Effects of Muscle Strength Training and Megestrol Acetate on Strength, Muscle Mass, and Function in Frail Older People

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OBJECTIVES: To determine the independent and combined effects of progressive resistance muscle strength training (PRMST) and megestrol acetate (MA) on strength, muscle mass, and function in older recuperative care patients.

DESIGN: Double-blind, randomized, controlled intervention using a two-by-two factorial design and conducted between 1999 and 2001.

SETTING: University-affiliated Department of Veterans Affairs hospital.

PARTICIPANTS: Twenty-nine patients (mean age 79.4 ± 7.4, 90% white) aged 65 and older and had recent functional decline.

INTERVENTIONS: After randomization to one of four treatment groups (low-resistance exercises plus 800 mg per day of MA or a placebo or high-intensity PRMST plus 800 mg/d of MA or placebo), subjects received training and the drug or placebo for 12 weeks.

MEASUREMENTS: Change in muscle strength, mid-thigh muscle area, and aggregate functional performance score as assessed using analysis of covariance.

RESULTS: Five subjects withdrew from the study before its completion. Based on intent-to-treat analyses, subjects who received high-intensity PRMST and placebo experienced the greatest strength gains. The addition of MA was associated with worse outcomes than with high-intensity exercise training alone, especially with regard to the leg exercises. Post hoc analysis demonstrated that subjects who received high-intensity PRMST and placebo experienced significantly greater percentage increases in leg strength than subjects in either of the MA treatment groups ($P < .05$ for each comparison). There was also a significant negative effect of MA on physical function. In general, subjects who received MA experienced a deterioration in aggregate physical function scores, whereas the remaining subjects improved ($-0.80 ± 0.40$ vs $0.48 ± 0.41$, $P = .04$). There was not a significant interaction between exercise and MA for any outcome.

CONCLUSION: High-intensity PRMST is a safe and well-tolerated exercise regimen for frail elderly patients. The addition of MA appears to blunt the beneficial effects of PRMST, resulting in less muscle strength and functional performance gains. **J Am Geriatr Soc 55:20–28, 2007.**

Key words: muscle strength; frail; megestrol acetate

As a consequence of illness, injuries, or major surgery, many older adults experience a loss of muscle mass and strength, leading to the development of profound deconditioning.[1–3] The physical decline is even worse when there is concomitant anorexia and nutritional deterioration, as occurs frequently when inflammation is present.[4,5] For such older adults, recovery from this compromised state is often slow or incomplete, and the frequent development of secondary complications that can cause further clinical deterioration or death often characterize the period of recuperation.[6–8] Because of this heightened risk and the slow rate at which energy stores and muscle strength are restored using currently established treatment modalities,[9–11] more-effective interventions for older people are desired. To this end, progressive resistance muscle strength training (PRMST) holds great promise. It 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.[12–14] It also appears to be effective in improving illness-induced weakness and muscle loss.[15] Megestrol acetate (MA), a powerful appetite stimulant, also offers the potential of benefit for frail older adults during recovery from illness. It has been shown to improve appetite and produce weight gain in men and women with acquired immunodeficiency syndrome, cancer, and other disabilities,[16–18] although most studies indicate that the weight gained represents primarily fat. MA's effects on strength and physical function during recovery from recent

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illness are not known. Because it induces increased nutrient intake, there is a theoretical basis to assume that it would accelerate functional recovery after illness when used alone or in combination with PRMST. At the time of this study, this possibility had not been examined previously. The purpose of this study was to test the efficacy of PRMST and MA, alone or in combination, to improve muscle strength, increase muscle mass, and accelerate functional recovery in frail elderly patients who had experienced recent functional decline as a consequence of illness.

METHODS

Patient Accrual

Subjects were referred to the study from the inpatient Geriatric Evaluation and Management Unit, the outpatient Geriatric Evaluation and Management Clinic, and the Transitional Care Unit at a Veterans Affairs hospital and the outpatient Geriatric Evaluation clinic within the Department of Geriatrics at the associated university hospital. Physicians were asked to refer patients who had recent illness-induced functional decline, were aged 65 and older, and were capable of giving informed consent. The exclusion criteria included a near-terminal medical disorder, unresolved malignancy, disabling arthritis or irreversible neurological disease that made a goal of independent ambulation unrealistic, and unstable cardiovascular disease.

After talking with the study personnel, four patients referred to the study changed their minds and decided not to enter the study. 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 of the remaining 30 referred patients received oral and written explanations of the study, including possible risks involved, and signed Health Insurance Portability and Accountability Act and informed-consent documents before entering the detailed screening phase of the study. Once consent was obtained, a study physician re-reviewed each subject's clinical data and performed a general physical examination. One referral gave his consent but was excluded from the study before randomization, because he did not meet all inclusion and exclusion criteria. All of the remaining patients referred to the study completed the screening evaluation successfully, provided consent, and were randomized as described below.

Overview of Protocol

The study was a double-blind (MA)/single-blind (PRMST) randomized, controlled experiment to establish the safety and efficacy of a 12-week treatment regimen consisting of PRMST alone or in combination with MA (800 mg/d orally) to increase muscle strength and improve functional ability in a population of elderly patients recuperating from recent illness-induced deterioration in physical function. Subjects were randomized to each of the two interventions (MA and PRMST) using a two-by-two factorial design.

Upon entry into the study, subjects were taught the proper techniques for using the weight lifting equipment. The knee, hip, and forearm extensors, as well as the muscles of the shoulder girdle were targeted for strengthening using two different exercises. Subjects performed hip extensions

on a hip-extension/leg-press chair and arm extensions from a seated position in a chest-press chair. Both of the exercise machines were pneumatic resistance devices that produce an isotonic force (Keiser Sports Health Equipment, Fresno, CA). Subjects then completed an introductory training course designed to allow them to become comfortable using the exercise equipment while exercising at low resistance.

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 subjects' heart rate below 110 bpm and to prevent excess fatigue. Sessions were terminated immediately if a subject experienced chest pain, severe shortness of breath, light-headedness, a more than 20 mmHg drop in blood pressure, a heart rate greater than 140 bpm, or a sustained elevation in blood pressure of more than 200/110 mmHg. 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 (ESS), were designed to minimize aerobic cardiovascular stress.

After completion of the introductory course, subjects also completed a comprehensive baseline evaluation that included a concise social, nutritional, functional status, and medical history and a complete clinical and laboratory nutritional assessment, as well as several measures of body composition, physical performance, and muscle strength. For all testing, the observers were blinded to subjects' group assignment. The same testing team was used throughout the study.

Body Composition Assessment

Two measures of body composition were performed.

1 Mid-thigh 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.[12,19] 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 tissue, 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% to 1.5%.

2 Lean body mass: Whole-body air-displacement plethysmography was used to obtain estimates of body density.[20] Body fat was then calculated from the total body density estimate using the equation of Siri.[21] 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 per protocol, as previously described: sit-to-stand, habitual gait speed, maximal safe gait speed, and stair climb maneuvers.[15] The test-retest reliability correlation coefficient of

each of these previously validated tests was 0.94 or greater ($P < .001$).[22]

Before the start of the study, it was recognized that the fact that many of the subjects would not be able to complete the performance tests upon entering the protocol was going to complicate measuring change in physical performance. 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 in median control time or less. The control population median times were established based on testing of 50 healthy, robust elderly volunteers (average age 75 ± 5). 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 (one repetition maximum (1RM)) was used as the primary indicator of muscle strength for each exercise.[23] 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 seconds between lifts. As reported previously, the test-retest correlation coefficients were 0.92 to 0.99 ($P < .001$),[22] consistent with those of other studies.[12,24]

Nutrient Intake Assessments

Upon entry into the study, each subject was given instructions in the assessment of dietary intake using a food record booklet and standardized method of how portions should be estimated for each type of food. During the first and last 2 weeks of the protocol, each subject completed the diaries each day. The diet records were coded and analyzed using Nutritionist Five software (version 2.0; First DataBank Inc., San Bruno, CA).

Start of Training Protocol

Randomization

After demonstrating competence in the use of the exercise equipment and completing all baselines assessments, subjects were randomized to one of four intervention groups as follows: Group 1 (low-resistance muscle toning plus placebo), Group 2 (low-resistance muscle toning plus MA), Group 3 (high-intensity PRMST plus placebo), and Group 4 (high-intensity PRMST plus MA). The study biostatistician (PKR) conducted randomization. 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 MA or placebo, thus maintaining the blind. Once randomized, subjects started the 12-week training protocol.

Low-Resistance Muscle-Toning Exercise (Groups 1 and 2) Protocol

The exercise control groups trained with low resistance. Throughout the entire 12 weeks of training, the subjects began each exercise with a warm-up set using approximately 10% of their 1RM. They then completed three sets of eight repetitions at 20% of their 1RM.

High-Intensity PRMST (Groups 3 and 4) Protocol

The targeted intensity of the resistance progression was set at 80% of 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 (8 repetitions) using 30% to 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 1RM. Every 4 weeks, strength retesting was conducted to be certain that the training resistance was at least 80% of 1RM.

Megestrol Acetate

Each subject received bottles of oral MA solution (oral suspension 40 mg/mL, Bristol-Myers Squibb Co., Princeton, NJ) or an equivalent volume of an identical-appearing placebo. Initially, subjects were instructed to take 5 mL (200 mg MA or placebo) once each day for the first 4 days. On study days, the subjects brought in their bottles for weighing and were witnessed taking the drug. They were also queried about possible side effects using a standardized checklist. On the remaining days, they took the drug at home. Because all subjects tolerated the drug (e.g., no nausea, vomiting, or other significant side effects), the dose was increased on Day 5 to 10 mL (400 mg) and again on Day 9 to 20 mL (800 mg).

Final Assessment

After completing the training sessions and discontinuing the daily ingestion of MA, 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.

Statistics

Change in muscle strength was the primary outcome. A two-factor analysis of variance (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 percentage changes in muscle strength. As part of the analyses, the significance of any exercise-by-MA interaction (positive or negative) was evaluated. If the interaction was not significant, then 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.
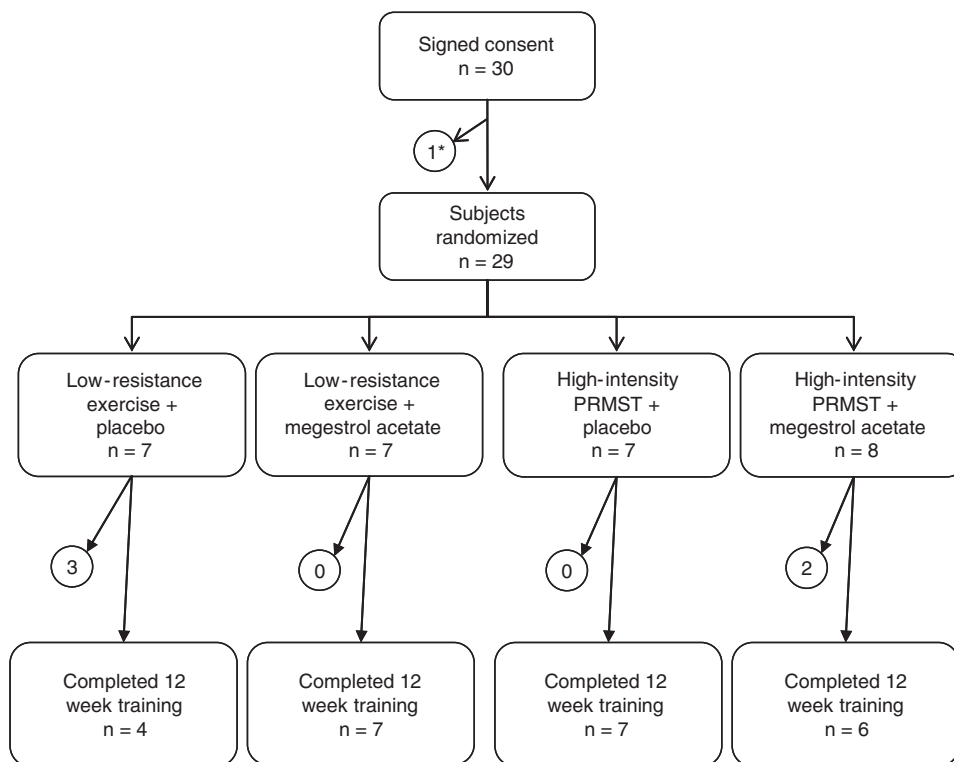
Figure 1. Study subject flowchart. The circles contain the number of subjects who withdrew before completion of the 12-week training. See text for the reasons subjects withdrew. *One subject withdrew after signing consent due to not meeting inclusion and exclusion criteria. PRMST = progressive resistance muscle strength training

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

The same analytical approach was used to evaluate the two secondary outcomes: change in physical performance and change in mid-thigh muscle cross-sectional area. Tests of hypotheses were declared significant at $P = .05$. The data were analyzed using SAS software (SAS Institute, Inc., Cary, NC).

RESULTS

All 29 subjects who entered the study between 1999 and 2001 were randomized as outlined in Figure 1. The subjects ranged in age from 65 to 93 (mean ± standard deviation 79.4 ± 7.4); 26 (90%) were white, 24 (83%) were men, and all had experienced a recent illness-induced decline in their level of physical functioning. At study entry, three subjects (10%) were unable to complete one or more of the functional tests even when allowed to use their hands and an assistive device. Eight subjects (28%) required the use of their hands to stand from a seated position, and 19 (66%) required the use of an assistive device to complete the gait speed tests. Although all of the subjects had multiple active

medical problems, the most common diagnostic categories were hypertension (71%), arthritis (67%), congestive heart failure (54%), chronic obstructive pulmonary disease (54%), coronary artery disease (42%), and cerebrovascular accident (38%). Indicative of their frailty, their referring geriatricians listed all subjects as being debilitated or deconditioned. All had lost more than 10 pounds in the prior year (24 subjects, 83%) or performed more slowly on ambulatory testing than the median for the reference population of healthy older adults (25 subjects, 86%). Other baseline characteristics of the study subjects are provided in Table 1.

Five subjects were withdrawn from the study before completing the 12-week exercise training protocol: three subjects from Group 1 and two from Group 4. In four cases, the subject was withdrawn after experiencing an exacerbation of an underlying medical problem. The remaining case was withdrawn when he developed ischemic changes (inverted T waves) on his electrocardiogram and an exacerbation of his chronic obstructive pulmonary disease 36 hours after exercising. Of those who completed the study, average compliance with the exercise sessions was 99.2 ± 1.8%, with no difference between groups.

Primary and Secondary Outcomes

For the arm and leg exercises, change in muscle strength was independent of age, race, sex, and baseline functional level, lean body mass, cross-sectional mid-thigh muscle area, self-assessment of health status, cognitive function, body mass index, strength, and serum albumin concentration. Change in leg strength, but not arm strength, was

Table 1. Admission Characteristics of Study Subjects (N = 29)

Variable	Group 1 Low-Resistance Muscle Toning+Placebo n = 7	Group 2 Low-Resistance Muscle Toning+MA n = 7	Group 3 High-Intensity PRMST+Placebo n = 7	Group 4 High-Intensity PRMST+MA n = 8	P-value
Age, mean ± SD	84.7 ± 4.6	81.4 ± 9.5	76.0 ± 6.6	76.0 ± 5.3	.05
Body mass index, kg/m², mean ± SD	20.5 ± 2.3	19.8 ± 3.0	20.0 ± 3.3	23.2 ± 5.6	.58
Total testosterone, ng/dL, mean ± SD	338.3 ± 305.3	315.2 ± 221.0	252.1 ± 250.5	443.5 ± 235.5	.54
Mini-Mental State Examination score, mean ± SD	24.0 ± 3.5	22.9 ± 5.2	26.1 ± 5.2	24.8 ± 3.7	.58
Albumin, g/L, mean ± SD	32.7 ± 3.4	34.1 ± 3.7	33.1 ± 6.5	36.4 ± 2.4	.35
Cholesterol, mg/dL, mean ± SD	212.7 ± 54.0	187.6 ± 81.8	201.3 ± 52.6	179.1 ± 19.0	.72
Hemoglobin, g/dL, mean ± SD	12.3 ± 1.6	12.9 ± 1.8	12.8 ± 1.2	13.4 ± 1.4	.57
Number of prescription medications, mean ± SD	5.7 ± 1.8	6.4 ± 3.5	5.6 ± 2.6	7.8 ± 2.4	.37
Total number of medications, mean ± SD	9.7 ± 2.5	10.9 ± 5.2	8.0 ± 2.3	12.1 ± 5.0	.27
Aggregate functional performance score, mean ± SD*†	7.9 ± 3.1	9.4 ± 1.3	10.1 ± 1.8	9.5 ± 2.7	.33
Number of active problems, mean ± SD	2.6 ± 1.5	2.1 ± 1.7	1.7 ± 1.3	2.9 ± 1.9	.56
Percentage of weight lost in previous year, mean ± SD	8.5 ± 6.1	8.5 ± 6.0	10.7 ± 9.3	10.8 ± 8.0	.89
Weight as a percentage of usual, pre-illness weight, mean ± SD	84.9 ± 7.4	91.0 ± 8.0	93.6 ± 8.0	90.9 ± 5.3	.20
Initial one-repetition maximum, mean ± SD†					
Chest, kg, mean ± SD	18.6 ± 7.7	19.5 ± 9.6	20.6 ± 10.7	28.9 ± 8.6	.13
Leg, kg, mean ± SD	65.1 ± 26.1	74.5 ± 32.6	75.3 ± 40.5	105.0 ± 37.5	.15
Mid-thigh cross-sectional muscle area, cm², mean ± SD†	77.8 ± 22.8	82.3 ± 25.1	84.2 ± 14.9	108.7 ± 26.5	.06
Self-assessment of health excellent or good, n (%)‡	2 (28.6)	0 (0.0)	4 (57.1)	3 (37.5)	.16
Married, n (%)	2 (28.6)	1 (14.3)	4 (57.1)	4 (50.0)	.37
White, n (%)	6 (85.7)	6 (85.7)	6 (85.7)	8(100.0)	.68
Male, n (%)	6 (85.7)	5 (71.4)	5 (71.4)	8(100.0)	.41
Independent in all ADLs, n (%)§	5 (71.4)	2 (28.6)	6 (85.7)	5 (62.5)	.19
Requires an assist device to walk, n (%)‖	5 (71.4)	5 (71.4)	4 (57.1)	5 (62.5)	1.00

* Each of four tests (sit-to-stand maneuver, habitual gait speed, maximal safe gait speed, and stair climb) was scored on a 4-point scale (0 = cannot complete task; 1 = needs assistance to complete task; 2 = completes task independently; 3 = completes task independently and in ≤median time for control population of healthy older people). The aggregate score represents the sum of these fours scores and can range from 0 to 12 points.
† All functional performance, strength, and muscle area data were log transformed before analysis (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.
§ Independent in all of the basic activities of daily living (ADLs; bathing, dressing, toileting, transferring, continence, and feeding) as measured using the Katz Index of ADLs.
‖ Required the use of an assist device to complete the initial gait speed test.
PRMST = progressive resistance muscle strength training; MA = megestrol acetate; SD = standard deviation.

positively correlated with baseline serum total testosterone concentration and amount of weight lost in the prior year. The change in mid-thigh cross-sectional muscle area was independent of all baselines variables. Change in aggregate functional score was correlated only with baseline score, the lowest aggregate scores at baseline being associated with the greatest improvement (correlation coefficient = − 0.48, $P = .008$).

The adjusted mean differences in strength by intervention group for each exercise are presented in Table 2. As shown, subjects who received high-intensity PRMST and placebo (Group 3) experienced the greatest strength gains. The addition of MA was associated with worse outcomes than high-intensity exercise training alone, especially with

regard to the leg exercises. Post hoc analysis demonstrated that subjects who received high-intensity PRMST and placebo (Group 3) experienced significantly greater percentage increases in leg strength than subjects in either of the MA treatment groups (Groups 2 and 4, $P < .05$ for each comparison). The main effects of the drug (MA vs placebo) and exercise (high-intensity PRMST vs low-resistance exercise) interventions on leg strength are shown graphically in Figure 2. Although the subjects who received MA had significantly worse outcomes than those who received placebo, there was considerable intersubject variability in this response, as demonstrated in Figure 3. There was also a significant negative effect of MA on physical function. In general, subjects who received MA experienced a deteri-

Table 2. Adjusted Mean Absolute or Percent Change for Each Outcome Based on Intent-to-Treat Analysis (N = 29)

| | Study Group | | | | P-value | | |
| Outcome Variable | Group 1 Low-Resistance Exercise+ Placebo (n = 7) | Group 2 Low-Resistance Exercise+MA (n = 7) | Group 3 High-Intensity PRMST+ Placebo (n = 7) | Group 4 High-Intensity PRMST+MA (n = 8) | Effect of Exercise | Effect of Drug | Inter-action |
	Mean Change ± Standard Error						
All subjects							
Chest press*							
Percentage	1.61 ± 5.46	2.66 ± 5.46	17.12 ± 5.46	9.53 ± 5.11	.048	.55	.43
Absolute, kg	0.08 ± 1.11	− 0.16 ± 1.11	3.77 ± 1.11	2.17 ± 1.03	.01	.41	.54
Leg press*							
Percentage	8.30 ± 5.93	− 1.53 ± 5.98	23.56 ± 6.05[†]	− 2.90 ± 5.70	.25	.006	.68
Absolute, kg	4.57 ± 5.88	0.18 ± 5.89	17.39 ± 5.98	− 1.22 ± 5.64	.34	.06	.24
Mid-thigh cross-sectional muscle area, percentage*	3.45 ± 3.38	2.07 ± 3.38	1.49 ± 3.38	− 3.00 ± 3.17	.30	.39	.64
Aggregate score[‡§]	0.21 ± 0.61	− 0.93 ± 0.58	0.76 ± 0.59	− 0.66 ± 0.54	.49	.04	.82
Weight, kg[‡]	0.68 ± 0.89	5.61 ± 0.89[‖]	− 0.85 ± 0.89	0.72 ± 0.83	.001	.001	.07
Body fat, kg[‡]	0.75 ± 1.69	9.50 ± 1.69[‖]	0.34 ± 1.69	1.98 ± 1.59	.03	.005	.04
Nonfat mass, kg[‡]	− 0.07 ± 1.23	− 3.89 ± 1.23	− 0.59 ± 1.23	− 1.25 ± 1.50	.39	.08	.20
Morning total serum testosterone, ng/dL[‡]	− 33.8 ± 69.9	− 281.5 ± 69.9	12.0 ± 69.9	− 346.2 ± 65.4	.89	<.001	.43
Morning serum cortisol, nmol/L[‡]	99.32 ± 70.90	− 173.27 ± 70.90	− 1.66 ± 70.90	− 154.78 ± 66.49	.56	.005	.40
Average daily nutrient intake as percentage of requirements[‡]	0.9 ± 8.1	15.6 ± 6.7	0.3 ± 6.7	21.0 ± 7.7	.76	.03	.68
Men	(n = 6)	(n = 5)	(n = 5)	(n = 8)			
Morning total serum testosterone, ng/dL[‡]	− 39.4 ± 71.9	− 397.0 ± 78.8	− 15.3 ± 78.8	− 346.2 ± 62.3	.48	<.001	.98

* Based on multifactor analysis of covariance of the log-transformed data (see text for details). After intervention groups, the only baseline covariates to enter the model for leg press were admission serum total testosterone and amount of weight lost in the prior year. None of the baseline covariates entered the models for chest press or mid-thigh cross-sectional muscle area.

[†] Significantly different from Groups 2 and 4 according to post hoc analysis. $P < .05$ for each comparison.

[‡] Based on multifactor analysis of covariance of the data (see text for details). After intervention groups, the only baseline covariate to enter the model for aggregate score was baseline aggregate score. For average daily nutrient intake (expressed as percentage of requirements), baseline weight, nutrient intake, and self-assessment of health entered as covariates. None of the baseline covariates entered the models for the other outcomes listed. For each variable, values presented are the average of the absolute differences between baseline and final values.

[§] Each of four tests (the sit-to-stand maneuver, habitual gait speed, maximal safe gait speed, and stair climb) was scored on a 4-point scale (0 = cannot complete task; 1 = needs assistance to complete task; 2 = completes task independently; 3 = completes task independently and in ≤median time for control population of healthy elderly). The aggregate score represents the sum of these fours scores and can range from 0 to 12 points.

[‖] Significantly different from the other three groups according to post hoc analysis. $P < .05$ for each comparison.

PRMST = progressive resistance muscle strength training; MA = megestrol acetate.

oration in aggregate physical function scores, whereas the remaining subjects improved (− 0.80 ± 0.40 vs 0.48 ± 0.41, $P = .04$). When only the 24 subjects who completed the 12-week exercise program were included in the analyses, the results were similar to the intent-to-treat analyses.

As also shown in Table 2, MA was associated with a significant drop in morning serum cortisol and total testosterone concentrations (especially in the male subjects). There was no consistent effect of exercise or MA on mid-thigh cross-sectional muscle area. Both the exercise and drug treatments had significant effects on weight. Subjects randomized to low-intensity training gained significantly more weight than did those in the high-intensity groups (3.2 ± 0.6 kg vs − 0.1 ± 0.6 kg, $P = .001$). Likewise, MA was associated with more weight gain than placebo (3.2 ± 0.6 kg vs − 0.1 ± 0.6 kg, $P = .001$). A comparison of the four intervention groups (Table 2) indicates that the subjects in Group 2 (low-resistance training plus MA) gained significantly more weight than the remaining subjects. The changes in body composition induced by the interventions also differed by group. The subjects who received MA gained more fat (5.74 ± 1.16 kg vs 0.55 ± 1.20 kg, $P = .005$) and tended to lose more lean mass (− 2.57 ± 0.84 kg vs − 0.33 ± 0.87 kg, $P = .08$) than those who received the placebo, although this latter difference did not reach statistical significance. When each of these within-group differences was examined as a function
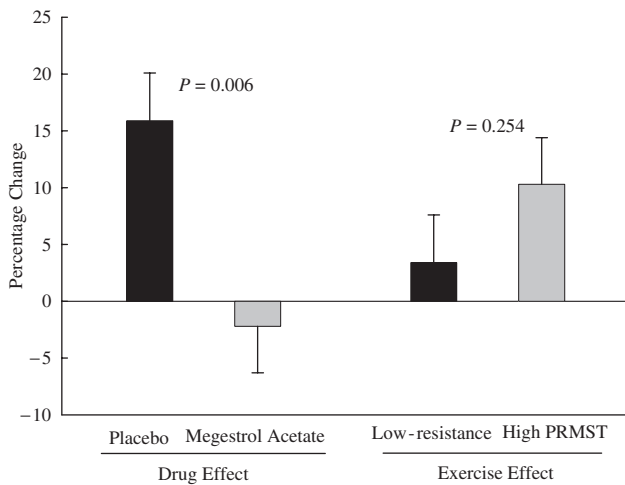
Figure 2. Percentage improvement in lower-extremity muscle strength by intervention for the 29 subjects based on intent-to-treat analysis. The results are based on muscle-strength testing using the leg press machine.

of time, the amount of fat gained and lean mass lost by the end of the 12-week intervention were significantly different from zero ($P < .006$ for each analysis) for the subjects who received MA. For those who received placebo, neither the fat nor lean mass change was significant ($P > .6$ both analyses).

Nutrient Intake

When nutrient intake was expressed as a percentage of calculated requirements, there was a significantly greater improvement in intake with MA than with placebo ($18.3 \pm 5.0\%$ vs $0.6 \pm 5.3\%$, $P = .03$). As shown in Table 2, there was not a significant exercise effect ($P = .76$), and there was no interaction between MA and exercise with regard to nutrient intake. By the end of the study, the subjects
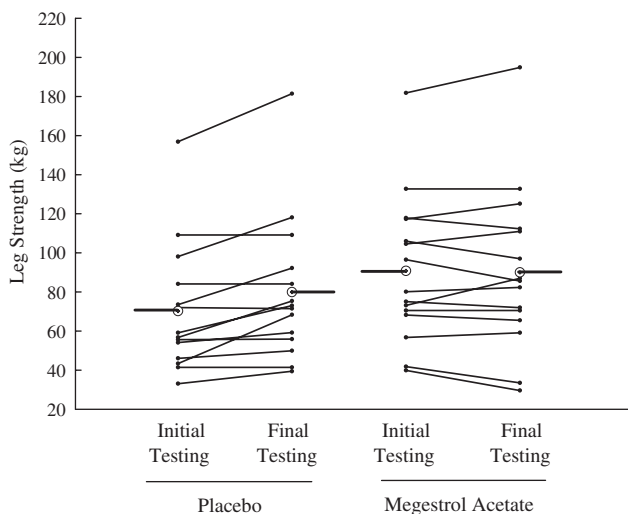
Figure 3. Initial and final lower-extremity strength testing results (1-repetition maximum) for each study subject grouped by drug intervention (megestrol acetate vs placebo). For subjects who did not complete the study, final strength was set equal to initial strength. The horizontal bars represent the group mean for the given time point.

receiving MA tended to consume a greater percentage of their calculated energy requirements per day than did the remaining subjects, although these differences were not significant ($91.4 \pm 11.5\%$ vs $78.8 \pm 12.1\%$, $P = .48$).

DISCUSSION

The results of this study indicate that MA is effective in stimulating greater nutrient intake and produces an increase in total body weight in frail, recuperative care patients. These finding are consistent with those of prior studies that also demonstrated appetite improvement and weight gain resulting from use of MA in various groups of frail individuals.[16–18] However, the more important finding from this study relates to the apparent affects of MA on muscle strength and physical function. It had originally been hypothesized that high-intensity PRMST would produce greater strength and muscle mass gains and functional improvement than the low-intensity exercises. It was also hypothesized that MA would likewise have positive effects on these outcomes and that these effects would be additive to those of exercise. The results of this study suggest that the opposite is true. Although MA produces greater weight gain than placebo, it appeared to blunt the positive effects of high-intensity exercise training, especially on leg strength. MA also appeared to cause significant deterioration in physical function (as indicated by the aggregate functional score change), although other studies have failed to demonstrate a negative effect of MA on physical function in frail older adults.[25]

Although MA resulted in an increase in body weight, the weight gain was predominantly fat. Most studies of MA that have included an examination of body composition have also reported that the majority of weight gain induced by MA has been in the form of fat.[26,27] In the current study, subjects who received MA also lost a significant amount of lean mass, particularly those in the low-resistance muscle toning plus MA group. Despite the apparent loss of lean mass with MA, there was not a consistent effect on mid-thigh cross-sectional muscle area as measured using computed tomography. This is in contrast to a previous study that demonstrated that the use of MA alone or in combination with testosterone was associated with a significant decline in mid-thigh cross-sectional muscle area during the 12-week intervention.[19] It was only the subjects randomized to receive both testosterone and high-intensity PRMST along with MA that experienced the expected increase in muscle mass. It is not clear why the results of the current study relating to muscle mass differed from those the previous study, but both studies found evidence for an antianabolic effect of MA.

The finding of a possible antianabolic effect of MA is consistent with what is known about the metabolic properties of this drug. Among its known effects, MA has glucocorticoid agonist and antagonist properties.[28,29] As demonstrated in the current study and other investigations of this drug, MA suppresses adrenal function.[28–32] A recent study demonstrated that a daily oral dose of 800 mg of MA results in a 90% reduction in the serum concentration of hydrocortisone and adrenocorticotropic hormone within 12 weeks.[29] It is estimated that this degree of hypothalamic-pituitary-adrenal suppression is equivalent to that which

25 mg per day of prednisone would produce.[29] In most cases, the glucocorticoid activity of MA is ostensibly sufficient to prevent clinically apparent adrenal insufficiency,[29] although there are case reports of acute adrenal insufficiency developing in patients while on this drug.[28,31,32] Thus, it is not clear whether MA has any true dose equivalency to glucocorticoids or whether it shares all of the same metabolic properties. Virtually nothing is known about the effects of MA on muscle metabolism.

Another potential antianabolic effect of MA is its suppression of testosterone in men and estradiol in women.[19,29,33,34] At a dose of 800 mg per day, MA results in castrate levels of testosterone in healthy older men after 12 weeks of therapy.[29] All of the male subjects in this study also had marked suppression of testosterone. Estradiol was not measured in the women. Whether the suppression of sex hormones is the primary factor leading to the apparent MA-induced loss of lean mass is not certain. Glucocorticoids can also induce a loss of lean body mass and muscle strength and a gain of fat mass.[35]

There are a number of limitations to this study. The sample size was small, and all of the subjects had multiple comorbid conditions that could have affected the results. There was also a somewhat inconsistent response to the interventions in the arms and the legs. The potential negative consequences of MA appeared to be more pronounced in the legs than arms. It is not clear from the study data why this difference would exist, but the results suggest a strong need for a more in-depth investigation of this drug before its widespread usage in recuperative care settings can be advocated. Given that MA is used widely to treat weight loss in older adults, especially those in nursing homes,[16,29] this is an important concern needing further clarification. The sex-specific effects of different-sized doses of MA, the co-administration of sex hormones, and various intervention durations all need to be investigated.

The duration of the interventions in this study may also have been a limitation. Based on prior studies of PRMST and MA, a 12-week intervention was judged to be adequate to demonstrate any possible beneficial effects of the combined treatments.[12,15] Given that only a modest change in muscle strength was demonstrated even in the high-intensity PRMST plus placebo group, this assumption may not have been correct. Whether the outcomes would be substantially different with an intervention of longer duration remains to be determined. It is also of interest that high-intensity PRMST appears to prevent MA-induced weight gain. A longer, more-detailed study may help to reveal the significance and mechanism of this interaction as well.

CONCLUSION

High-intensity PRMST is a safe and well-tolerated exercise regimen for frail elderly patients. The addition of MA appears to blunt the beneficial effects of PRMST, resulting in less muscle strength and functional performance gains.

ACKNOWLEDGMENTS

Author Contributions: Dennis H. Sullivan conceptualized and designed the study, interpreted the results, and was primary author of the manuscript. Paula K. Roberson was involved in study concept and design, data analysis, and critical revision of the manuscript. Eugene S. Smith and J. Allen Price were involved in study concept and design and interpretation of data. Melinda M. Bopp was involved in study concept and design, acquisition of data, and preparation of the manuscript.

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