Perioperative Testosterone Supplementation Increases Lean Mass in Healthy Men Undergoing Anterior Cruciate Ligament Reconstruction

A Randomized Controlled Trial

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Background: Rehabilitation after repair of the anterior cruciate ligament (ACL) is complicated by the loss of leg muscle mass and strength. Prior studies have shown that preoperative rehabilitation may improve muscle strength and postoperative outcomes. Testosterone supplementation may likewise counteract this muscle loss and potentially improve clinical outcomes.

Purpose: The purpose was to investigate the effect of perioperative testosterone administration on lean mass after ACL reconstruction in men and to examine the effects of testosterone on leg strength and clinical outcome scores. It was hypothesized that testosterone would increase lean mass and leg strength and improve clinical outcome scores relative to placebo.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: Male patients (N = 13) scheduled for ACL reconstruction were randomized into 2 groups: testosterone and placebo. Participants in the testosterone group received 200 mg of intramuscular testosterone weekly for 8 weeks beginning 2 weeks before surgery. Participants in the placebo group received saline following the same schedule. Both groups participated in a standard rehabilitation protocol. The primary outcome was the change in total lean body mass at 6 and 12 weeks. Secondary outcomes were extensor muscle strength, Tegner activity score, and Knee injury and Osteoarthritis Outcome Score.

Results: There was an increase in lean mass of a mean 2.7 ± 1.7 kg at 6 weeks postoperatively in the testosterone group compared with a decrease of a mean 0.1 ± 1.5 kg in the placebo group ($P = .01$). Extensor muscle strength of the uninjured leg also increased more from baseline in the testosterone group (+20.8 ± 25.6 Nm) compared with the placebo group (–21.4 ± 36.7 Nm) at 12 weeks ($P = .04$). There were no significant between-group differences in injured leg strength or clinical outcome scores. There were no negative side effects of testosterone noted.

Conclusion: Perioperative testosterone supplementation increased lean mass 6 weeks after ACL reconstruction, suggesting that this treatment may help minimize the effects of muscle atrophy associated with ACL injuries and repair. This study was not powered to detect differences in strength or clinical outcome scores to assess the incidence of testosterone-related adverse events.

Clinical Relevance: Supraphysiological testosterone supplementation may be a useful adjunct therapy for counteracting muscle atrophy after ACL reconstruction. Further investigation is necessary to determine the safety profile and effects of perioperative testosterone administration on leg strength and clinical outcomes after surgery.

Registration: NCT01595581 (ClinicalTrials.gov).

Keywords: testosterone; anterior cruciate ligament reconstruction; rehabilitation; lean mass; randomized controlled trial

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The anterior cruciate ligament (ACL) is essential for providing stability to the knee, and a rupture can lead to significant limitations in activity and knee function as well

as an increased long-term risk for osteoarthritis.[17,50] An initial knee injury is also associated with rapid loss of muscle mass and strength in the affected leg.[17,21,41] Surgical reconstruction of the ACL is commonly performed and widely regarded as essential for those who wish to return to competitive sports. Nonetheless, the trauma of surgical repair and postoperative mobility limitations can exacerbate the loss of muscle mass and strength, which may prolong the already arduous rehabilitation process and potentially impair long-term outcomes.[3,24] One study reported that 60% of patients undergoing ACL reconstruction did not return to preinjury activity levels within 2 years.[17]

The loss of muscle mass and strength can be minimized with preoperative rehabilitation, which has been associated with a faster return to sports.[48] Another potential method to prevent muscle loss may be androgen supplementation. Intramuscular testosterone has been shown to increase muscle mass and strength, independent of exercise, and could conceivably prevent muscle loss after surgical reconstruction of the ACL.[8,45,54]

Perioperative quadriceps strength is a significant predictor of knee function 2 years after ACL reconstruction, and thus, improving perioperative quadriceps weakness may play an important role in optimizing patient outcomes.[14] Much of the perioperative loss in muscle mass and strength may be attributable to limited mobility and motion of the knee, both of which have been shown to contribute to muscle catabolism.[32] Testosterone induces anabolic activity directly by increasing myofibrillar protein synthesis and indirectly by inducing muscle growth via growth hormone and insulin-like growth factor–1.[12,47,53] Testosterone has also shown promise as adjuvant therapy in orthopaedic surgery and has been shown to improve outcomes such as the early ability to stand after total knee arthroplasty.[2] Furthermore, studies have demonstrated that testosterone supplementation sufficient to increase muscle mass is possible without adverse effects on lipids, mood, or behavior.[4,7,42]

The purpose of this randomized controlled trial was to determine if weekly testosterone administration, beginning 2 weeks before surgery and ending 6 weeks after surgery, could effectively prevent short-term catabolic loss of lean mass in patients undergoing ACL reconstruction and structured rehabilitation. This study also assessed short-term changes in dynamic muscle strength and patient-reported outcome measures. It was hypothesized that perioperative testosterone administration would increase lean mass, leg extensor strength, and clinical outcome scores after ACL reconstruction to a greater degree than placebo. This is the first study to investigate the effect of testosterone on lean mass after ACL reconstruction in young, healthy, eugonadal male patients.

METHODS

Study Design and Participants

Patients with a diagnosis of an ACL rupture were recruited from those seen at the Department of Orthopaedic Surgery at a tertiary-care academic center. Men aged 18 to 50 years who presented with clinically diagnosed acute ACL insufficiency were screened for eligibility. This study was limited to men because of the sex-specific side effects of testosterone, and the age range of 18 to 50 years was chosen to reflect the commonly studied age range for this particular injury.[8,38] The upper age limit was established to increase the probability that the study participants would be eugonadal.[11,22,36,42,43] Inclusion criteria were (1) a history of trauma to a previously uninjured knee within the preceding 8 months, (2) ACL insufficiency as determined by a clinical examination, and (3) a score of 5 to 9 on the Tegner activity scale (TAS) before the injury, with a score of 5 indicating participation in recreational sports and a score of 9 indicating participation in competitive sports at a nonprofessional level. Major exclusion criteria included previous surgery to the affected knee or concomitant injuries to the posterior cruciate ligament and collateral ligaments. Patients with a cartilage injury representing full-thickness loss down to bone were also excluded. Additionally, patients who had unstable, longitudinal meniscal tears that required repair and those with subsequent postoperative motion limitations that interfered with the rehabilitation protocol were excluded. All aspects of the study were conducted at a tertiary-care academic center and were approved by the relevant institutional review board. The study was registered as a clinical trial on May 8, 2012 (NCT01595581). All eligible participants received information about the trial orally and in writing.

Participants were randomly assigned to receive testosterone or placebo treatment. The study statistician performed simple 1:1 randomization and provided the assigned interventions to the research pharmacist before study initiation. Except for the pharmacist and statistician, all persons involved were blinded to the treatment assignment, including the surgeon, investigators, study team, physical therapist, and patients.

Study recruitment lasted from January 2012 to September 2014. Eighty-six patients were screened, and 14 participants enrolled in the study. One participant dropped out because of missed surgery. This left 13 patients in the study: 6 in the testosterone group and 7 in the placebo group. Twelve participants completed all evaluations, with 1 participant missing the 24-week study visit. Participant flow (CONSORT [Consolidated Standards of Reporting Trials]) is shown in Figure 1.

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Ethical approval for this study was obtained from the University of Southern California's Institutional Review Board.

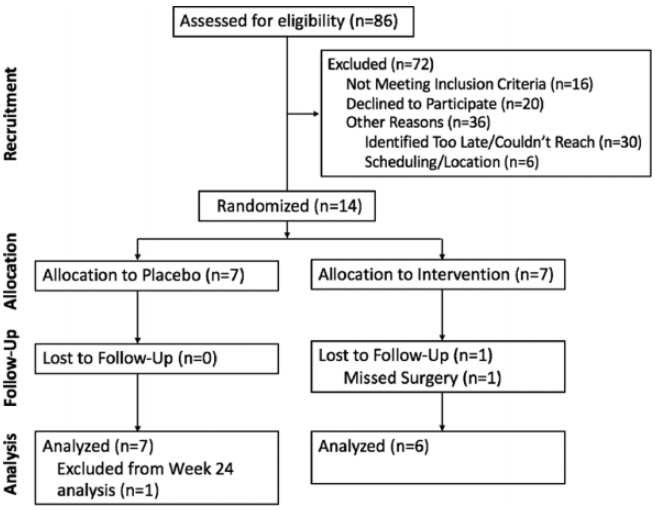

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing the flow of participants during the study.

Intervention

The testosterone group received a 200-mg dose of intramuscular testosterone cypionate weekly for 8 weeks beginning 2 weeks before surgery. The 200-mg/wk regimen was selected with the aim of being a sufficient dose to provide an anabolic stimulus but low enough to minimize the likelihood of any adverse events.[6,8,9]

Control participants in the placebo group followed the same schedule of injections with an intramuscular saline dose instead of testosterone. All participants followed a standard-of-care, structured rehabilitation protocol, as determined by a licensed physical therapist, beginning shortly after surgery.

Study Drug Administration and Safety

Common markers of endocrine function were monitored for all participants because of the potential for systemic side effects of testosterone. Serum testosterone was measured to the nearest one-tenth (ng/dL) by a competitive radioimmunoassay using a solid-phase polyclonal antibody. A previous study has shown that the coefficient of variation for serum testosterone measured by this method was $\leq$7.7%.[46] Blood analysis was performed throughout the study, monitoring pituitary hormones (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), prostate-specific antigen (PSA), alanine aminotransferase (ALT), hematocrit, hemoglobin, and white blood cell at 2 weeks preoperatively, 1 day preoperatively, and 2, 6, 12, and 24 weeks postoperatively. Informed consent documentation included a discussion of the possible but uncommon risks of testosterone such as allergic reactions, liver function test alterations, breast tenderness, hair growth or loss, polycythemia, and mood or mental changes. Potential adverse events were monitored during study visits.

Orthopaedic Surgery

Surgical reconstruction was performed in all participants within 8 months after the injury by a board-certified orthopaedic surgeon and was preceded by meniscal repair, as needed, at the discretion of the surgeon. Surgery was performed by 1 of 4 knee surgeons, each of whom regularly performed more than 40 ACL reconstructions annually. Graft choice, tourniquet use, time to surgery, and all other surgical decisions were left to the normal practice of the orthopaedic surgeon.

Outcome Measures

The primary outcome was the change in total lean body mass from baseline, while secondary outcomes included muscle strength and the Knee injury and Osteoarthritis Outcome Score (KOOS). Patients were evaluated 2 weeks before surgery, 1 day before surgery, and 6, 12, and 24 weeks after surgery. Lean mass was measured by whole-body dual-energy x-ray absorptiometry using the Lunar iDXA system (General Electric Healthcare).[44,46] Lean body mass was measured to the nearest one-tenth of a kilogram (kg), and previous studies evaluating the precision of the Lunar iDXA system have demonstrated a coefficient of variation <1% for total lean body mass measurements.[40]

Tests of maximal extensor strength were performed on the participants' affected and unaffected legs using a NORM dynamometer (Cybex) following the standard protocol for concentric extension at a speed of 60 deg/s.[20,34] Patients were positioned on an adjustable chair and secured to the equipment and were instructed to perform 5 concentric leg extensions with 30 seconds of rest in between. Movements were performed at an angular velocity of 60 deg/s, and the peak torque of leg extension was recorded to one-tenth of a newton-meter (Nm). A previous study demonstrated high relative reliability (0.90-0.98) for peak torque values obtained from the NORM dynamometer for knee extensor tests.[23]

At each study visit, participants were asked to complete the KOOS questionnaire, which has been validated for use in measuring functional outcomes of patients who have undergone ACL reconstruction and has a reported test-retest reliability between 0.75 and 0.93.[19,39] The KOOS is scored from 0 to 100, with 0 representing extreme knee problems and 100 signifying normal knee function. The TAS was also administered at each study visit to determine preinjury physical activity levels. The TAS has been validated for assessing clinical outcomes in the setting of knee surgery, with high test-retest reliability in this setting.[11,31] The TAS is scored from 1 to 10, with 0 representing disability and 10 signifying participation in a professional sport.

Statistical Analysis

All patients who were assigned to a treatment were included in statistical analyses, except for 1 participant who was dropped from the study because he did not undergo his scheduled ACL surgery. Between-group comparisons were made with the Mann-Whitney *U* test for continuous variables or the Fisher exact test for categorical variables. All statistical analyses were carried out using Stata Version 13 (StataCorp).

TABLE 1
Baseline Characteristics[a]

	Placebo (n = 7)	Testosterone (n = 6)	*P* Value
Age, mean ± SD, y	26.2 ± 4.1	30.4 ± 9.3	.39
Race/ethnicity, n			
White	5	3	
Black	0	1	
East Asian	2	1	
Hispanic	0	1	
Autograft, n	4	4	>.99
Meniscal tear, n	4	2	.59

[a]*P* values were calculated using the Mann-Whitney *U* test and Fisher exact test as appropriate.

An a priori power analysis was performed using nQuery Version 4 (Stasols) to estimate the number of participants needed to find a statistically significant difference in lean mass. Preliminary data were taken from a study that found a change in lean mass of 3.0 ± 1.5 kg in healthy men receiving testosterone.[46] Using a significance level of 0.05 and a power of 0.80, a sample size of 6 participants per group was calculated to observe similar effects. Assuming a dropout rate of 20%, it was estimated that 14 patients would be needed in total.

RESULTS

Baseline Characteristics

The 14 participants ranged from 19 to 46 years in age. Table 1 presents the baseline characteristics for the 2 treatment groups. There were no statistically significant baseline differences in lean mass or leg strength between the groups. However, the difference in strength of the injured leg between the testosterone and placebo groups approached significance ($P = .06$).

Of the 13 patients enrolled in the study, 6 underwent repair for meniscal tears. There was no statistically significant difference in the distribution of meniscal tears between the 2 study groups ($P = .59$) (Table 1). Eight patients received an autograft for ACL reconstruction (6 hamstring, 2 bone–patellar tendon–bone), while 5 patients were repaired using allografts (4 semitendinosus, 1 bone–patellar tendon–bone). The percentage of patients receiving autografts was not significantly different between the groups ($P > .99$).

Blood Analysis

Serum testosterone levels in the testosterone and placebo groups were not significantly different at baseline (mean ± SD: 414.3 ± 151.6 vs 366.4 ± 82.6 ng/dL, respectively; $P = .48$) but were significantly higher in the testosterone group at 1 day before surgery (860.2 ± 253.6 vs 330.1 ± 118.7 ng/dL, respectively; $P < .01$), 2 weeks postoperatively (1058.5 ± 268.1 vs 350.6 ± 53.6 ng/dL, respectively; $P < .01$), and 6 weeks postoperatively (745.5 ± 173.1 vs 419.1 ± 71.6 ng/dL, respectively; $P < .01$). Serum testosterone levels were not significantly different at 12 and 24 weeks postoperatively (Table 2 and Figure 2). A similar pattern was observed in serum LH and FSH levels. There were no significant between-group differences in baseline LH and FSH levels ($P > .05$), while LH and FSH levels were significantly lower in the testosterone group at 1 day preoperatively as well as at 2 and 6 weeks postoperatively ($P < .01$). At 12 and 24 weeks postoperatively, there were no significant between-group differences in LH and FSH levels.

Primary and Secondary Outcomes

The increase in whole body lean mass was significantly greater in the testosterone group at 6 weeks after surgery compared to the placebo group: the testosterone group gained a mean of 2.7 ± 1.7 kg of lean mass compared to patients in the placebo group, who lost a mean 0.1 ± 1.5 kg of lean mass ($P = .01$) (Figure 3). At 12 weeks, the testosterone group tended to maintain a higher lean mass gain (2.2 ± 3.5 kg) relative to the placebo group (0.0 ± 1.1 kg) but not to the point of statistical significance ($P = .15$). At 24 weeks, there was no significant difference in lean mass gain between the testosterone group (2.13 ± 5.30 kg) and placebo group (1.05 ± 1.18 kg) ($P = .64$) (Table 3).

The change in extensor strength of the uninjured leg was significantly greater at 12 weeks postoperatively in the testosterone group (+20.8 ± 25.6 Nm) compared to the placebo group (–21.4 ± 36.7 Nm) ($P = .04$) (Figure 4). The change in extensor strength of the uninjured leg did not significantly differ between the testosterone and placebo groups at 1 day preoperatively ($P = .86$), 6 weeks postoperatively ($P = .34$), or 24 weeks postoperatively ($P = .31$). There were also no significant between-group differences at any time point in absolute extensor strength of the uninjured leg, absolute extensor strength of the injured leg, or change in extensor strength of the injured leg (all $P > .05$) (Figure 5). As previously noted, baseline extensor strength of the injured leg between the testosterone (152.8 ± 38.8 Nm) and placebo (111.0 ± 32.3 Nm) groups approached significance ($P = .06$).

There were no statistically significant differences in KOOS or TAS scores between the groups at 6 or 12 weeks ($P = .67$ and $P = .65$, respectively). There were no reports of any adverse effects of testosterone treatment, including cellulitis at the local injection site, throughout the duration of the study.

DISCUSSION

The present study demonstrated that young, healthy, eugonadal male patients experienced a significant increase in lean mass 6 weeks after ACL reconstruction with testosterone supplementation of 200 mg/wk compared to a slight decrease in lean mass at the same time point in patients receiving placebo. There were no adverse effects with this dosage observed over the course of this study. The observed effect has not previously been reported in this population in the perioperative period but is supported by similar results from other studies investigating the effects of testosterone administration on lean mass in other populations.[7-10,43] Increased lean mass has previously been shown to positively correlate with muscle strength, including leg extensor

TABLE 2
Blood Sample Analysis[a]

	Preoperative		Postoperative			
	2 wk	1 d	2 wk	6 wk	12 wk	24 wk
Testosterone, ng/dL						
Placebo	366.4 ± 82.6	330.1 ± 118.7	350.6 ± 53.6	419.1 ± 71.6	408.4 ± 113.7	439.7 ± 107.0
Testosterone	414.3 ± 151.6	860.2 ± 253.6	1058.5 ± 268.1	745.5 ± 173.1	393.0 ± 156.4	442.3 ± 193.9
P value	.48	**<.01**	**<.01**	**<.01**	.84	.98
LH, mIU/mL						
Placebo	4.6 ± 1.2	3.9 ± 2.1	5.4 ± 2.4	5.8 ± 1.2	4.3 ± 1.3	4.8 ± 1.9
Testosterone	6.1 ± 3.2	0.6 ± 0.6	0.2 ± 0.3	0.1 ± 0.0	4.7 ± 2.2	4.9 ± 2.4
P value	.25	**<.01**	**<.01**	**<.01**	.70	.91
FSH, mIU/mL						
Placebo	4.0 ± 1.8	3.6 ± 1.6	3.3 ± 1.2	3.9 ± 1.6	3.5 ± 1.5	3.4 ± 1.3
Testosterone	3.7 ± 1.6	0.5 ± 0.3	0.1 ± 0.1	0.1 ± 0.1	3.6 ± 2.1	3.3 ± 1.8
P value	.71	**<.01**	**<.01**	**<.01**	.94	.94
PSA, ng/mL						
Placebo	0.6 ± 0.3	0.5 ± 0.3	0.7 ± 0.4	0.6 ± 0.3	0.5 ± 0.2	0.6 ± 0.3
Testosterone	0.6 ± 0.1	0.7 ± 0.2	0.8 ± 0.3	0.7 ± 0.2	0.6 ± 0.3	0.7 ± 0.4
P value	.96	.30	.45	.48	.39	.57
ALT, U/L						
Placebo	26.3 ± 10.8	25.7 ± 11.0	23.1 ± 9.4	34.7 ± 22.9	27.6 ± 4.4	23.7 ± 12.9
Testosterone	19.5 ± 13.0	18.7 ± 12.4	48.8 ± 81.8	19.8 ± 8.7	32.2 ± 25.0	25.0 ± 13.5
P value	.33	.30	.42	.16	.64	.86
Hematocrit, %						
Placebo	46.3 ± 2.4	43.3 ± 2.7	43.5 ± 2.2	45.4 ± 2.2	45.6 ± 1.8	44.3 ± 1.4
Testosterone	44.9 ± 2.5	44.3 ± 4.0	45.1 ± 2.1	47.5 ± 3.2	46.7 ± 2.1	44.4 ± 1.8
P value	.33	.60	.22	.20	.33	.89
Hemoglobin, g/dL						
Placebo	15.7 ± 0.6	15.0 ± 0.9	14.8 ± 0.8	15.5 ± 0.8	15.5 ± 0.6	15.0 ± 0.5
Testosterone	15.6 ± 0.5	15.3 ± 1.2	15.2 ± 0.8	16.3 ± 1.0	15.8 ± 0.7	15.2 ± 0.5
P value	.62	.65	.35	.13	.48	.42
WBC, $\times 10^3/\mu L$						
Placebo	7.0 ± 2.3	5.9 ± 2.2	6.3 ± 1.7	5.8 ± 1.6	6.2 ± 1.8	5.9 ± 1.3
Testosterone	5.2 ± 0.6	6.1 ± 1.8	7.3 ± 1.4	6.1 ± 0.7	5.7 ± 0.8	5.1 ± 0.9
P value	.09	.85	.29	.68	.55	.30

[a]Data are reported as mean ± SD. *P* values were calculated using the Mann-Whitney *U* test. Boldfaced *P* values indicate statistical significance ($P < .05$). ALT, alanine aminotransferase; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PSA, prostate-specific antigen; WBC, white blood cell.

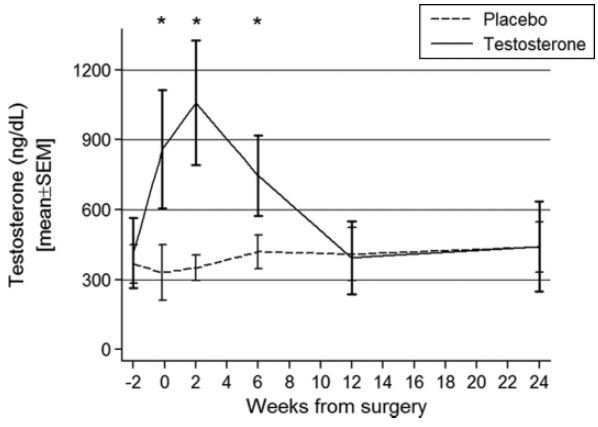

Figure 2. Serum testosterone levels by week. Line plot of testosterone levels at 2 weeks before surgery; 1 day before surgery; and 2, 6, 12, and 24 weeks after surgery. Data shown are the means ± standard errors of serum testosterone (ng/dL) as measured by blood analysis. An asterisk (*) indicates a significant between-group difference.

strength, and in this case may aid in postoperative rehabilitation by offsetting the loss of leg strength associated with an initial injury, surgery, and immobility.[1,13,25,35,37] Importantly, the increase in lean mass from testosterone administration was maintained at 12 weeks after surgery despite serum testosterone levels returning to baseline, suggesting that the effects of acute testosterone administration in this population persist even in the absence of elevated serum testosterone levels. Furthermore, there was no observed decrease below baseline observed in serum testosterone levels in the testosterone group. Our results suggest that testosterone therapy may be useful as an adjunct to postoperative physical therapy in eugonadal patients by causing an increase in lean mass that persists for an extended period without residual disturbance of baseline serum testosterone levels.

The increase in lean mass in the testosterone group and increased strength in the uninjured leg at 12 weeks postoperatively suggest that the chosen dose of 200 mg was sufficient to induce a physiological response. Nonetheless,

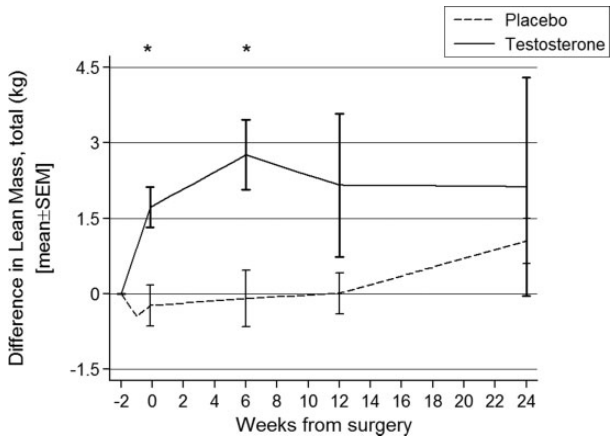

Figure 3. Effect of testosterone on the change in lean mass from baseline. Line plot of the change in lean mass from baseline at 1 day before surgery and 6, 12, and 24 weeks after surgery. Baseline lean mass was measured at 2 weeks before surgery and normalized to 0. Data shown are the means ± standard errors of the change in lean mass (kg). An asterisk (*) indicates a significant between-group difference.

the present study did not find significant differences in clinical scores between the testosterone and placebo groups. This may be attributable to the small sample size and resulting lack of power to detect differences on these outcome measures. Prior research has suggested that perioperative supraphysiological testosterone supplementation may improve clinical outcomes, including rehabilitation milestones such as early standing after knee replacement surgery.[2] The present study also did not find a significant difference in postoperative strength of the injured leg between the testosterone and placebo groups. This may in part be because of the baseline difference in injured leg strength between the 2 study groups, which approached significance. Future studies with larger sample sizes may be able to avoid baseline imbalance between study groups and achieve power to detect potential differences in clinical outcome measures and leg strength.

As testosterone is a potent hormone acting on various organ systems, side effects and safety of the intervention were paramount concerns. Although the recent literature has reported an increased association of cardiovascular risk with testosterone therapy, these studies focused on testosterone replacement therapy for an extended duration and

TABLE 3
Lean Mass, Leg Extensor Strength, and Clinical Outcomes[a]

	Preoperative		Postoperative		
	2 wk	1 d	6 wk	12 wk	24 wk
Lean mass, kg					
Placebo	59.0 ± 4.0	58.8 ± 4.0	58.9 ± 4.5	59.0 ± 4.4	60.4 ± 4.1
Testosterone	60.2 ± 9.3	62.0 ± 8.4	63.0 ± 9.9	62.4 ± 11.5	62.4 ± 13.5
P value	.75	.39	.35	.48	.74
Change in lean mass, kg					
Placebo	0.00 ± 0.00	–0.23 ± 1.08	–0.09 ± 1.48	0.01 ± 1.08	1.05 ± 1.18
Testosterone	0.00 ± 0.00	1.72 ± 0.98	2.76 ± 1.70	2.16 ± 3.48	2.13 ± 5.30
P value		.01	.01	.15	.64
Uninjured extensor strength, Nm					
Placebo	198.7 ± 38.1	191.1 ± 29.9	191.7 ± 32.1	177.3 ± 34.5	184.7 ± 31.6
Testosterone	205.3 ± 85.4	202.2 ± 76.1	221.7 ± 104.6	226.2 ± 97.3	223.7 ± 92.9
P value	.86	.73	.48	.24	.35
Change from baseline: uninjured extensor strength, Nm					
Placebo	0.0 ± 0.0	–7.6 ± 55.8	–7.0 ± 48.3	–21.4 ± 36.7	–6.3 ± 51.5
Testosterone	0.0 ± 0.0	–3.2 ± 23.9	16.3 ± 32.5	20.8 ± 25.6	18.3 ± 24.4
P value		.86	.34	.04	.31
Injured extensor strength, Nm					
Placebo	111.0 ± 32.3	128.6 ± 24.7	77.6 ± 39.8	104.4 ± 44.3	133.3 ± 44.3
Testosterone	152.8 ± 38.8	152.2 ± 58.9	99.3 ± 48.1	134.5 ± 67.5	172.0 ± 77.2
P value	.06	.35	.39	.36	.31
Change from baseline: injured extensor strength, Nm					
Placebo	0.0 ± 0.0	17.6 ± 21.6	–33.4 ± 37.4	–6.6 ± 40.3	19.0 ± 33.9
Testosterone	0.0 ± 0.0	–0.7 ± 39.9	–53.5 ± 35.8	–18.3 ± 52.7	19.2 ± 60.9
P value		.32	.35	.66	.99
Knee injury and Osteoarthritis Outcome Score					
Placebo	66.9 ± 19.7	71.0 ± 13.1	65.5 ± 13.0	73.2 ± 15.0	86.6 ± 8.3
Testosterone	76.5 ± 15.8	71.7 ± 15.5	63.2 ± 10.6	76.7 ± 9.9	84.0 ± 9.4
P value	.39	.93	.73	.64	.63
Tegner activity score					
Placebo	3.1 ± 1.3	3.4 ± 0.8	3.3 ± 1.0	4.0 ± 0.6	6.0 ± 1.4
Testosterone	3.5 ± 1.5	3.3 ± 1.2	3.0 ± 0.9	4.0 ± 0.9	5.0 ± 1.5
P value	.66	.87	.59	.99	.27

[a]Data are reported as mean ± SD. *P* values were calculated using the Mann-Whitney *U* test.

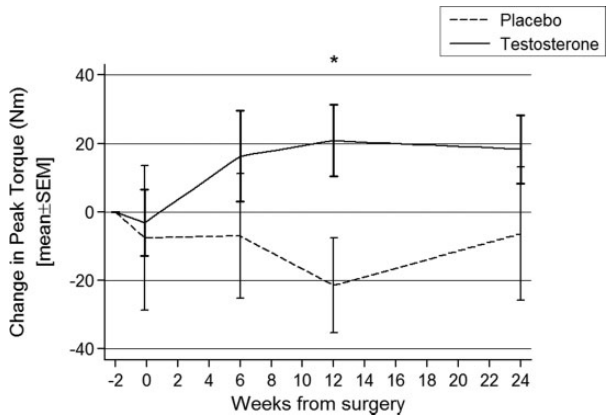

Figure 4. Effect of testosterone on the change in strength of the uninjured leg from baseline. Line plot of the change in peak extension torque of the uninjured leg from baseline to 1 day before surgery and 6, 12, and 24 weeks after surgery. Baseline extension torque was measured at 2 weeks before surgery and normalized to 0. Data shown are the means ± standard errors of the change in peak extension torque (Nm). An asterisk (*) indicates a significant between-group difference.

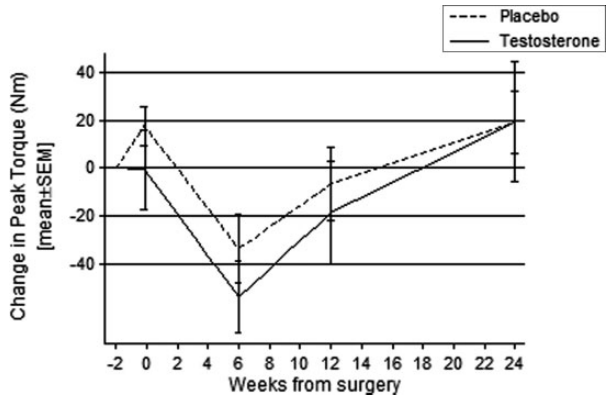

Figure 5. Effect of testosterone on the change in strength of the injured leg from baseline. Line plot of the change in peak extension torque of the injured leg from baseline to 1 day before surgery and 6, 12, and 24 weeks after surgery. Baseline extension torque was measured at 2 weeks before surgery and normalized to 0. Data shown are the means ± standard errors of the change in peak extension torque (Nm). An asterisk (*) indicates a significant between-group difference.

were primarily administered to hypogonadal men.[15,55] Other studies in healthy young men have found no significant adverse events from testosterone supplementation below 600 mg/wk.[7,9,51] A 200-mg/wk dose for 8 weeks was thought to be sufficient to provide an anabolic stimulus while minimizing the risk of adverse effects.[‡] As expected, the testosterone dose and pattern of administration used in this clinical trial did not produce any adverse effects. The lack of adverse events suggests that testosterone administration at 200 mg/wk may be safe in young, healthy men undergoing surgery. However, because safety was not a primary or secondary outcome of this study, future studies specifically investigating the safety of testosterone administration in patients undergoing ACL surgery are necessary to conclusively determine the safety of perioperative testosterone supplementation in this population. It is also necessary to consider that a higher dose of testosterone supplementation may achieve greater physiological effects while maintaining safety. Prior studies of perioperative testosterone supplementation have used 600 mg/wk of testosterone enanthate for 4 weeks and 600 mg/wk for 10 weeks.[2,7] The goal in dosing was to elevate testosterone levels in the testosterone group to approximately 1000 to 1200 ng/dL; however, serum levels reached a peak mean value of 860 ng/dL. Thus, future studies may choose to adjust the treatment dose to see more pronounced effects of testosterone administration but should consider that significant cardiovascular risks have been associated with supplementation of >600 mg/wk with a duration of >6 months.[6,8,9] Finally, this study did not specifically monitor for potential adverse effects of testosterone on graft healing.

The main limitation of the present study is the relatively small sample size. The challenge of recruiting patients for ACL clinical trials has been previously noted in the literature, including a study by Frobell et al[16] that indicated more than 5 patients must be screened for every person ultimately included in an ACL study. Although the present study was sufficiently powered for the outcome of lean mass, the small sample size and wide age range of patients selected may have contributed to a failure to document differences in baseline leg strength and other factors affecting clinical outcomes. The small sample size also meant that, despite randomization, the results could not be adjusted for confounding variables. These included physical therapy duration and frequency, as well as prior activity level, which may not have been equally distributed between the groups. Other potential confounding variables were the presence of meniscal tears and variable graft types. While patients with unstable, longitudinal meniscal tears were excluded from the present study, 6 patients underwent meniscal repair during surgery. Although there was no significant difference in the number of patients with meniscal tears between the groups, the presence of meniscal tears may have had an outsized influence on clinical outcome measures by affecting patients' weightbearing status after surgery. Likewise, the distribution of graft types was not significantly different between the groups, but previous studies have shown that graft type may influence outcomes of ACL repair.[5,33,52] Furthermore, postoperative imaging of the graft was not performed. Future studies may consider investigating the specific relationships between the presence of meniscal tears, graft type, and patient outcomes in the setting of testosterone supplementation. Additionally, the relatively young age of the participants could have influenced the magnitude of the lean mass increases seen in this study, and these results may be less generalizable to older patients.[9,17,22,28,43] Finally, this study was

[‡]References 8-10, 18, 26, 27, 29, 30, 34, 49, 51.

limited to nonprofessional athletes, as testosterone is a banned substance as defined by the World Anti-Doping Agency's prohibited list.

CONCLUSION

This is the first study investigating the effects of perioperative testosterone supplementation in young, healthy men after ACL reconstruction. Patients receiving an 8-week course of 200 mg/wk of testosterone cypionate were found to have a greater increase in lean mass at 6 weeks after ACL reconstruction compared to patients administered placebo. The increase in lean mass suggests that testosterone may help minimize the effects of muscle atrophy associated with injuries, surgery, and immobility. This increase in lean mass was found to persist after the return of serum testosterone levels to baseline. Further investigation is necessary to determine the safety profile and effects of perioperative testosterone administration on leg strength and clinical outcomes after surgery.

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