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Testosterone Administration Preserves Protein Balance But Not Muscle Strength during 28 Days of Bed Rest*

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ABSTRACT

Decrements in muscle strength as a result of prolonged bed rest are well defined, but little is known about potential countermeasures for preventing loss of strength under this condition. The purpose of this study was to determine whether testosterone administration would preserve protein balance and muscle strength during prolonged bed rest. Ten healthy men (age, 36 ± 2 yr; height, 177.2 ± 3.4 cm; weight, 80.5 ± 3.9 kg; mean ± SE) were admitted to our in-patient metabolic unit. After a 1-week ambulatory run-in period, each subject was confined to bed for 28 days at 6° head-down tilt while receiving a daily oral dose of T_3 (50 μg/day). During the bed rest/T_3 period, six of the men were randomized to receive testosterone enanthate by im injection (T; 200 mg/week) while four received placebo in a double blind fashion. Nitrogen balance was determined throughout, and whole body [^{13}C]leucine kinetics were assessed at baseline and on day 26 of bed rest. Before bed rest and on the third day of reambulation, the muscle strength of the knee extensors and flexors and shoulder extensors and flexors was determined at 60°/s on a Cybex isokinetic dynamometer. Despite improved [^{13}C]leucine kinetics and maintenance of nitrogen balance and lean body mass in T-treated subjects, little preservation of muscle strength, particularly in the knee extensors, was noted. Muscle strength [reported as the best work repetition in foot-pounds (FtLb)] for right knee extensors declined (P = 0.011) similarly in both groups; from 165 ± 15 to 126 ± 18 FtLb in T-treated men and from 179 ± 22 to 149 ± 13 FtLb in placebo-treated men. Overall, there was less of a decline in extension and flexion strength of the shoulder compared to the knee, with no benefit from T. These results suggest that in the absence of daily ambulatory activity, T administration will not increase or, in the case of this bed rest model, preserve muscle strength. (*J Clin Endocrinol Metab* **84:** 207–212, 1999)

EXPOSURE to microgravity results in decreased mechanical loading of skeletal muscles that have antigravity functions. Associated with such unloading are losses in muscle mass and strength that could lead to structural and functional deficits of the musculoskeletal system (1). Not only could these deficits impair muscular function during space flight, but they could affect performance during emergency situations upon return to a 1G environment. Thus, there is a need to develop effective countermeasures against skeletal muscle unloading during space flight.

The pattern of muscle atrophy and weakness that occurs with space flight is also evident with prolonged bed rest (2). Thus, bed rest with 6° head-down tilt has become the most frequently used human ground-based model to study the consequences of space flight. We have recently shown that addition of low dose T_3 treatment to the standard bed rest model accelerates whole body protein turnover and augments the loss of lean body mass (3). This model has the potential of shortening the time needed to study the usefulness of countermeasures against skeletal muscle unloading. Identification of successful countermeasures against bed rest-induced skeletal muscle atrophy is not only important for management of the physiological consequences of microgravity in space, but is of more general clinical interest because chronic disease, illness, or injury can bring about forced and prolonged bed rest.

Few studies have been able to maintain muscular strength and/or fitness at ambulatory levels during prolonged bed rest (4). Exercise has been the most often studied countermeasure under this condition, and it appears that high intensity, intermittent, isotonic exercise shows the most promise for attenuation of both cardiovascular and musculoskeletal deconditioning (5, 6). Certain pharmacological agents, growth factors, or anabolic hormones may have beneficial effects during situations of skeletal muscle unloading. Further, such agents could reduce the time and extra energy requirements associated with exercise regimens during space flight or bed rest. For example, testosterone is known to promote muscle protein synthesis (7), and recent studies have shown that chronic administration of testosterone increases lean body and muscle mass and improves muscle strength (8, 9). In this study, we tested the hypothesis that testosterone administration would preserve protein mass and muscle strength during prolonged bed rest with T_3 treatment.

Materials and Methods

Conditions of the study

This study involved a 40-day stay at the Pennington Biomedical Research Center Inpatient Metabolic Unit. The first 7 days served as a diet stabilization period before 28 days of strict 6° head-down bed rest. All subjects continued to live on the unit for 5 days after reambulation. Baseline testing was completed during the 7-day stabilization period, and reassessments of the baseline measures were made during the final

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week of bed rest and/or during the 5-day recovery period. During the bed rest period, all subjects received a daily dose of T_3 (3). Briefly, subjects were given a 100-μg oral loading dose on day 1 of bed rest and thereafter received five 10-μg oral doses given every 4 h (omitting the 0200 h dose) for a total dose of 50 μg/day T_3. Subjects were not permitted to deviate from the head-down tilt position and were monitored continuously by the Metabolic Unit nursing staff. Lateral and rolling movement was allowed. Excretory functions were accomplished while strict bed rest was maintained. The subjects did, however, shower daily on a horizontal platform in a private bathing room (~15–30 min). Body weight was measured daily, and the subjects were maintained on a isocaloric mixed diet (28–30% fat) throughout the study. Adequate protein calories were maintained so that the subjects received at least 1.2 g/kg·day. While in bed, subjects had available to them reading materials, radio, a compact disk or cassette player, TV, videocassette movies, a computer, and computer games. Subjects were housed two per room, but could visit other subjects (via gurney) in a common area just in front of the nurse's station.

Study subjects

Ten men (five Caucasian, four African American, and one Indian) between the ages of 31–47 yr volunteered for this study, which was approved by the Louisiana State University institutional review board. Informed consent was obtained from all subjects after the purpose and procedures of the study were described. All were healthy, as indicated by clinical examination and blood and urine screening tests. Their physical characteristics are presented in Table 1. During the bed rest/T_3 period, six of the men were randomized to receive testosterone enanthate (T) while four received placebo (P) in a double blind fashion. T/P was given by im injection, and a loading dose for T (75 mg/day) was given for the first 3 days of bed rest. Thereafter, the T dose was 200 mg/week, given as a single im injection.

Tests and measures

Serum testosterone and thyroid hormone measurements. Total serum testosterone was measured by RIA using a Coat-A-Count kit (Diagnostics Products Corp., Los Angeles, CA). The precision of this measure ranges from 9–13%, with a sensitivity of approximately 4 ng/dL. Both the intra- and interassay coefficients of variation were between 5–10% for the range of concentrations measured. Blood samples were drawn in the morning (0700 h) after an overnight fast before bed rest; on days 1, 2, and 3 of bed rest/T_3; and at the end of weeks 2, 3, and 4. Serum thyroid hormone (T_3) and TSH concentrations were measured by microparticle enzyme immunoassay on an Abbott IMx analyzer (Abbott Laboratories, North Chicago, IL); T_4 levels were measured with a fluorescence polarization immunoassay.

TABLE 1. Subject characteristics

Treatment	Baseline	Bed rest + T_3
Age (yr)		
Testosterone	36.3 ± 2.6	
Placebo	35.2 ± 3.7	
Ht (cm)		
Testosterone	175.3 ± 5.0	
Placebo	180.1 ± 4.4	
BW (kg)		
Testosterone	78.9 ± 4.9	77.9 ± 4.9[a]
Placebo	82.0 ± 7.1	78.1 ± 7.1
Lean body mass (kg)		
Testosterone	56.5 ± 2.2	58.2 ± 2.5[a]
Placebo	59.4 ± 4.4	57.9 ± 4.3
% Body fat		
Testosterone	26.2 ± 3.0	25.0 ± 2.6
Placebo	25.8 ± 1.5	25.9 ± 1.7

Baseline measures of body weight, lean body mass, and percent body fat were not different between groups. In comparison to placebo (n = 4), the testosterone group (n = 6) gained lean body mass and lost less body weight during the bed rest/T_3 period. Data are the mean ± SE.

[a] $P < 0.05$.

Body composition. Dual energy x-ray absorptiometry (DEXA) was used to determine the effect of bed rest/T_3 treatment and testosterone countermeasure on lean body mass. The instrument used was a Hologic QDR 2000 (Hologic, Inc., Waltham, MA) operated with the Enhanced Array Whole Body Software Package, version 5.678A. The reported precision for DEXA determination of lean body mass is on the order of 1–2%. DEXA determinations were made before bed rest during the 7-day stabilization period and during the final week of bed rest.

Nitrogen balance. Starting with in-patient day 1 and continuing through the ambulatory recovery period, all urine and feces were collected for nitrogen balance studies. Urine was collected in polyethylene bottles with no preservatives added. The completeness of urine collection was determined by daily urinary creatinine measurements. Fecal collection periods were 7 days, separated by administration of an indigestible fecal marker (carmine red dye). Correction for fecal loss was made by quantitating the nonabsorbable marker polyethylene glycol, which was given with meals (10 mL as 10% solution). Nitrogen was determined on daily urine volumes and 7-day food and fecal compositions. Urine and fecal nitrogen was measured by chemiluminescence using a model 703C pyrochemiluminescent system (Antek Instruments, Inc., Houston, TX). Fecal nitrogen was determined after 7-day stool composites were homogenized with a known volume of deionized water. Food nitrogen was determined using a Perkin Elmer model 2410 nitrogen analyzer (Norwalk, CT). Nitrogen balance was determined by subtracting fecal and urinary nitrogen excretion from nitrogen intake. Skin and sweat nitrogen loss was estimated (10), and balance figures were corrected for these estimates.

Whole body protein turnover. Whole body protein turnover was determined during a primed, constant rate infusion of L-[1-^{13}C]leucine using the reciprocal pool approach (11, 12). Assessment of whole body protein turnover was made on day 5 of the 7-day stabilization period (*i.e.* before bed rest) and on the 26th day of bed rest/T_3. After an overnight fast, tracer infusions were started at 0800 h. L-[1-^{13}C]leucine was infused for 3 h at a constant rate of 3.6 μmol/kg·h after priming doses of $NaH^{13}CO_3$ (0.087 mg/kg; to prime the bicarbonate pool) and [1-^{13}C]leucine (4.8 μmol/kg). Blood samples were taken from a forearm vein at −5, 120, 135, 150, 165, and 180 min relative to the start of the infusion for analysis of [^{13}C]α-ketoisocaproic acid enrichment by gas chromatography-mass spectrometry (Hewlet Packard 5988A, Palo Alto, CA). Breath samples were collected at the same time points for the analysis of $^{13}CO_2$ by gas isotope ratio-mass spectrometry (MAT 252, Finnigan, Bremen, Germany). The CO_2 production rate was determined by indirect calorimetry using a SensorMedics 2900Z metabolic cart (Yorba Linda, CA). This measurement was carried out for 30 min, beginning 1 h after the start of tracer infusion. The rates of whole body leucine turnover (*i.e.* leucine R_a), oxidation, and nonoxidative disposal (NOLD; *i.e.* protein synthesis) were calculated as previously described (12, 13).

Muscle strength testing. Muscle strength testing was performed on day 3 of the 7-day stabilization period and after 72 h of reambulation. The muscle strength of the knee extensors and flexors and shoulder extensors and flexors was determined at 60 and 180°/s on a Cybex isokinetic dynamometer (NORM System, Cybex, Medway, MA). The exercise testing center is about 0.5 mile from the clinical facility; thus, the walk from the clinic to the exercise laboratory served as a warm-up before testing. Knee extension and flexion testing were performed first. The instrument was then reconfigured for shoulder flexion and extension measurements, which were made in the supine position. After proper instruction, the subject was allowed three practice repetitions of the motion being tested to familiarize himself with the movement. Then, five maximal repetitions were performed during each action at each speed, and data from the best work repetition were recorded. Verbal encouragement was given, and the pre- and post-bed rest tests were conducted by the same investigator. Right and left limbs were tested, but the changes associated with bed rest and/or testosterone treatment were quantitatively similar. Therefore, for the sake of clarity, only data from the dominant limb are presented. In all cases this was the right leg and shoulder.

Statistical analysis

Data were analyzed by repeated measures ANOVA. Changes in nitrogen balance over time were calculated by subtracting baseline values from pooled values for 7-day periods during bed rest and were analyzed by repeated measures ANOVA. Reported nitrogen balance data were not corrected for nonphysiological losses (*i.e.* blood sampling). Data are presented as the mean ± SEM, and statistical significance was set at $P < 0.05$.

Results

The two groups were similar with respect to age, weight, and body composition before the start of the bed rest protocol (Table 1). The bed rest/T_3 treatment was tolerated well by all subjects. Headaches, nausea, and abdominal discomfort were common symptoms, primarily at the beginning. Two subjects had difficulty voiding, experienced periods of constipation, and complained of indigestion. One subject had frequent backaches and complained occasionally of leg aches. Many of these symptoms were alleviated with common medications. There were no complications or side-effects associated with T administration, and the symptoms mentioned above were experienced equally in the T- and P-treated groups.

Serum testosterone values were similar in the P- and T-treated subjects before bed rest (*i.e.* 609.6 ± 63.6 *vs.* 558.8 ± 81.5 ng/dL). All T-treated subjects showed a significant rise in serum testosterone by the second week of the study ($P < 0.05$). By the end of the study, serum testosterone had increased 2.5-fold in the T-treated subjects and was 2-fold greater than that observed in the P-treated subjects (Fig. 1).

By week 4 of bed rest/T_3 treatment, serum concentrations of T_3 had increased ($P < 0.0001$) an average of 173% over baseline, with no difference between groups (*i.e.* from 1.23 ± 0.06 to 3.35 ± 0.23 nmol/L). T_4 levels declined to 48% of baseline (from 8.59 ± 0.54 to 4.11 ± 0.41 nmol/L), and TSH was almost completely suppressed (*i.e.* 1.27 ± 0.19 *vs.* 0.08 ± 0.02 mU/L) in both groups.

After 28 days of bed rest, the men in the P group lost an average of 3.9 kg of body weight (*i.e.* from 82.0 ± 7.1 to 78.1 ± 7.1 kg). Body weight in the T-treated subjects declined by only 1.0 kg (78.9 ± 4.9 to 77.9 ± 4.9 kg). This treatment × time interaction was statistically significant ($P = 0.002$). Lean body mass declined by 1.5 kg in the P group, whereas the T-treated subjects experienced nearly a 2-kg increase in lean mass (*i.e.* 1.7 ± 0.9 kg); again, the treatment × time interaction was statistically significant ($P = 0.04$).

Figure 2 shows that nitrogen balance was near zero in both groups before bed rest, although it did tend to be more negative in the P group (*i.e.* −1.02 ± 1.3 *vs.* 0.67 ± 0.56 g/day). During bed rest/T_3, nitrogen balance decreased in the P group, reaching a nadir of −5.77 ± 1.88 g/day during week 3. A negative nitrogen balance was observed during the first week of bed rest in T-treated men, but thereafter nitrogen balance approached and then exceeded zero, such that by week 4 of bed rest the T-treated subjects were in positive nitrogen balance (*i.e.* +3.15 ± 1.02 g/day). The treatment × time interaction for nitrogen balance was statistically significant ($P < 0.05$).

Before bed rest, fasted rates of leucine R_a, oxidation, and NOLD were similar between the T and P groups (Table 2). Twenty-six days of bed rest with T_3 treatment increased leucine R_a by 22% in P-treated subjects and by 11% in T-treated subjects (main effect of time, $P < 0.01$). Although leucine oxidation increased by 33% in P-treated men, there was a 10% decrease in oxidation for T-treated men (treatment × time interaction, $P < 0.01$). NOLD increased to a similar extent in the T and P groups; however, relative to the prebed rest measurement, protein balance (*i.e.* NOLD − leucine R_a) was maintained in T-treated subjects while it became more negative in P-treated subjects (Table 2; treatment × time interaction, $P < 0.01$).

Tables 3 and 4 give the slow (60°/s) and fast (180°/s) speed isokinetic strength results for lower and upper body musculature, respectively. After bed rest/T_3, general reductions in lower body strength were observed in both the T and P groups, whereas little change in upper body strength was noted. Thus, normal use of the arms during 28 days of bed rest most likely maintained shoulder muscle strength. A similar observation has been made previously (4). Knee ex-

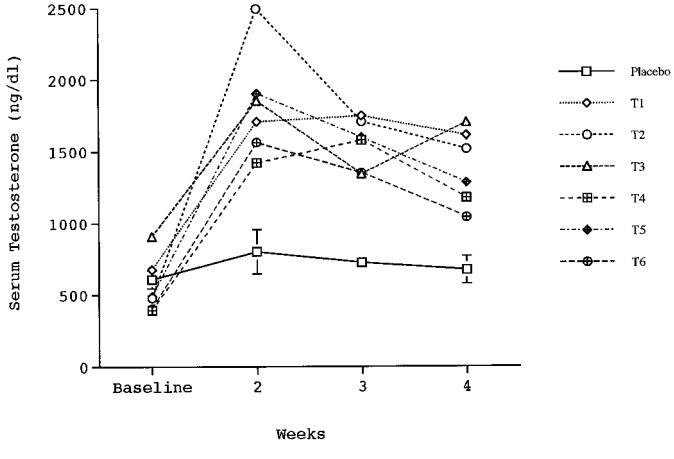

FIG. 1. Serum testosterone levels (nanograms per dL) before and throughout bed rest/T_3. The *solid line* shows average testosterone levels, over time, for the P group (n = 4), whereas individual data points are plotted for the T group. By the second week of bed rest, serum testosterone was increased an average of 2.5-fold in the T group and was nearly 2-fold greater than that in the P group by the end of the bed rest period.

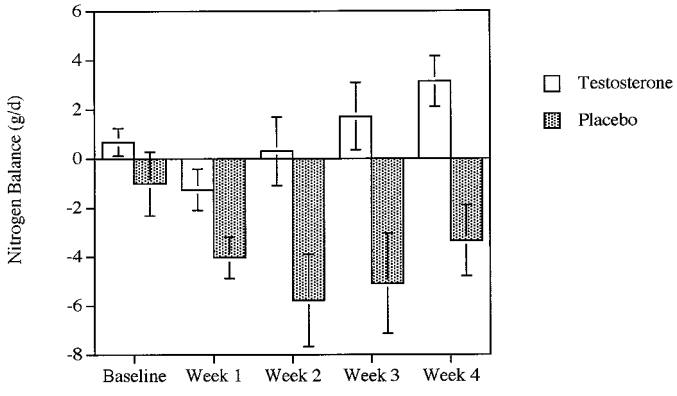

FIG. 2. Nitrogen balance (grams per day) before and throughout bed rest/T_3. Although nitrogen balance became negative in P-treated subjects, it approached and then exceeded zero by 4 weeks of bed rest in T-treated subjects. This treatment (T *vs.* P) × time interaction was statistically significant (*, $P < 0.05$).

TABLE 2. Whole body leucine kinetics before and after bed rest/T_3 in testosterone- and placebo-treated groups

Treatment	Baseline	Bed rest + T_3
Leucine Ra (μmol/kg LBM·h)		
Testosterone	157 ± 6	174 ± 9[a]
Placebo	148 ± 6	181 ± 8[a]
Oxidation (μmol/kg LBM·h)		
Testosterone	31 ± 1	28 ± 2
Placebo	27 ± 3	36 ± 2[b]
NOLD (μmol/kg LBM·h)		
Testosterone	126 ± 6	146 ± 9[a]
Placebo	121 ± 6	145 ± 7[a]
Balance (μmol/kg LBM·h)		
Testosterone	−31 ± 1	−28 ± 2
Placebo	−27 ± 3	−36 ± 2[b]

Leucine Ra and NOLD were significantly increased from pre- to post-bed rest in both the testosterone- and placebo-treated groups. However, leucine oxidation increased more, and leucine balance was more negative after bed rest in the placebo-treated group. Data are the mean ± SE.

[a] Main effect, $P < 0.01$.

[b] Time × treatment interaction, $P < 0.01$.

tension strength at 60°/s declined by 24% in the T-treated group and by 17% in the P-treated group (main effect of time, $P < 0.05$). Average reductions of 30% and 15% for knee flexion strength at 60°/s were observed in the T- and P-treated groups, but this only approached statistical significance ($P = 0.08$). Except for the knee extensors, there was no significant change in the lower or upper body fast speed (180°/s) strength measurements in either of the groups. As an example, force production during knee extension at 180°/s declined by approximately 7% ($P < 0.05$) in both the T- and P-treated groups.

Discussion

Loss of lean body mass during space flight is one of several documented consequences of weightlessness and is of significant concern during long duration flights or extended stays aboard space stations. Loss of muscle strength is one functional outcome associated with lean tissue depletion. Muscle atrophy and weakness also occur after strict bed rest (14–19). Although much effort has gone into validating the bed rest model for simulated weightlessness, little work has been performed to identify practical countermeasures to its consequences. As testosterone administration has been shown to promote skeletal muscle protein synthesis (7) and enhance muscular strength (8, 9), we tested the hypothesis that T administration would preserve muscle strength during prolonged bed rest. Further, we believed that any preservation of muscle strength would be due to maintenance of lean body (muscle) mass. The results from this investigation do not support these hypotheses.

There has been a long-standing interest in the use/abuse of testosterone for promoting increases in muscle mass and strength, particularly in athletes, in whom it is not only a medical but an ethical concern. Clinical studies on the effects of steroids on muscle mass and strength have been inconclusive (20); many have significant shortcomings. A wide range of doses and types of anabolic-androgenic steroids has been used, which makes comparison difficult. To date, there still has not been a well designed and controlled experiment for one particular steroid establishing the dose-response curve for its effects on muscle strength and/or mass. Nonetheless, recent studies suggest that short term (10 weeks) treatment with mega doses of T (600 mg/week) is safe and promotes muscle mass and strength gains, particularly when combined with weight-lifting exercise (8), and that replacement dosing in healthy older men promotes muscle protein synthesis (9) and improves strength and function (9, 21).

Testosterone administration preserved lean body mass in our bed-rested subjects, but significant decrements in knee extension strength were still observed, indicating that without ambulatory activity, testosterone administration will not increase or, in the case of a bed rest model, prevent declines in muscle strength/function. Previous studies have consistently reported greater loss in strength relative to reduction in muscle cross-sectional area after prolonged bed rest (18, 19, 22). This led to studies in which it was concluded that decreased neural drive and/or reduced electromechanical efficiency contribute to the loss of strength (22). Furthermore, Bamman *et al.* (23) reported that resistance exercise training during bed rest maintained muscle fiber cross-sectional area and training-specific strength, but not maximum voluntary isometric contraction. Thus, effective countermeasures against bed rest-induced muscle atrophy and weakness will need to counteract not only declines in muscle mass but the general neural deconditioning that results from prolonged bed rest. In the present investigation, repeat measures of muscle strength were performed on the third day of reambulation. Thus, there was opportunity for recovery of neuromuscular activity patterns, yet knee extension strength was still significantly less than baseline values regardless of treatment (P *vs.* T). This is interesting and could be interpreted to suggest that testosterone administration will not enhance the early recovery of muscle strength after a period of unloading or zero gravity. The observed 24% reduction in knee extension strength in the T-treated group is similar to muscle strength losses in other bed rest studies (16, 19). Thus, comparisons with not only the P group in the present investigation but with results from previous studies provide no indication that testosterone administration preserves muscle strength during prolonged bed rest.

Given the established effects of thyroid hormone on myosin heavy chain composition and skeletal muscle function (24), it could be argued that daily administration of T_3 confounded experimental design and limited our ability to interpret results. Both the P and T-treated groups received T_3; consequently, any effect of T_3 on skeletal muscle during the bed rest period was likely to be equivalent in both groups. The conclusion that testosterone administration preserves lean body mass but not muscle strength was made relative to the P group, and therefore is valid.

In rats, excess thyroid hormone is known to shift myosin heavy chain isoform composition from slow (type I) to fast (type II), with a corresponding shift in the force velocity-curve (25). Prolonged bed rest does not alter human myosin heavy chain isoform composition (22, 23), fast and slow speed isokinetic muscle strength of the knee extensors decline equally (19, 22), and there is no change in the force-velocity relationship (22, 24). After bed rest with T_3 treatment, we observed that reductions in isokinetic knee

TABLE 3. Knee extension and flexion strength of the right leg before (T1) and after (T2) 28 days of 6° head down tilt bed rest/T_3 in testosterone- and placebo-treated groups

	T1 60°/s	T2 60°/s	T1 180°/s	T2 180°/s
Knee extension BWR (FtLb)				
Testosterone	165 ± 15	126 ± 18[a]	115 ± 8	107 ± 7[a]
Placebo	179 ± 22	149 ± 13[a]	111 ± 13	104 ± 12[a]
Knee flexion BWR (FtLb)				
Testosterone	92 ± 11	64 ± 11	68 ± 11	47 ± 7
Placebo	99 ± 13	84 ± 7	45 ± 11	42 ± 5

Significant reductions in knee extension strength from pre- to post-bed rest were noted in both groups; however, there was only a trend ($P = 0.08$) for a reduction in knee flexion strength from pre- to post-bed rest. Data are the mean ± SE. BWR, Best work repetition.
[a] $P < 0.05$.

TABLE 4. Shoulder extension and flexion strength of the right arm before (T1) and after (T2) 28 days of 6° head down tilt bed rest/T_3 in testosterone- and placebo-treated groups

	T1 60°/s	T2 60°/s	T1 180°/s	T2 180°/s
Shoulder extension BWR (FtLb)				
Testosterone	134 ± 8	122 ± 18	86 ± 10	88 ± 15
Placebo	130 ± 7	120 ± 9	62 ± 10	76 ± 8
Shoulder flexion BWR (FtLb)				
Testosterone	121 ± 5	99 ± 16	91 ± 6	75 ± 12
Placebo	113 ± 6	107 ± 6	57 ± 8	70 ± 9

There was no effect of bed rest or treatment on slow or fast speed shoulder muscle strength. Data are the mean ± SE.

extension strength at 180°/s were smaller (~7%) than those measured at 60°/s (~20%), and this was true for both the P- and T-treated subjects. Furthermore, the ratio of strength measured at 180 to 60°/s was increased after bed rest and T_3, whereas in other studies it has remained constant (19, 22, 26). These observations suggest that during bed rest, T_3 administration may alter the *in vivo* force-velocity characteristics of human skeletal muscle. Potentially, this may come about as a result of a shift in myosin heavy chain composition from slow to fast. Accordingly, as a slow to fast myosin heavy chain isoform shift has been reported after 11 days of space flight (27), bed rest plus T_3 administration may better mimic the effects of microgravity on human skeletal muscle function.

Our goal was to achieve total serum testosterone levels that were in a low supraphysiological range; this goal was accomplished. Clearly, this resulted in a significant anabolic response, as both whole body nitrogen balance and leucine kinetics were improved by T treatment. Hence, lean body mass gain in the T-treated subjects was the result of protein accretion, presumably in skeletal muscle, indicating that the observed dissociation between maintenance of lean body mass and muscle strength in this bed rest investigation is robust. To our knowledge, no previous studies have attempted to preserve lean body mass and strength during prolonged bed rest with testosterone administration. Results from animal studies suggest that anabolic steroid treatment of hind limb-suspended female rats spared fast twitch muscle (planteris) weight and protein content (28). Further, steroid treatment plus functional overload were more effective than functional overload alone at reversing the fast twitch muscle atrophy associated with hind limb suspension (29). Unfortunately, neither of these two studies assessed muscle force production or contractile properties *in situ*. Evans and Ivy (30) presented data suggesting that testosterone (propionate form) administration in male rats also attenuates the fast twitch muscle atrophy associated with hind limb immobilization. This was true whether the rats were intact or castrated.

Typically, long duration submaximal exercise is emphasized during space flight, primarily in an attempt to maintain cardiovascular reserve and to guard against orthostatic intolerance. As might be predicted, this approach has generally proven to be ineffective at preventing muscle atrophy and the decline in muscle strength (1). Greenleaf (4) recently reported that in addition to maintaining peak oxygen uptake during 30 days of bed rest at 6° head-down tilt, high intensity, intermittent isotonic cycle ergometry exercise maintained knee extensor strength (*i.e.* −4 *vs.* −16 Newton meters (Nm) for control/no exercise). However, there were indications that the subjects in the exercise group were experiencing chronic fatigue, and this could limit its use, in a practical sense, during space flight excursions. Testosterone administration in conjunction with such exercise may reduce the amount of work (time and volume) needed to maintain muscle strength at or near the accustomed level while at the same time providing enough stimulus to maintain cardiovascular reserve. Further, combined programs of hormone administration and exercise may offer a more time- and energy-efficient way to prevent against the general deconditioning associated with space flight and/or prolonged bed rest.

In summary, the general muscular deconditioning of weight-bearing limbs during prolonged bed rest (28 days) is not attenuated with T (200 mg/week) administration. This regression in functional capacity occurred despite nearly a 2-kg increase in lean body mass in the treated subjects. Thus, maintenance of contractile force during periods of bed rest-induced inactivity or gravity unloading is not simply related to the preservation of muscle or lean body mass. Effective countermeasures will also need to provide some level of functional loading as well as influence neuromuscular recruitment and activity patterns.

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