690 ± 256	3932 ± 288
Type IIa CSA (μm^2)*,†,‡	4652 ± 226	6565 ± 233	3265 ± 354	3454 ± 188
Type IIx CSA (μm^2)*,†,‡	3959 ± 310	5659 ± 454	2840 ± 378	2984 ± 177
Mean CSA (μm^2)*,†,‡	4666 ± 304	6327 ± 208	3373 ± 259	3612 ± 204
Type I area (%)	55.1 ± 6.5	44.5 ± 5.3	52.6 ± 3.6	52.0 ± 2.8
Type IIa area (%)†	28.1 ± 4.7	44.5 ± 4.8	29.8 ± 3.2	35.3 ± 3.6
Type IIx area (%)†	16.8 ± 3.3	11.0 ± 3.1	17.6 ± 2.5	12.7 ± 1.9
MHCI (%)	42.0 ± 4.8	41.3 ± 5.9	41.5 ± 4.5	44.3 ± 5.5
MHCIIa (%)	40.5 ± 3.7	45.3 ± 4.0	38.1 ± 2.8	39.2 ± 4.8
MHCIIx (%)†	17.5 ± 1.9	13.4 ± 2.1	20.4 ± 3.8	16.5 ± 4.1

Notes: Values are mean ± *SE*. CSA = cross-sectional area; MHC = myosin heavy chain.

*Main gender effect, $p < .05$; †main training effect, $p < .05$; ‡Gender × Training interaction, $p < .05$.

protocol. Extracted RNA was precipitated from the aqueous phase with isopropanol and, after being washed with ethanol, dried and suspended in a known volume of nuclease free water. The RNA concentration was determined by optical density at 260 nm (using an OD_{260} unit equivalent to 40 μg/ml), and samples were stored frozen at −80°C to be used subsequently in determining specific mRNA expression, using relative reverse transcription-polymerase chain reaction (RT-PCR) procedures.

RT.—One microgram of total RNA was reverse transcribed for each muscle sample, using the SuperScript II from Gibco BRL (Carlsbad, CA) and a mix of oligo dT and random primers (200 ng/reaction) in a 20-μl total reaction volume at 45°C for 50 minutes, according to the provided protocol. At the end of the RT reaction, the tubes were heated at 85°C for 5 minutes to stop the reaction and were stored frozen at −80°C until used in the PCR reactions for specific mRNA analyses.

PCR.—A relative RT-PCR method using 18S as internal standard (Ambion, Austin, TX) was applied to study the mRNA expression of IGF-1, IGFR1, and myogenin. In each reaction, 18S ribosomal RNA was coamplified with the target cDNA (mRNA) to serve as an internal standard and to allow correction for differences in starting amounts of total RNA. For the 18S we used either the Classic or the Alternate 18S Internal Standards (Ambion), which yield 488 base pairs, or 324 base pairs, respectively. The 18S competimers–primers were mixed at an optimized ratio specific for each target mRNA, and this ratio was 10:1 for IGF-1, 12:1 for IGF-1 receptor, and 13:1 for myogenin. For each primer set, PCR conditions were optimized so that both the target mRNA and 18S product yields were in the linear range of the semilog plot when the yield is expressed as a function of the number of cycles. For each specific target mRNA, the RT and PCR reactions were carried out under identical conditions, using the same reagents premix for all the samples to be compared in the study. One microliter of each RT reaction was used for the PCR amplification. The PCR reactions were carried out in the presence of 2mM $MgCl_2$, using standard PCR buffer (Gibco), 0.2mM dNTP, 1 μM specific primer set, 0.5 μM 18S primer–competimer mix and 0.75 unit of DNA Taq polymerase (Gibco) in 25 μl total volume. Primers for IGF-1 were as follows: 5′ sense; GTGCTGCTTTTGTGATTTCTT and 3′ antisense; CAATACATCTCCAGCCTCCTTA. Primers for IGFR1 were 5′ sense; ACAAAGGGCCATCGTTCATCC and 3′ antisense; GCACAGCAGGGGCAGTCG. Primers for myogenin were 5′ sense; GCTTCGAACCACCAGGCTACG and 3′ antisense; AGGTGAGGGAGTGCAGGTTGTG. Amplifications were carried out in a Stratagene Robocycler with an initial denaturing step of 3 minutes at 96°C, followed by 25 cycles of 1 minute at 96°C, 1 minute at 58°C, 1 minute at 72°C, and a final step of 3 minutes at 72°C. PCR products were separated on 2% agarose gel by electrophoresis and stained with ethidium bromide, and signal quantification was conducted by laser scanning densitometry. With the use of this method, each specific mRNA signal was normalized to its corresponding 18S. Representative results are shown in Figure 1.

Serum Hormone Concentrations

Total IGF-1, testosterone, and DHEA-S were determined in fasted morning serum samples withdrawn before and after 26 weeks of PRT. Total IGF-1 was determined by immunoradiometric assay (Diagnostic Systems Laboratories, Webster, TX), using ^{125}I (intra-assay coefficient of variation [CV] = 5.73%). The range of the standard curve for this assay is 8–1000 ng/ml. Total testosterone (TT) was determined by solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA), using ^{125}I (intra-assay CV = 7.97%). The lower limit of detectability (90% bound) for this assay is 10.4 ng/dL. DHEA-S was determined by solid-phase radioimmunoassay (Diagnostic Products Corporation), using ^{125}I (intra-assay CV = 6.86%). The lower limit of detectability (90% bound) for this assay is 3.9 ng/dL. Samples within subjects for a given hormone were assayed in random order during a single run.

Data Analysis

Data are reported as mean ± *SE*. Gender differences in descriptive variables were tested by independent *t* tests. For all variables measured before and after training, main training and gender effects and Gender × Training interactions were tested by 2 × 2 repeated measures analysis of variance (ANOVA). For each ANOVA model with a significant Gender × Training interaction, analysis of covariance (ANCOVA) models were tested post hoc by using (as covariate) each of several factors potentially influential in muscle growth, namely pretraining, average, and before-to-after change scores in serum IGF-1 or DHEA-S, or muscle mRNAs for IGF-1, IGFR1, or myogenin. Serum TT could not be used as a covariate as it was not a continuous variable. Zero-order correlations were tested between before-to-after changes in myofiber size or strength and changes in serum hormones or muscle

myogenic transcripts. Correlations were also tested among the serum and muscle factors measured.

For each exercise, 1RM was evaluated every 25 days. As the knee extension exercise is a single joint movement recruiting the quadriceps (site of muscle biopsy) independent of the hip extensors, we evaluated knee extension 1RM results in serial fashion for this report. Eight serial 1RM evaluations were performed over the duration of the training period. We tested gender and training effects by 2×8 repeated measures ANOVA. As a way to adjust for gender differences in absolute strength, 1RM data were analyzed as the ratio of 1RM at a given time point to the corresponding pretraining value. Time-point-specific strength increases within gender were evaluated post hoc by using the least squares difference (LSD) test. Statistical significance was set at $p < .05$ for all tests.

Results

Descriptive characteristics are shown in Table 1. Gender comparisons revealed no significant differences in age or bodyweight. Men were taller with more fat-free mass (FFM) and a lower body fat percentage ($p < .05$). For both men and women, the whole-body PRT program resulted in increased FFM (men 2.6 kg; women 1.7 kg) and reduced body fat (men −2.9%; women −3.1%; $p < .05$), whereas body weight was unchanged. No Gender × Training interaction was noted for FFM or body fat percentage.

Myofiber CSA results are shown in Table 2. To assess the presence of type II myofiber atrophy, we compared pretraining data from these older subjects to myofiber sizes we previously published in premenopausal women (47) and young men (44). In these older subjects, the preferential type II myofiber atrophy typically associated with sarcopenia of aging was found in pretraining data from both genders, and it was most notable in type IIx myofibers. In each gender group, type IIx myofibers were significantly smaller than type I myofibers ($p < .05$), whereas the sizes of types I and IIa myofibers were not significantly different. In contrast, the sizes of type I and type II myofibers were not significantly different in the younger subjects from our prior work.

As indicated by significant gender effects and significant Gender × Training interactions, myofibers of all three types (I, IIa, IIx) were larger in men and responded to PRT with greater hypertrophy ($p < .05$). The influence of gender on the hypertrophic response was marked, as relative increases in size for myofiber types I, IIa, and IIx were 29%, 41%, and 43% in men and 7%, 6%, and 5% in women. Clearly, the significant training effect in the ANOVA model for each fiber type was driven by the men. Analyses of *relative* hypertrophy between genders (*t* tests on percent change scores) indicated greater relative hypertrophy among men for type IIa myofibers only.

Changes in myofiber type area and MHC distribution are presented in Table 2. No gender differences or Gender × Training interactions were found for any of these variables. Both type IIx myofiber area distribution and MHCIIx distribution decreased with PRT in men and women ($p < .05$). The area distribution of type IIa myofibers increased concomitantly in both gender groups ($p < .05$).

Table 3. Muscle mRNA Levels and Serum Hormone Concentrations

	Men		Women	
Parameter	Pretraining	Posttraining	Pretraining	Posttraining
Muscle mRNA levels				
IGF-1/18S (OD ratio)	0.33 ± 0.04	0.35 ± 0.05	0.33 ± 0.06	0.61 ± 0.21
IGFR1/18S (OD ratio)‡	0.52 ± 0.03	0.61 ± 0.06	0.69 ± 0.10	0.63 ± 0.07
Myogenin/18S (OD ratio)	0.31 ± 0.03	0.35 ± 0.03	0.35 ± 0.05	0.38 ± 0.17
Serum hormones				
IGF-1 (ng ml^{-1})	176.9 ± 16.3	191.2 ± 14.4	147.7 ± 24.2	152.6 ± 28.1
Testosterone (ng dl^{-1})*	550.8 ± 21.6	498.7 ± 44.1	16.6 ± 1.9	15.4 ± 0.6
DHEA-S (ng dl^{-1})	111.3 ± 20.3	108.5 ± 24.8	48.6 ± 8.7	43.4 ± 8.0

Notes: Values are mean ± *SE*. OD = optical density; IGF-1 = insulin-like growth factor 1; IGFR1 = IGF receptor type 1; DHEA-S = dehydroepiandrosterone sulfate.

*Main gender effect, $p < .05$; ‡Gender × Training interaction, $p < .05$.

Table 3 displays pretraining and posttraining levels of selected serum hormones and muscle gene transcripts thought to be potentially important in muscle growth. Among the serum hormones, only the obvious gender difference in testosterone was significant ($p < .001$), whereas a gender difference in DHEA-S levels approached significance ($p = .09$). Training did not affect any of the hormone levels. Muscle expression of IGF-1 and myogenin mRNA did not differ by gender and was not influenced by training (although an acute response to PRT cannot be ruled out because we obtained biopsies 4 days after PRT on average). A Gender × Training interaction was noted for expression of IGFR1, which slightly rose (17%) and fell (9%) in men and women, respectively.

Zero-order correlations were tested among serum hormones and muscle gene transcript levels (not including TT, as it was not a continuous variable). Serum levels of IGF-1 and DHEA-S were not related before or after training. No significant relationships were noted between serum IGF-1 and muscle IGF-1 or IGFR1 mRNAs before or after training. Muscle transcript levels of IGF-1 and IGFR1 were not correlated. IGF-1 and myogenin transcript levels were not related before or after PRT.

The substantial variability in myofiber hypertrophy between genders could not be explained by any of the serum or muscle factors, as no significant correlations were found between before–after difference scores in myofiber size and before–after difference scores in serum IGF-1, DHEA-S, or muscle IGF-1, IGFR1, or myogenin mRNA. Further, Gender × Training interactions for myofiber hypertrophy remained in post hoc ANCOVA analyses covarying with before–after difference scores for each serum hormone or muscle gene transcript. The sizes of myofiber types I, IIa, and IIx prior to training did not correlate with pretraining levels of any of these factors. Overall, these findings indicate the gender differences in initial fiber size and in PRT-induced myofiber hypertrophy

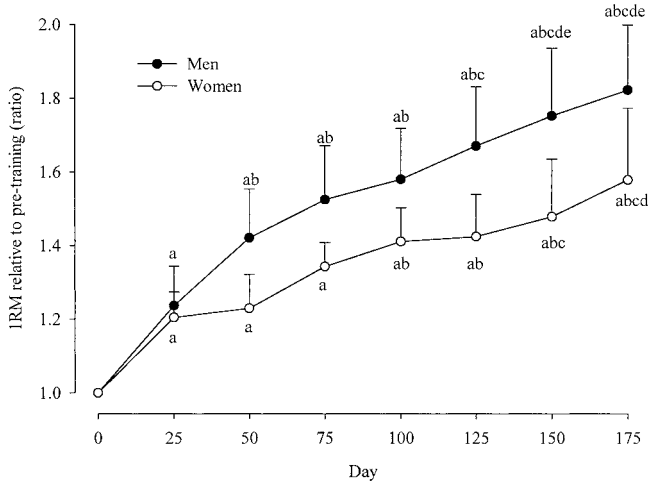

Figure 2. Knee extension one-repetition maximum (1RM) results across time for men and women relative to pretraining 1RM. For each time point, 1RM–pretraining 1RM was computed; a–e: significantly different from a, pretraining (Day 0); b, Day 25; c, Day 50; d, Day 75; e, Day 100. $p < .05$.

could not be attributed to varying levels of circulating IGF-1 or DHEA-S, nor to expression of the myogenic gene transcripts studied.

Results of serial 1RM knee extension tests are shown in Figure 2. Both genders increased strength substantially. However, an analysis of only before-to-after PRT gains in strength revealed a significant Gender × Training interaction, indicating men gained more absolute strength than women ($p < .05$). Relative strength gains were also significantly greater in men (82%) than in women (58%) ($p < .05$). The values displayed in Figure 2 are relative to pretraining 1RM and reveal gender differences in strength development across the 26-week period of PRT. Following an initial early rise in 1RM for both genders (Day 25), relative strength gains among women were blunted compared with men. For example, 1RM for women did not significantly exceed the Day-25 value until Day 100, whereas 1RM strength increased from Day 25 to Day 50 in men and steadily climbed thereafter.

Discussion

In this study we have demonstrated that the myofiber hypertrophic response to the same PRT program is greater in older men than in older women. Mean increases in myofiber size were 40% in men and 7% in women. In their study of single myofibers, Trappe and colleagues (18) reported no Gender × Training interactions when comparing increases in myofiber diameter; however, the relative increase in type IIa myofiber diameter among men was significant whereas no change was noted in women. Further, single myofibers from men exhibited significantly greater improvements in maximum shortening velocity and power. Tracy and associates (17) and Ivey and associates (16) tested for Gender × Training interactions by using muscle volume determined by magnetic resonance imaging as the measure of muscle size. Both groups report a significant interaction for quadriceps hypertrophy after 9 weeks of PRT in older adults, with men exhibiting greater gains. Ivey and colleagues (16) found that the gender difference remained after they adjusted for pretraining muscle volume. These data combined suggest an important gender difference in the hypertrophic response to 3 days per week PRT among older adults. At odds with these data, Hakkinen and associates (4) found substantial gains in myofiber size in older women following a strength–power training program performed 2 days per week, suggesting that older women may benefit from reduced frequency PRT and a combination of heavier and lighter loads. These findings suggest the typical 3 days per week PRT program may not be the best model for older women.

In this report we attempted to explain the gender difference by covarying for a number of potential modulators of myofiber size. However, none of our targeted covariates influenced the gender differences or Gender × Training interactions. Serum IGF-1 is positively related to rates of muscle protein synthesis and has been measured extensively in recent studies of sarcopenia (49). IGF-1 is known to decline with age and is related to the decline in lean mass in cross-sectional studies across a wide age spectrum (33,34). In this study of load-induced hypertrophy, however, covarying for serum IGF-1 did not alter the influence of gender on either initial myofiber size or the magnitude of hypertrophy following PRT. Additionally, zero-order correlations tested across both genders showed no significant relationships between serum IGF-1 and absolute or relative changes in myofiber size. Others have shown that elevating serum IGF-1 by means of exogenous growth hormone treatment does not enhance the hypertrophic effects of PRT in older men (50), and PRT alone does not alter serum IGF-1 levels (51). The importance of circulating IGF-1 in load-mediated local skeletal muscle hypertrophy has been questioned (52) and, in our group of older adults, serum IGF-1 appeared to have no influence.

Similarly, serum levels of DHEA-S did not influence the hypertrophic response in this study. DHEA-S treatment has previously been shown to increase serum IGF-1 in older men and women (53), and declining levels of both DHEA-S and IGF-1 correlate with lower levels of muscle power in older women (54). We found no relationships between DHEA-S and initial myofiber size nor between DHEA-S and the magnitude of myofiber hypertrophy in men and women, despite twofold greater DHEA-S levels in men (not statistically significant).

Testosterone has been shown to influence the hypertrophic response to PRT. Bhasin and colleagues report greater PRT-induced hypertrophy with supraphysiologic doses of testosterone in young men (55). Although the present data and that of others (5,35,56) indicate that PRT alone does not alter resting serum concentrations of testosterone, there is limited evidence suggesting endogenous testosterone levels are related to the magnitude of PRT-induced hypertrophy in older women (24) and strength gain in men (5,35) and women (5). Additionally, testosterone treatment in female rats has been shown to induce satellite cell proliferation (57), considered by many to be a requisite process during myofiber hypertrophy. When we tested zero-order correlations in our group of 9 eugonadal older men with fairly homogeneous TT levels, we found no significant relation-

ships between endogenous TT and absolute or relative changes in myofiber size or 1RM strength. Despite this, it remains entirely possible that the markedly higher endogenous levels of TT in the men compared with the women might have potentiated hypertrophy by some as yet unknown mechanism, as we report average TT levels 33-fold greater in men. The bimodal nature of TT levels in these two gender groups, however, precluded the application of TT as a covariate, and therefore the present study design cannot provide any conclusive evidence regarding the importance of endogenous testosterone in load-mediated hypertrophy.

The marked gender difference in TT levels is certainly not unique to older adults, and data on gender differences in PRT-induced hypertrophy among younger and middle-aged adults are equivocal. For example, Staron and associates (58) reported myofiber hypertrophy results after 20 weeks of PRT in young women of similar magnitude to those reported by others in men, whereas Ivey and associates found a significant gender effect with greater hypertrophy in men in a sample of both young and older men and women (16). It is therefore not clear whether endogenous testosterone levels play a pivotal role in PRT-induced hypertrophy. Resistance training studies that compare eugonadal to untreated hypogonadal men would perhaps shed some light on this question.

The role of locally expressed IGF-1 in muscle hypertrophy and satellite cell activation has received significant attention as of late (25,59,60). Additionally, there is evidence that high resting levels of muscle IGF-1 expression may play a role in preventing age-related sarcopenia (37). Myogenin appears to be an important modulator of myogenesis, as its expression increases during both myoblast differentiation (61) and overload-induced myofiber hypertrophy (25,62). Hespel and colleagues (30) have recently reported increased myogenin protein expression during resistance-training-induced hypertrophy in humans. Myogenin activity is thought to be at least partially mediated by IGF-1, as recent evidence indicates myogenin gene expression is increased during IGF-1 stimulated myoblast differentiation (63). For these reasons we determined if expression of these transcripts, as well as expression of IGFR1, was different between genders before training or could account for gender effects on hypertrophy. A gender difference in basal muscle IGF-1 mRNA expression might be expected, because increasing testosterone levels have been associated with increased IGF-1 mRNA levels in skeletal muscle (36). However, there were no gender differences in pretraining levels, and neither IGF-1 nor myogenin expression changed after PRT. As a result, neither one demonstrated utility as a covariate.

Certainly PRT-induced strength accrual is multifactorial and is only partially mediated by myofiber hypertrophy. Despite the finding of more pronounced gains in men, relative strength improvement in the women was substantial by the end of the study (58%). The limited hypertrophy found in women suggests that the primary adaptation leading to enhanced strength was neurologically mediated. Neural adaptations occur during the early weeks of a PRT program and thus are thought to account for the early rapid increases in strength (64). It is noteworthy that the women experienced an early rise in strength similar to men (see Figure 2). By Day 25, 1RM was elevated 21% in women and 24% in men. Thereafter, strength gains tapered in women with the next significant rise not occurring until Day 100, whereas 1RM strength in the men rose fairly consistently across the 26 weeks. Consistent with data from other laboratories (65), we found no significant correlation between changes in myofiber size and changes in strength, indicating large individual variability in the amount of strength gain attributable to hypertrophy versus neural adaptations.

Our results demonstrate that the training regimen was sufficient to induce in both genders the reduction in MHCIIx distribution characteristic of resistance training programs (38,39). Although the mechanism(s) responsible for this shift in myosin phenotype are not known, it precedes measurable hypertrophy during resistance training (38), and it is noted with no significant myofiber hypertrophy during endurance and sprint training (66,67). On the basis of these data, it is not surprising to find MHCIIx downregulation in women in the current study (despite blunted hypertrophy), as the load-mediated molecular signals regulating myosin phenotype obviously differ from those regulating the net rate of myofibrillar protein synthesis.

Conclusions

In conclusion, we found marked gender differences in both absolute and relative myofiber hypertrophy and strength accrual following identical PRT programs in the older men and women studied. Although the muscles of both men and women demonstrated similar MHC plasticity with a reduction in MHCIIx distribution, men exhibited superior myofiber hypertrophy and strength gain. These Gender $\times$ Training effects remained after covarying for a number of potential modulators of muscle mass and/or strength. Future studies should determine whether acute responses to a single resistance exercise bout (e.g., acute changes in local myogenic gene or protein expression) differ by gender. Such findings may aid in unraveling the apparent gender influence on myofiber hypertrophy in older adults. Additionally, the potential role of endogenous testosterone levels should be carefully considered.

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