Effects of Muscle Strength Training and Testosterone in Frail Elderly Males

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[1]Geriatric Research Education and Clinical Center, Central Arkansas Veterans Healthcare System, Little Rock, AR; [2]Donald W. Reynolds Department of Geriatrics and [3]Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock AR; [4]Geriatric and Extended Care Service, Central Arkansas Veterans Healthcare System, Little Rock, AR; [5]Department of Cardiology, University of Arkansas for Medical Sciences, Little Rock, AR; and [6]Pharmacy Service, Central Arkansas Veterans Healthcare System, Little Rock, AR

ABSTRACT

SULLIVAN, D. H., P. K. ROBERSON, L. E. JOHNSON, O. BISHARA, W. J. EVANS, E. S. SMITH, and J. A. PRICE. *Med. Sci. Sports Exerc.*, Vol. 37, No. 10, pp. 1664–1672, 2005. **Purpose:** Determine the independent and combined effects of progressive resistance muscle strength training (PRMST) and testosterone on strength, muscle mass, and function in hypogonadal elderly male recuperative care patients. **Methods:** Between 1999 and 2004, 71 subjects (mean age 78.2 ± 6.4 yr, 86% white) were enrolled. After baseline one-repetition maximum (1RM) strength testing and then randomization to one of four treatment groups (low-resistance (20% of the 1RM) exercises and weekly injections of either 100 mg of testosterone enanthate or placebo or high-intensity PRMST (≥80% 1RM) and weekly injections), each subject received training and injections for 12 wk. **Results:** Ten subjects withdrew from the study before its completion. Based on intent-to-treat analyses, strength improved in all groups, but was greater with high-intensity PRMST compared with low-resistance exercise (e.g., leg press, (mean ± SE), 28 ± 4 vs 13 ± 4%, $P = 0.009$). Although testosterone led to significantly greater increases in midthigh cross-sectional muscle area compared with placebo (7.9 ± 1.3 vs 2.4 ± 1.4%, $P = 0.005$), it produced only a nonsignificant trend toward greater strength gains (e.g., leg press 25 ± 4 vs 16 ± 4%, $P = 0.144$). Change in aggregate functional performance score (the sum of 4 functional performance test scores) did not differ between the four intervention groups nor with high-intensity PRMST compared with low-resistance exercise (7 ± 5 vs 15 ± 5%, $P = 0.263$). There was not a significant interaction between exercise and testosterone for any outcome. **Conclusion:** High-intensity PRMST is as safe and well tolerated as a similarly structured low-resistance exercise regimen for very frail elderly patients, but produces greater muscle strength improvements. The addition of testosterone leads to greater muscle size and a trend toward greater strength but did not produce a synergistic interaction with exercise. Neither intervention had a significant effect on functional performance. **Key Words:** EXERCISE, AGING, HORMONE REPLACEMENT, REHABILITATION

As a consequence of illness, injuries, or major surgery, many older adults experience loss of muscle mass and strength during recovery, especially when nutrient intake is poor or inflammation is present. As a consequence, the individual often becomes profoundly deconditioned (17,26). During recovery, additional complications occur frequently leading to further clinical deterioration or death (17,29). Because of the high complication rates associated with this debilitated state and the slow rate at which energy stores and muscle strength are repleted using currently established treatment modalities (4,23,29), more effective interventions for the elderly are desired. To this end, progressive resistance muscle strength training (PRMST) holds great promise. When used alone or in combination with nutritional supplementation, PRMST has been shown to be a safe and effective means of increasing muscle mass and strength and improving functional status in select groups of frail older adults (10,12,19,32). In hypogonadal men, there is some evidence to suggest that the effectiveness of PRMST can be augmented by the use of testosterone (2,13,31). However, there is little experience using either approach to treat frail older men who have become deconditioned as a result of recent illness. The purpose of this study was to test the efficacy of PRMST and testosterone administration, alone or in combination, to improve muscle strength, increase muscle mass, and accelerate functional

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recovery in frail elderly men who had experienced a recent functional decline as a consequence of an illness.

METHODS

Patient Accrual

Subjects were referred to the study from the inpatient Geriatric Evaluation and Management (GEM) Unit, the outpatient GEM clinic, and the Transitional Care Unit (TCU) at a Veterans Administration hospital. Physicians were asked to refer patients who had a recent functional decline and were ≥ age 65. Other inclusion criteria included a serum total testosterone <480 ng·dL^{-1} (i.e., below the lowest 2.5 percentile of healthy young men (1)) and the ability to give informed consent. The exclusion criteria included a near terminal medical disorder, unresolved malignancy, prostate specific antigen (PSA) $>$ 10 ng·mL^{-1}, abnormal prostate exam suggestive of prostate cancer, a history of prostate cancer, disabling arthritis or irreversible neurologic disease that made a goal of independent ambulation unrealistic, and unstable cardiovascular disease.

In accordance with the ethical standards of the Department of Veterans Affairs and the human research advisory committee of the University of Arkansas for Medical Sciences, all patients referred to the study received oral and written explanations of the study, including possible risks involved, and signed Health Insurance Portability and Accountability Act (HIPAA) and informed-consent documents before entering the study. After entering the study, a study physician rereviewed each subject's clinical data and performed a general physical exam including a rectal exam to exclude a prostate mass. In the rare case in which they were not already available, a PSA and total testosterone were measured. After talking with the study personnel, three patients referred to the study changed their minds and decided not to enter the study. Two referrals gave their consent but were excluded from the study before randomization because they did not meet all inclusion and exclusion criteria. All of the remaining patients referred to the study completed the screening evaluation successfully, were consented, and randomized as described below.

Overview of Protocol

The study was a double-blinded (testosterone)/single-blinded (PRMST) randomized-controlled experiment to establish the safety and efficacy of a treatment regimen consisting of PRMST alone or in combination with weekly testosterone injections to increase muscle strength and improve functional independence in a population of elderly patients.

Walking, stair climbing, and rising from a chair are primary components of functional independence. For this reason, the muscle groups that are essential in the performance of these activities were targeted for intervention (12,33). This was accomplished using two exercises, each performed on a different machine. Knee and hip extensors were targeted for strengthening using a leg-press machine. To allow greater contributions from the arms in the performance of the aforementioned functional activities, forearm extensors and the muscles of the shoulder girdle were targeted for strengthening using a chest-press machine. Both of the exercise machines were pneumatic resistance devices that produced an isotonic force (Keiser Sports Health Equipment, Fresno, CA) and were operated from a seated position.

Upon entry into the study, subjects carefully re-reviewed the study protocol with the research assistants and then completed an introductory training course exercising on each machine at low resistance. The course was designed to allow each subject to become comfortable using both pieces of exercise equipment while also adhering to proper lift techniques.

For each exercise, subjects completed an appropriate warm-up set then performed three sets of eight repetitions. The rate of the repetitions and the amount of rest between sets was adjusted throughout the study as needed to keep the subject's heart rate below 110 bpm and to prevent excess fatigue. Sessions were terminated immediately if a subject experienced chest pain, severe shortness of breath, lightheadedness, a $>$20 mm Hg drop in blood pressure, a heart rate $>$140 bpm, or a sustained elevation in blood pressure $>$200/110 mm Hg. Subjects were also encouraged to terminate a session whenever they felt too weak or ill to continue. These criteria developed by an expert panel of three geriatricians and a cardiologist were designed to minimize cardiovascular stress.

After successful completion of the introductory training course, subjects completed a comprehensive baseline evaluation. This evaluation included a concise social, nutritional, functional status, and medical history and a complete clinical and laboratory nutritional assessment. It also included several measures of body composition, physical performance, and muscle strength. The entire battery of assessments was generally completed within two days. The physical performance testing was completed as part of the first day assessment. The order in which the individual physical performance tests were performed was varied randomly. The strength testing was completed on the second day and the order of the tests was also varied randomly. For all testing, the observers were blinded to a subject's group assignment. The same testing team was used throughout the study.

Complication-Risk Assessment

In order to provide an indication of each subject's health status, a complication-risk assessment was completed at study admission. The GRU Risk-Assessment Instrument was utilized for this assessment. Developed and validated in prior studies of older recuperative care patients, this instrument utilizes the Katz Index of Activity Daily Living score, serum albumin, current weight expressed as percentage of usual weight, midarm muscle circumference, number of prescription medications, and presence of renal disease (i.e., blood urea nitrogen greater than 30) to generate a risk

probability score (28). When validated in a population of geriatric rehabilitation patients using a predetermined threshold to define "high risk," the instrument predicted who would develop an illness-related complication during the hospitalization with a sensitivity, specificity, and overall predictive accuracy of 77%.

Body Composition Assessment

Two measures of body composition were performed:

1. **Midthigh fat-free muscle area**: This was determined with computerized tomography using a HiSpeed scanner (General Electric Medical Systems, Waukesha, WI). A single 10-mm slice was obtained at the midpoint between the right iliac crest and the patella of the dominant leg (12,16). The stored images were transferred to a personal computer where they were analyzed using medical imaging software (SliceOmatic version 4.2, TomoVision, Montreal, Canada). Based on ranges of attenuation values, cross-sectional areas of muscle, adipose, and bone areas were determined to the nearest 0.01 cm^2. The intraindividual coefficient of variation of this technique for measurements of muscle and fat area was 1.0–1.5%.
2. **Lean body mass**: Whole body air displacement plethysmography was used to obtain estimates of body density (11). Body fat was then calculated from the total body density estimate using the equation of Siri (25). Lean body mass was taken as the difference between total body mass and fat mass.

Physical Performance Testing

Four tests of physical performance were conducted as follows:

- **Sit-to-stand maneuver**: Starting from a seated position in an armchair (standard seat height of 44 cm) with hands on thighs, subjects were instructed to stand fully erect, sit down, and then stand erect again as fast as possible. A subject was allowed to push off using his arms against the arms of the chair if incapable of completing the test otherwise. The average of three trials was utilized.
- **Habitual and maximal safe gait speed tests**: For the habitual gait speed test, subjects were instructed to walk 100 feet while ambulating at the speed at which they felt most comfortable. For the second test, subjects were asked to repeat the course while walking as fast as they could without losing balance or becoming unduly fatigued. If it was necessary, subjects were allowed to walk behind a wheelchair or walker. Human help was also provided if required to prevent falls. One trial of each test was performed.
- **Stair climb**: After a slow-paced warm-up climb, subjects were instructed to walk up one flight (11 steps, each 18 cm high and 30 cm deep) as fast as possible without losing their balance or becoming unduly fatigued. All subjects wore safety belts, were provided standby assistance, and were required to step on each step. Handrails could be used if desired. Human help was provided if required. At a given testing session, only one trial of this test was performed.

Each event was recorded by the same observer using a handheld stopwatch. The amount and type of assistance was also noted. Based on repeated testing of 50 healthy and 15 comparably frail older adults (three trials each), the test-retest reliability correlation coefficient of each of these tests was established to be ≥ 0.94 ($P < 0.001$).

Before the start of the study, it was recognized that measuring change in physical performance was going to be complicated by the fact that many of the subjects would not be able to complete the performance tests upon entering the study. For this reason, scores were generated according to the amount of time and assistance required to complete these four tests. Points were assigned for each test as follows: 0, could not complete task; 1, needed assistance to complete task (e.g., use of arms for standing, human help for stair climbing or walking); 2, completed task independently but time was greater than the median time for a control population; and 3, completed task independently and in equal to or less than the median control time. The control population median times were established based on testing of 50 healthy robust elderly volunteers (average age 75 $\pm$ 5 yr). By summing the points, an aggregate score in the range of 0 to 12 was generated.

Testing of Muscle Strength

The maximal weight that could be lifted correctly in a single repetition (i.e., the one-repetition maximum or 1RM) was used as the primary indicator of muscle strength for each exercise (18). During testing, the subject's electrocardiogram was monitored continuously and vital signs were measured repeatedly. The left and right extremities were tested together. For each exercise station, the subject completed a warm-up set at approximately 20% of the estimated 1RM. During testing, the amount of resistance was increased after each lift. Subjects were allowed to rest for 30 s between lifts. As reported previously, the test-retest correlation coefficients were 0.92–0.99 ($P < 0.001$) (27), consistent with those of other studies (21,12).

Start of Training Protocol

Randomization. After completing all baselines assessments, subjects were immediately randomized to one of four intervention groups as follows: group 1 (low-resistance muscle toning + placebo); group 2 (low-resistance muscle toning + testosterone); group 3 (high-intensity PRMST + placebo); and group 4 (high-intensity PRMST + testosterone). Randomization, conducted by the study biostatistician, was stratified in order to assure that the four groups were comparable at baseline. Subjects whose initial aggregate score was less than 8 were randomized separately from those whose score was 8 or greater. Within each stratum, subjects were randomized to one of the four intervention

groups within blocks to assure that there were roughly equal numbers of subjects in each group at the end of the study. The block sizes were always multiples of four and were randomly varied to minimize the ability to deduce the assignment for a particular subject in advance. A sealed envelope was sent to the pharmacy informing them of the subject's assignment to either testosterone or placebo, thus maintaining the blind. Once randomized, subjects started the 12-wk training protocol beginning the next training session, which were generally held every Monday, Wednesday, and Friday.

Low-resistance muscle toning exercise (groups 1 and 2) protocol. The exercise control groups trained with very low resistance. Throughout the entire 12 wk of training, the subjects began each exercise with a warm-up set using approximately 10% of the 1RM. They then completed three sets of eight reps at 20% of their original 1RM.

High-intensity PRMST (groups 3 and 4) protocol. The targeted intensity of the resistance progression was set at 80% of the 1RM. To avoid injuries, subjects trained at 20% of 1RM for the first week. During weeks 2 through 12, the subjects began each exercise with a warm-up set (eight reps) using 30–40% of 1RM. Beginning the first session of week 2, the resistance for each exercise was set at 50% of 1RM. Beginning week 3, the resistance was set as high as the subject could tolerate for three sets, with the original target 80% of the 1RM. Every 4 wk strength retesting was conducted to be certain that the training resistance was at least 80% of the 1RM.

Testosterone. On the second visit of each of the 12 intervention weeks, each subject received an intramuscular injection of either testosterone enanthate (groups 2 and 4) or an equivalent volume of an identical appearing placebo (groups 1 and 3). For the first week, 0.5 cm^3 was given (50 mg of testosterone or placebo). For the remaining 11 wk, 1.0 cm^3 was given (100 mg or placebo).

Final Assessment

After completing the training sessions and receiving the last testosterone/placebo injection, each subject returned for the final posttraining evaluation. All measures of body composition, physical performance, and muscle strength testing were repeated as were the baseline blood studies including a trough (1 wk postinjection) serum testosterone. The posttraining evaluation was begun within 3 d of the last exercise session and was completed over the same time frame as the initial evaluation.

Statistics

Change in muscle strength was the primary outcome. A two-factor ANOVA was performed on the difference between each subject's admission and final log-transformed muscle strength data. Using this approach, the log scale differences in means were interpretable as percent changes in muscle strength. As part of the analyses, the significance of any exercise by testosterone interaction (either positive or negative) was evaluated. If the interaction was not significant, the main effects were reported. For each intervention, the significance of any change over time was assessed using a one-group paired *t*-test. For the first set of analyses, all subjects were included per intent-to-treat principles. For subjects who dropped from the study, final test results were set equal to baseline results.

ANCOVA was used to adjust for potentially important between group differences in baseline variables such as functional status or other indicators of health status. The baseline variables of interest were identified by univariate analyses. Only the baseline variables that differed significantly by group for either intervention or were associated with the outcome were included in the ANCOVA. If ANOVA or ANCOVA revealed a significant effect, then the individual groups were compared using Tukey's multiple comparison procedure.

The same analytic approach was used to evaluate the two secondary outcomes, change in physical performance and change in midthigh muscle cross-sectional area. Tests of hypotheses were declared significant at the $P = 0.05$ level. The data were analyzed using SAS Institute software (22).

RESULTS

All 71 subjects who entered the study between 1999 and 2004 were randomized as outlined in Figure 1. The subjects ranged in age from 65 to 93 yr (mean ± SD = 78.2 ± 6.4 yr), 61 (86%) were white, and all had experienced a recent decline in their level of physical functioning. At study entry, 19 subjects (27%) were unable to complete one or more of the functional tests even when allowed to use their hands and an assistive device. Thirty-three subjects (46%) required the use of an assistive device to complete the gait speed tests. On average, the subjects had four active and five stable medical problems and were taking 9 ± 5 regular use prescription medications and 2 ± 2 as-needed medications. Although all of the subjects had multiple active medical problems, the most common diagnostic categories included hypertension (82%), anxiety or depression (56%), coronary artery disease (50%), arthritis (46%), benign prostatic hypertrophy (44%), diabetes (40%), and congestive heart failure (30%). All subjects were listed as being debilitated or deconditioned. There were no statistically significant differences between the intervention groups at baseline (Table 1).

Ten subjects dropped out of the study before completing the 12-wk exercise training protocol. Seven of these subjects were withdrawn from the study when they developed an exacerbation of an underlying medical problem. In one case, the outside monitors felt that the exercise could possibly have contributed to the illness exacerbation. This subject developed an exacerbation of his chronic obstructive pulmonary disease and a non-Q wave myocardial infarction 3 d after a high-intensity workout. There were no serious problems related to the use of testosterone. Average change in PSA was not significantly greater for those who received testosterone compared to placebo (0.84 ± 1.67 vs 0.35 ± 1.59 $ng \cdot mL^{-1}$, $P = 0.210$) and the maximal within group increase was the same (6.31 vs 6.31 $ng \cdot mL^{-1}$). The change in hemoglobin (Hb) was also slightly greater in the testos-

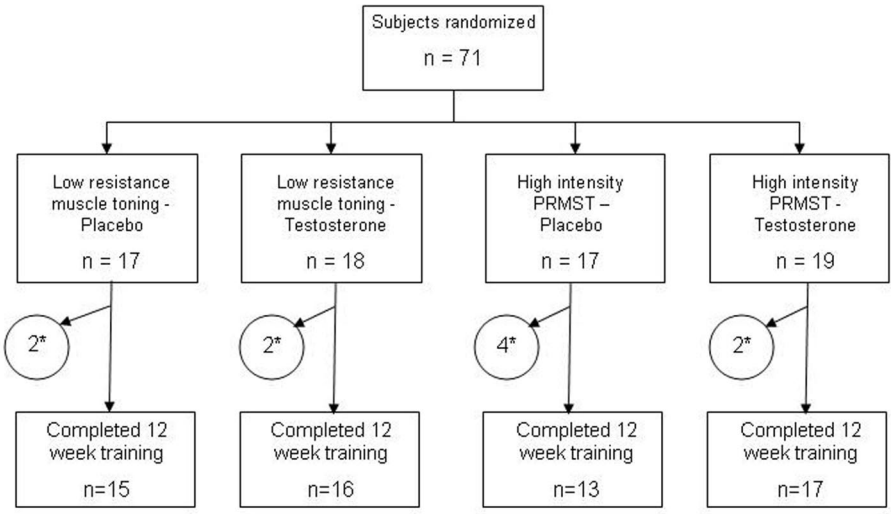

FIGURE 1—Study flow diagram. *The circles contain the number of subjects who withdrew before completion of the 12-wk training.

terone groups (0.92 ± 1.24 vs 0.18 ± 1.83 g·dL^{-1}, P = 0.056). Of those who completed the study, average compliance with the exercise sessions was 98.9 ± 3.3%, with no difference between groups.

Based on the GRU risk-assessment instrument, 33 study subjects (46%) were classified as "high risk" at study entry. Using the raw scores from this instrument, the average predicted probability for developing a complication for the study population was 0.36 ± 0.23. There was no difference in risk classification or predicted probability scores between groups at study admission (Table 1). The seven subjects who withdrew from the study due to illness had only a slightly but nonsignificantly higher predicted probability (0.49 ± 0.20 vs 0.35 ± 0.23, P = 0.133).

TABLE 1. Admission characteristics of study subjects.*

	Drug†		Exercise†	
Variable	Placebo (N = 34)	Testosterone (N = 37)	Sham (N = 35)	High (N = 36)
	Mean ± Standard Deviation			
Age (yr)	78.3 ± 6.6	78.1 ± 6.3	78.6 ± 5.2	77.8 ± 7.4
Katz index of ADL	1.3 ± 1.8	2.1 ± 2.8	1.4 ± 2.1	2.0 ± 2.6
Body mass index (kg·m^{-2})	26.2 ± 4.7	26.1 ± 4.7	26.7 ± 5.0	25.7 ± 4.4
Total testosterone (ng·dL^{-1})	331.9 ± 173.2	293.5 ± 141.2	308.4 ± 146.2	313.9 ± 169.0
Mini mental state exam	25.6 ± 3.5	24.2 ± 3.9	24.8 ± 3.2	24.8 ± 4.3
Albumin (g·L^{-1})	36.1 ± 5.0	34.9 ± 4.6	35.8 ± 3.9	35.1 ± 5.6
Pre-albumin (mg·L^{-1})	260.3 ± 58.9	237.6 ± 71.0	259.9 ± 60.2	238.6 ± 70.0
Cholesterol (mg·dL^{-1})	176.3 ± 33.3	167.1 ± 34.1	175.6 ± 30.4	167.3 ± 37.0
Hemoglobin (g·dL^{-1})	12.9 ± 1.6	12.7 ± 1.6	12.9 ± 1.6	12.7 ± 1.5
No. of RX medications	7.9 ± 4.2	9.9 ± 5.2	9.2 ± 4.6	8.7 ± 5.1
Total No. of medications	10.8 ± 5.3	12.4 ± 5.2	11.5 ± 4.9	11.8 ± 5.7
Aggregate functional performance score‡§	7.3 ± 3.0	6.8 ± 2.9	7.1 ± 2.7	7.0 ± 3.2
Education (yr)	11.8 ± 4.2	10.8 ± 3.8	10.9 ± 4.3	11.6 ± 3.7
Initial 1RM§**				
Chest (kg)	26.1 ± 11.1	25.7 ± 10.3	26.8 ± 10.4	25.1 ± 10.9
Leg (kg)	125.3 ± 77.8	118.3 ± 67.4	120.6 ± 67.7	122.7 ± 77.1
Midthigh cross-sectional muscle area (cm^2)§	107.5 ± 29.3	107.7 ± 29.6	108.8 ± 31.5	106.4 ± 27.2
Risk probability††	0.33 ± 0.21	0.40 ± 0.24	0.34 ± 0.21	0.39 ± 0.25
	N (%)			
Self-assessment health‡‡				
Excellent/good	14 (41.2)	17 (45.9)	13 (37.1)	18 (50.0)
Fair/poor	20 (58.8)	20 (54.1)	22 (62.9)	18 (50.0)
White collar worker	11 (32.4)	10 (27.0)	11 (31.4)	10 (27.8)
Marital status, married	16 (47.1)	23 (62.2)	21 (60.0)	18 (50.0)
Race, white	29 (85.3)	32 (86.5)	28 (80.0)	33 (91.7)

* Includes 71 subjects who entered the study.
† $P > 0.05$ on all bivariate comparisons of intervention and control groups.
‡ Each of four tests (the sit-to-stand maneuver, habitual gait speed, maximal safe gait speed, and stair climb) was scored on a four-point scale (0, cannot complete task; 1, needs assistance to complete task; 2, completes task independently; 3, completes task independently and in less than or equal to median time for control population of healthy elderly). The aggregate score represents the sum of these four scores and can range from 0 to 12 points.
§ All functional performance, strength, and muscle area data were log transformed prior to analysis (see text for details).
** Initial 1RM, the first one-repetition maximum strength test performed (see text for details).
†† Predicted probability for developing a complication based on the GRU risk-assessment instrument (See text for details).
‡‡ Subjects were asked to rate how well they felt their own health was during the majority of the 12 months prior to study entry with choices being excellent, good, fair, or poor.

TABLE 2. Adjusted mean absolute and percent change for each outcome based on intent-to-treat analysis ($N = 71$).*

	Study Group				*P* Value		
Outcome Variable	Group 1 Low-Resistance Exercise + Placebo ($N = 17$)	Group 2 Low-Resistance Exercise + Testosterone ($N = 18$)	Group 3 High-Intensity PRMST + Placebo ($N = 17$)	Group 4 High-Intensity PRMST + Testosterone ($N = 19$)	Effect of Exercise	Effect of Drug	Interaction
	mean (± SE)						
Chest press							
% change	6.72 ± 4.22	19.08 ± 4.10	†23.11 ± 4.22	‡26.67 ± 3.99	0.005	0.058	0.290
Absolute change (kg)	1.47 ± 1.42	†5.80 ± 1.39	‡7.20 ± 1.42	‡7.46 ± 1.34	0.010	0.104	0.149
Leg press							
% change	7.50 ± 5.78	18.03 ± 5.61	24.83 ± 5.78	31.04 ± 5.46	0.009	0.144	0.704
Absolute change (kg)	9.72 ± 7.04	25.49 ± 6.84	†35.99 ± 7.04	†39.41 ± 6.66	0.005	0.169	0.374
Midthigh cross-sectional muscle area							
% change	3.58 ± 1.92	7.28 ± 1.87	1.22 ± 1.92	8.61 ± 1.82	0.785	0.005	0.330
Aggregate score§							
% change	13.27 ± 7.45	16.53 ± 7.22	13.11 ± 7.40	0.33 ± 7.00	0.263	0.514	0.277

* Based on multifactor analysis of covariance of the log-transformed data (see text for details).
† $P < 0.05$ compared to group 1.
‡ $P < 0.01$ compared to group 1.
§ Each of four tests (the sit-to-stand maneuver, habitual gait speed, maximal safe gait speed, and stair climb) was scored on a four-point scale (0, cannot complete task; 1, needs assistance to complete task; 2, completes task independently; 3, completes task independently and in less than or equal to the median time for control population of healthy elderly). The aggregate score represents the sum of these four scores and can range from 0 to 12 points.

Primary and Secondary Outcomes

For both the arm and leg exercises, improvement in muscle strength was independent of age, race, and baseline primary diagnosis, functional level, lean body mass, cross-sectional midthigh muscle area, self-assessment of health status, cognitive function, and serum testosterone. The adjusted mean differences in strength by intervention group for each exercise are presented in Table 2. As shown, the high-intensity PRMST exercises led to significantly greater improvements in muscle strength compared with the low-resistance exercises. However, both the high-intensity PRMST and low-resistance exercise groups experienced improvements in leg and arm strength by the end of the 12-wk training period ($P < 0.001$ all analyses). Also shown, there was a trend toward greater strength improvement with testosterone compared to placebo for both the arm and leg exercises, but neither of these differences reached statistical significance, and the interactions between testosterone and exercise were not significant.

Although the high-intensity leg exercises led to greater leg strength, they did not significantly affect midthigh cross-sectional muscle area. In contrast, testosterone led to significantly greater increases in midthigh cross-sectional muscle area compared with placebo. This effect was independent of age, race, exercise group, and other baseline variables, and there was not a significant interaction between testosterone and exercise. The adjusted mean differences in midthigh cross-sectional muscle area by intervention group are presented in Table 2. The final trough serum testosterone concentration could only be determined for the 61 subjects who completed the exercise training protocol. Of this group, those who received testosterone had significantly higher testosterone concentrations compared to those who received placebo ((mean ± SD) 804.4 ± 282.7 vs 303.5 ± 126.7 ng·dL^{-1}, $P < 0.001$). There was no difference in testosterone by exercise group (623.8 ± 404.9 vs 526.7 ± 251.3 ng·dL^{-1}, $P = 0.268$), and there was no drug–exercise interaction with regards to the testosterone concentration ($P = 0.080$).

There was not a significant difference in aggregate physical performance score change between any intervention groups (Table 2). The strongest predictor of change in aggregate score was baseline score; the lowest aggregate scores at baseline were associated with the greatest improvement ($r = -0.31$, $P = 0.009$).

When only the 61 subjects who completed the 12-wk exercise program were included in the analyses, the results were similar to the intent-to-treat analyses except that the between group differences were larger. Because the interaction between exercise and testosterone was nonsignificant for all outcomes, the main effects were examined separately. The results are shown in Figures 2 and 3. Consistent with absolute improvement in strength during the study (see Fig. 2), the average percent change in leg press strength was greater for those who were in the high-intensity PRMST compared with low-resistance training groups (33.6 ± 4.3 vs 14.4 ± 4.2%, $P = 0.002$). For the chest press, the difference was also significant (30.0 ± 3.0 vs 14.5 ± 2.9%, $P < 0.001$).

DISCUSSION

This study indicates that high-intensity PRMST is as well tolerated but more effective at improving strength than low-resistance exercises in very frail older men. However, both exercise interventions led to significant strength improvements by the end of the training program. This raises important questions about the relative benefit of each exercise protocol. Most of the previously published studies used nonexercising controls (3,4,10,12,19,23). Strength changes of such nonexercising controls have been reported to range from −1 to 6%, indicating that training effects or possibly

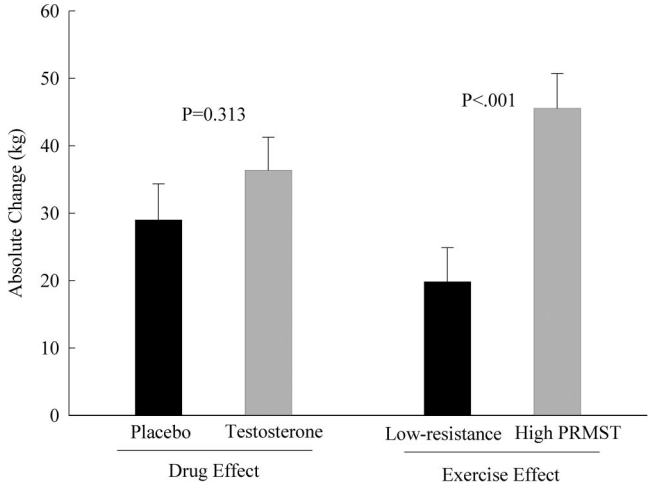

FIGURE 2—Change in lower extremity muscle strength (kg) by intervention for the 61 subjects who completed the 12-wk training. The results are based on muscle strength testing using the leg press machine.

nonstudy-related changes in overall health may account for some of the performance improvement resulting from resistance training (12,14,15,24,30,32). Of the studies that evaluated low- to moderate-resistance muscle strengthening exercises (i.e., <50% of the 1RM), a majority reported strength improvements in the range of 5–10%, consistent with our results (3,4,23). Greater strength gains have only been reported with training at higher resistances. However, it is probably not valid to judge the relative effectiveness of differing exercise intensities based on separate studies. Of the studies that directly compared the strength gains resulting from training at differing levels of exercise resistance, the results have been mixed. Several found progressively greater strength gains with increasingly greater training resistance (8,24,30). Other studies found that subjects who worked out using moderate resistance (40–50% of their 1RM) had strength gains equal to those who trained using high resistance (≥80% of their 1RM) (32). Given that high resistance is often difficult to attain without exercise equipment and that very frail older adults face many obstacles to gaining access to such equipment, more work is needed to determine the optimal training resistance for this population (17,29).

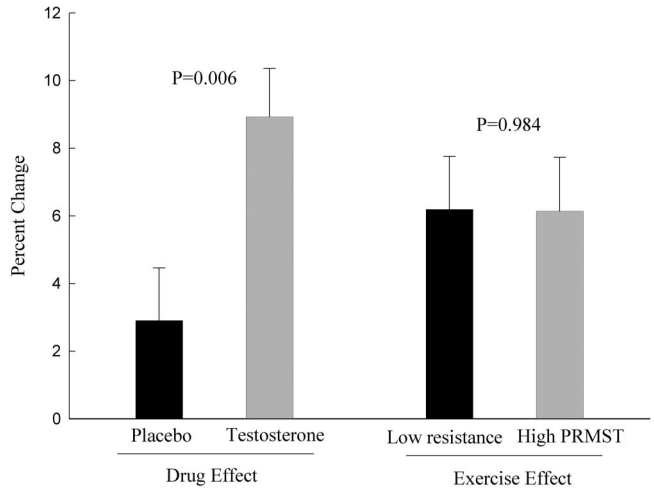

FIGURE 3—Percent change in midthigh cross-sectional muscle area by intervention for the 61 subjects who completed the 12-wk training.

Besides the training resistance, there were other differences between the high-intensity PRMST and the low-resistance training protocols. Subjects in the high-intensity PRMST groups performed 1RM testing every 4 wk. If there was a significant training effect associated with performing the 1RM test, this would have given these subjects an advantage over the exercise control groups. The subjects in the low-resistance training groups performed 1RM testing only at the start and end of the study. As the intervention title indicates, the training resistance for the high-intensity PRMST groups was progressively increased throughout the study as tolerated by the subjects. Because the training resistance of the other two groups was maintained at 20% of the original 1RM, this factor may also have contributed to the differences in outcomes between the groups.

This study did not provide a definitive answer to the question of whether testosterone supplementation is an effective method of improving strength in frail older hypogonadal males when used either alone or as an adjunct to PRMST. Although there was a trend toward greater strength gains in those subjects who received testosterone compared to placebo, neither the main effect nor the interaction between testosterone and exercise reached statistical significance. Based on the data from this study, a much larger sample size (in the 200–300 range) would be needed to address this important question. However, this remains an important issue. In a recent study, Bhasin et al. found that healthy older men are as responsive as young men to the anabolic effects of graded doses of testosterone on skeletal muscle (7). Both age groups experienced a significant increase in leg strength in response to weekly injections of 125 mg of testosterone enanthate for 20 wk. On average, the older nonexercising subjects who received this dose experienced a 28-kg (10%) gain in leg strength. This is comparable to the average increase in leg strength that subjects in the low-resistance arm of our study experienced in response to testosterone. However, in our study, the effect of testosterone on strength did not reach statistical significance. This indicates that there was a relatively larger amount of variability in the level of responsiveness of our study subjects to testosterone compared with the healthy subjects studied by Bhasin et al. This variability in responsiveness was possibly a consequence of the heavy burden of comorbid health impairments afflicting the subjects in our study population. Because such frail/infirm older adults are at high risk for adverse clinical outcomes and often fail to respond to other types of rehabilitative therapies, the strong trend toward improvement with testosterone is encouraging. Further study of the effects of this hormone in promoting strength gains in this population are warranted.

The main effect of testosterone in the current study appeared to be stimulation of muscle hypertrophy. It was not possible to determine what changes within the muscle

were induced by the testosterone that led to the hypertrophy. However, the effect of the testosterone on the muscle was different than that of exercise. The high-intensity exercises produced greater increases in muscle strength than the testosterone while having little effect on muscle mass. The fact that the strength-generating capacity of muscle was more strongly influenced by exercise than testosterone suggests that testosterone was not inducing the same structural, metabolic, and/or neural changes as exercise. It is possible that the testosterone-induced hypertrophy represented primarily an increase in muscle water content. However, it is well documented that testosterone induces an increase in the fractional synthetic rate of proteins in muscle (9,31). If this results in a greater mass of structurally sound contractile proteins within the muscle, it may take more than 12 wk of therapy with testosterone in order to attain the maximal effects on muscle strength or the greatest level of synergy with exercise. Several recent studies that demonstrated strength improvements with testosterone therapy in healthy older men provided the intervention from 5 to 36 months (7,20). It may take even longer to demonstrate benefit in frail health-impaired older men.

Although we had hypothesized that improvement in physical performance would be greater among the subjects receiving the high-intensity PRMST compared with the low-resistance exercises, this was not demonstrated. Part of the explanation for this negative finding may relate to the method used to assess change in function. We compared change in aggregate scores, which may not have been a very sensitive method for assessing the effects of the interventions on functional performance in the entire study population. The instrument was limited in its ability to detect improvement in those individuals who had high initial scores. However, when we performed secondary analyses including only those subjects who were able to complete the functional tests at both the beginning and end of the study, there was no difference between the groups in percent change in performance times (data not shown). As suggested by prior studies, it is possible that a longer period of intervention is needed to induce a clinically significant improvement in physical performance (2,5).

This study indicated that both interventions were safe and well tolerated by the study subjects, despite their frailty. The dropout rate appeared to be a reflection primarily of the fact that very frail subjects were recruited for this study. There was not an observation only control group that could be used to as a comparison group to formally assess whether participation in this study increased overall risk of adverse clinical events. However, the study population was very similar to a cohort of 350 geriatric recuperative care patients that had participated in a previous outcomes study (28). The average predicted probability of developing a complication based on the GRU risk-assessment instrument in the original cohort was 0.37 ± 0.24, which was nearly identical to the average for the participants in this study (0.36 ± 0.23). The actual rate of clinically significant inhospital complications in the original cohort was 36%, which was well above the rate for the subjects who participated in this study.

There was also little direct evidence to suggest that the exercise training or testosterone contributed to any of the adverse outcomes. The adverse events appeared to be randomly distributed among the groups. No subject developed a serious complication within 24 h of a high-intensity workout or 1RM testing, and no subject developed an abnormally elevated Hb while receiving testosterone, a potential consequence of this intervention (6,13). The serum PSA fluctuated widely in all study groups, perhaps because many of these subjects had chronic recurrent urologic problems. There was no evidence found that the short course of testosterone provided as part of this study contributed significantly to any of these urologic concerns.

CONCLUSION

High-intensity PRMST is as safe and well tolerated as a similarly structured low-resistance exercise regimen for very frail elderly recuperative care patients, but produces greater muscle strength improvements. The addition of testosterone leads to greater muscle size and a trend toward greater strength but does not produce a synergistic interaction with exercise. Based on the analytic methods utilized in this study, neither intervention appears to have a significant effect on functional performance.

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