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Research Article

Research Article

A Novel Liver-targeted Testosterone Therapy for Sarcopenia in Androgen Deprived Men With Prostate Cancer

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Abstract

Objective: Androgen deprivation therapy (ADT) reduces muscle and bone mass, increasing frailty in men with prostate cancer. The liver mediates the whole body anabolic effects of testosterone. Based on first-pass metabolism, liver-targeted testosterone treatment (LTTT) entails oral delivery of a small dose of testosterone that does not raise peripheral blood testosterone levels. LTTT reduces blood urea and stimulates protein anabolism in hypogonadal men and postmenopausal women. We investigated whether LTTT prevents loss of lean and bone mass during ADT.

Method: A 6-month, double-blind, placebo-controlled study of testosterone 40 mg/day in 50 men. Primary outcome measures were lean mass and bone mineral content (BMC). Testosterone, urea and prostate-specific antigen (PSA) were monitored. Patients were withdrawn if PSA exceeded 4 ng/mL.

Results: 42 patients completed the study. Mean (95% CI) testosterone rose during LTTT but not placebo treatment [Δ 2.2 (1.3-3.0) *vs* –0.7 (–1.5 to 0.2) nmol/L; $P < 0.01$]. Mean PSA level did not change significantly during either treatment. Blood urea fell [Δ –0.4 (–0.9 to –0.1) mmol/L] during LTTT but not placebo [Δ 0.05 (–0.8 to 0.9) mmol/L]. BMC [Δ 49 (5 to 93) g; $P < 0.02$] and lean mass [Δ 0.8 (–0.1 to 1.7) kg; $P = 0.04$) increased compared to placebo. Five patients on LTTT withdrew from increased PSA levels, all returning to baseline levels.

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Conclusion: LTTT shows promise as a simple therapy for preventing sarcopenia and bone loss during ADT. LTTT may induce reversible PSA rise in some patients. Further studies are required to optimize LTTT dose in ADT. LTTT has potential application in other catabolic states in men and women.

Key Words: oral testosterone, anabolism, sarcopenia, hypogonadism

Prostate cancer is the second-most frequent cancer diagnosis made in men and the fifth leading cause of death worldwide [1]. Suppression, blockade, or removal of testosterone is a cornerstone of managing advanced prostate cancer, a classical androgen-dependent malignancy. Androgen deprivation therapy (ADT) is effective adjuvant treatment that improves survival [2]. Because ADT is often prescribed for extended times, these patients suffer from long-term catabolic consequences of hypogonadism [3]. As the 5-year disease survival continues to improve with the development of novel therapeutic options, healthy survivorship is an important consideration.

ADT induces profound skeletal muscle loss, bone loss, and adiposity [2,3]. The ensuing sarcopenia reduces muscle strength and physical function, diminishing quality of life [4,5]. Up to 2.5% of lean mass is lost within the first 6 to 12 month, continuing at a lower rate thereafter [6-8]. The annualized loss of lean body mass (LBM) is about 10 times that which occurs with aging [9,10]. Similarly, there is parallel rapid and progressive loss of bone amounting to 2% to 3% within 6 to 12 months [6,7], increasing the risk of fracture [11,12]. Thus, prevention of sarcopenia and bone mineral loss during ADT remains a major treatment frontier for prostate cancer.

The liver plays a central role in whole-body protein metabolism. It is the metabolic hub from which amino acids are exported to peripheral tissues such as muscle for protein synthesis and to which amino acids are returned after breakdown for disposal via the urea pathway. The liver is the catabolic gateway for nitrogen disposal. The hepatic control of amino acid turnover and their partitioning between anabolic and catabolic destinations are regulated by anabolic hormones [13]. Androgens enhance protein anabolism by inhibiting hepatic urea production, facilitating a greater flow of amino acid for synthesis of proteins in muscle, bone, and other lean tissues [14-16].

Low dose liver-targeted testosterone therapy (LTTT) is a novel approach based on substantial developmental work to androgenize the liver while minimizing any increase in peripheral testosterone concentrations. We discovered that selective exposure of the liver to testosterone by oral delivery stimulates whole body protein anabolism in hypogonadal males indistinguishable from parenteral delivery that increases testosterone levels in peripheral blood [17,18]. This is achieved by delivering a small 40-mg dose of crystalline testosterone orally in 3 divided doses. This regimen did not increase testosterone levels in peripheral blood of hypogonadal men indicating complete first-pass hepatic degradation [19]. In postmenopausal women, the same dose of LTTT reduced protein breakdown and enhanced anabolism to a similar extent compared to hypogonadal men without causing androgen excess in peripheral blood [18].

These findings led to this pilot study of the efficacy and safety of 6 months of a 40-mg dose of LTTT in preventing or reversing protein and bone catabolism in patients with prostate cancer treated with ADT.

Method

Study Design and Participants

This is a single-center study from the Princess Alexandra Hospital, which delivers multidisciplinary care for over 1000 men with prostate cancer each year. The study is a prospective, randomized, double-blind, placebo-controlled, parallel arm trial of 6 months duration of 40 mg of crystalline oral testosterone or placebo involving 50 men with prostate cancer on ADT.

The study was approved by the Metro South Human Research Ethics Committee in 2016 and was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice. The trial is registered with Australian New Zealand Clinical Trials Registry ACTRN12616001166460. All patients provided written informed consent before enrolment.

Men with prostate cancer were recruited from the hospital's clinic and community support groups from clinic notices and consumer seminars. Inclusion criteria were 18 to 80 years of age and commencing or receiving ADT. Exclusion criteria were nonprostatic metastatic disease; coexisting conditions that affect LBM such as liver disease, renal insufficiency, and diabetes mellitus; systemic illness that required medications such as glucocorticoids; thyroid dysfunction; participation in an exercise or weight-control program; or compromised physical mobility that required assistance with daily living.

Procedure

A total of 176 patients were referred for inclusion, of whom 96 were excluded based on eligibility criteria, and an additional 30 were excluded based on blood screening eligibility, leaving 50 for participation (Fig. 1). Participants were recruited into acute or chronic groups in a ratio of 2:3. The acute group consisted of a recent diagnosis, commencing ADT within 6 weeks, and demonstrating treatment responsiveness from a fall in prostate-specific antigen (PSA). The chronic group consisted of patients receiving ADT for a duration of greater than 4 months and showing no progression of prostate cancer from PSA measurements and imaging-based staging.

Randomization and Masking

Patients were randomized in a 1:1 ratio using a 4 × 4 block design to balance numbers of active and placebo allocations within the acute and chronic groups which comprised 20 and 30 patients, respectively. The blinding and allocation were conducted by the unblinded trial pharmacist (Y.S.); the active and placebo medications were compounded on a per patient bases. The allocations were recorded in the study medication logs and were unmasked on completion of the study. A clinical trial prescription was issued for the dispensing of the study medications to each participant. The unblinding information was retained by pharmacy in a password-protected file by the principal investigator.

Safety

All patients underwent a safety screen for hematology and body biochemistries to exclude liver, kidney, and thyroid dysfunction. These measurements were repeated at 6 months. PSA was measured at 0, 3, and 6 months. Patients were withdrawn if the PSA concentration rose by more than 50% or to more than 4 ng/mL at any time during the follow-up.

Those withdrawn from the trial were reviewed immediately and again 3 months later with PSA measurements. Unblinding was undertaken only after termination of the trial.

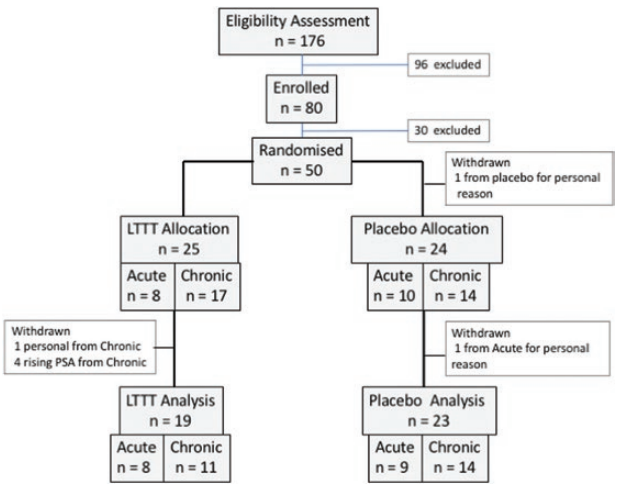

Figure 1. Consort diagram showing the flow of patient numbers through the phases of recruitment, randomization, treatment, and analysis. Patients with prostate cancer compose 2 groups, an acute group initiating androgen deprivation therapy (ADT) and a chronic group on stable ADT with controlled disease for at least 4 months.

Outcome Measures

We tested the hypothesis that LTTT increases lean and bone mass. The primary outcome measures were LBM and total bone mineral content (BMC). These were quantified by dual X-ray absorptiometry (Hologic absorptiometer Model QDR 4500A, software version 12.6), which also estimated fat mass [20]. These measurements were performed at 0 and 6 months.

Trial Medications

Unesterified crystalline USP grade testosterone in capsules containing 13.3 mg was prepared by a compounding pharmacy on a per patient basis. Subjects took 3 capsules daily approximately 8 h apart, totaling 40 mg/day. Matching placebo capsules were prepared and taken in an identical manner.

Assays

Testosterone, PSA, thyroid-stimulating hormone (TSH), and free thyroxine (fT4) were measured by immunoassay Beckman Coulter (Brea, CA, USA) at the Department of Clinical Chemistry, Queensland Pathology. The limit of detection for testosterone was 0.35 nmol/L and a between assay coefficient of variation (CV) of 5.7%. The PSA assay had a detection limit of 0.0 8 ug/L and an assay CV of 5.4%. The TSH and fT4 assays had a detection limit of 0.003 mU/L and 3.2 pmol/L, respectively, and corresponding CVs of 4.2% and 6.7%, respectively.

Statistical Analysis

The data were analyzed using a mixed-effect model to compare LTTT and placebo treatment effects over time. Descriptive analysis of change from baseline in patient groups (LTTT *vs* placebo and acute *vs* chronic) and outcomes were based on the linear regression model, which included age, body mass index, renal function, and thyroid function (TSH and fT4) as covariates. We calculated least-squares mean estimates with 95% CIs of treatment

Table 1. Baseline demographic, biochemical, endocrine and body composition data in men with prostate cancer who were recruited to LTTT or placebo treatments comprising patients who were undergoing acute or chronic androgen deprivation therapy

	Intervention		Group	
	LTTT	Placebo	Acute	Chronic
	n = 25	n = 24	n = 19	n = 30
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Age, years	69 (65-73)	70 (67-74)	69 (65-74)	70 (68-73)
Weight, kg	87 (79-95)	89 (80-98)	88 (70-92)	89 (80-97)
Hb, g/L	135 (131-139)	133 (127-139)	134 (130-140)	134 (129-139)
PSA, nmol/L	1.0 (0.3-1.7)	1.1 (0.7-2.1)	0.8 (0.5-1.9)	1.2 (0.6-1.9)
Testosterone, nmol/L	0.7 (0.5-0.9)	1.3 (0.5-2.1)	1.0 (0.4-1.5)	1.0 (0.4-1.6)
Urea, mmol/L	6.9 (6.4-7.5)	6.4 (5.6-7.2)	6.4 (5.7-7.2)	6.8 (6.2-7.4)
Creatinine, mmol/L	85 (79-91)	81 (74-81)	81 (75-88)	84 (78-90)
ALT, IU/L	28 (22-35)	27 (21-33)	26 (20-33)	28 (23-34)
AST, IU/L	21 (19-23)	20 (17-22)	20 (16-23)	21 (19-23)
TSH, mIU/L	1.5 (1.1-1.9)	1.4 (1.0-1.8)	1.2 (0.8-1.7)	1.6 (1.3-1.9
fT4, pmol/L	10.9 (10.1-11.6)	10.7 (9.9-11.5)	10.7 (9.7-11.7)	10.8 (10.2-11.4)
LBM, kg	54.0 (50.8-57.3)	52.3 (48.9-55.8)	52.7 (50.0-55.7)	53.4 (50.0-56.7)
FM, kg	30.0 (24.9-35.1)	33.0 (27.8-38.2)	30.7 (26.0-35.4)	31.6 (26.4-36.6)
BMC, kg	2.9 (2.7-3.1)	2.9 (2.7-3.0)	2.9 (2.7-3.1)	2.9 (2.6-3.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMC, bone mineral content; FM, fat mass; fT4, free thyroxine; Hb, hemoglobin; LBM, lean body mass; LTTT, liver-targeted testosterone therapy; PSA, prostate specific antigen; TSH, thyroid stimulating hormone.

differences between the groups. Treatment-by-subgroup interactions were examined. Because LTTT reduces urea production and stimulates protein anabolism [15-18], we employed a Bayesian approach to the anabolic hypothesis by considering statistical significance as a *P*-value of <0.05 using a 1-tailed test.

Sample size estimates were drawn from studies reporting body compositional change after ADT [6,21]. The primary outcome measures were LBM and BMC. The average loss over 6 to 9 months for LBM was 1% to 2.6% with an SD of 1.7% to 3.4 % [5,6,21] and for BMD, 1.9% to 2.4% with an SD of 1.5% to 2.5% [6,7,22]. We considered that LTTT treatment prevent a decline of 1% in LBM and of 2% in BMC as clinically significant. We estimated that a sample size of 40 (20 per group) is required to achieve a significance difference at 0.05 level with 80% power. We set out to enroll 50 subjects allowing for a 15% dropout rate.

Results

Fifty patients were enrolled into the study (Fig. 1). One withdrew after enrollment after reconsidering participation. The remaining 49 comprised 19 ADT-naïve (acute) and 30 ADT-treated (chronic) patients treated for a median duration of 420 days (range 135-3020 days). All ADT-naïve patients were entered into the trial at 6 weeks after on confirming a PSA reduction from ADT-induced hypogonadism. Testosterone concentrations in all patients fell into the castrate range (below 1.6 nmol/L) (Table 1). There was no significant difference in mean testosterone and PSA concentrations between the acute and chronic ADT groups (Table 1). The mean age, weight, LBM, fat mass, and BMC were similar in the groups in whom full count, biochemistries, liver, renal and thyroid function were all normal.

The 49 patients were randomly allocated to LTTT (n = 24) and placebo (n = 25) treatments. The baseline characteristics of the LTTT and placebo groups are shown in Table 1. There was no significant difference between the LTTT and placebo groups for baseline hematological, biochemical, thyroid, testosterone, PSA, LBM, BMC, and fat mass. There was no significant difference in these parameters between the acute and chronic ADT groups.

During treatment, 5 patients withdrew from the study in the LTTT group due to a rising PSA, and 2 patients withdrew from the placebo group for personal reasons. Thus, 42 patients completed the study, 19 of 24 in the LTTT group and 23 of 25 in the placebo group (Fig. 1).

Results of Intervention

There was no significant change in hemoglobin, electrolytes, liver transaminases, creatinine, TSH, and fT4 levels in both placebo and LTTT groups during the study (Tables 2 and 3).

In the 42 patients who completed the study, mean plasma testosterone level increased by 2.2 nmol/L ($P = 0.01$) during LTTT but did not change significantly during placebo treatment. The difference in testosterone concentration between treatments was statistically significant ($P < 0.01$). The mean PSA concentration did not change significantly during LTTT or placebo treatments. The difference in mean and in the change in PSA levels between treatments were not statistically different ($P = 0.07$).

Because androgens inhibits hepatic urea synthesis, we investigated whether blood urea levels fell during LTTT

Table 2. Hemoglobin, biochemistries, body composition and physical function in patients with prostate cancer undergoing androgen deprivation therapy before and 6 months after placebo or LTTT

	Placebo		LTTT	
	Baseline	6 months	Baseline	6 months
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Weight, kg	90.0 (80.2 to 99.8)	90.6 (80.9 to 100.2)	91.3 (79.3 to 103.3)	92.4 (80.5 to 104.3)
Hb, g/L	134 (128 to 139)	131 (125 to 138)	134 (126 to 140)	135 (127 to 143)
PSA, nmol/L	0.99 (0.16 to 1.83)	0.78 (–0.36 to 1.59)	0.29 (–0.73 to 1.32)	1.22 (0.23 to 2.22)
Testosterone, nmol/L	1.40 (0.67 to 2.1)	0.71 (0.03 to 1.38)	0.66 (–0.24 to 1.56)	3.1 (2.28 to 3.9)
Urea, mmol/L	6.5 (5.8 to 7.3)	6.7 (5.9 to 7.5)	7.4 (6.5 to 8.3)	6.8 (5.8 to 7.7)
Creatinine, mmol/L	82 (75 to 90)	81 (72 to 90)	85 (76 to 94)	80 (69 to 91)
ALT, IU/L	27 (21 to 33)	26 (20 to 32)	27 (20 to 35)	26 (19 to 33)
AST, IU/L	20 (17 to 22)	19 (16 to 22)	20 (17 to 23)	20 (16 to 23)
TSH, IU/L	1.4 (1.0 to 1.8)	2.0 (1.4 to 2.5)	1.6 (1.1 to 2.0)	1.6 (0.8 to 2.2)
Free T4, pmol/L	10.7 (9.8 to 11.6)	11.1 (10.2 to 12.0)	10.9 (9.9 to 12.0)	10.7 (9.6 to 11.8)
Lean mass, kg	52.3 (49.0 to 55.7)	52.1 (48.6 to 55.6)	55.8 (52.1 to 59.4)	56.3 (52.4 to 60.2)
BMC, g	2.89 (2.70 to 3.09)	2.85 (2.64 to 3.05)	3.02 (2.80 to 3.23)	3.03 (2.80 to 3.25)
Fat mass, kg	33.0 (28.0 to 38.0)	33.8 (28.5 to 39.0)	32.1 (26.5 to 37.7)	32.8 (27.1 to 38.6)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMC, bone mineral content; FM, fat mass; fT4, free thyroxine; Hb, hemoglobin; LBM, lean body mass; LTTT, liver-targeted testosterone therapy; PSA, prostate specific antigen; TSH, thyroid stimulating hormone.

Table 3. Changes in hemoglobin, biochemistries, body composition, and physical function in patients with prostate cancer undergoing androgen deprivation therapy after 6 months of placebo or LTTT

	Placebo	LTTT	LTTT—Placebo	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	*P*
Δ Weight, kg	0.7 (–0.3 to 1.7)	1.2 (0.3 to 2.1)	0.5 (–0.9 to 1.8)	0.5
Δ Hb, g/L	–2.9 (–6.4 to 0.6)	0 (–4 to 4)	3 (–2 to 8)	0.2
Δ PSA, nmol/L	–0.1 (–0.9 to 0.8)	0.55 (–0.14 to 1.25)	0.6 (–0.5 to 1.7)	0.07
Δ Testosterone, nmol/L	–0.7 (–1.5 to 0.2)	2.2 (1.3 to 3.0)*	2.9 (1.6 to 4.0)	0.01
Δ Urea, mmol/L	0.1 (–0.8 to 0.9)	–0.4 (–0.9 to –0.1)*	–0.4 (–1.5 to 0.6)	0.1
Δ Creatinine, mmol/L	–1.6 (–6.5 to 3.1)	–4.6 (–14.6 to 5.5)	–2.9 (–13.1 to 7.3)	0.8
Δ ALT, IU/L	1 (5 to 6)	–4 (–10 to 2)	–3 (–12 to 6)	1.0
Δ AST, IU/L	1 (–3 to 6)	–1 (–4 to 2)	–2 (–8 to 4)	0.8
Δ TSH, IU/L	0.6 (–0.1 to 1.2)	0.0 (–0.3 to 0.4)	–0.5 (–1.3 to 0.2)	0.2
Δ Free T4, pmol/L	0.4 (–0.4 to 1.1)	–0.2 (–1.1 to 0.7)	–2.2 (–4.7 to 0.3)	0.3
Δ Lean mass, kg	–0.2 (–0.8 to 0.3)	0.5 (–0.2 to 1.3)	0.8 (–0.1 to 1.7)	0.04
Δ BMC, g	–44 (–69 to –18)	6 (–33 to 45)	49 (5 to 93)	0.014
Δ Fat mass, kg	0.7 (0.0 to 1.5)*	0.7 (–0.3 to 1.7)*	0.0 (–1.2 to 1.2)	1.0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMC, bone mineral content; FM, fat mass; fT4, free thyroxine; Hb, hemoglobin; LBM, lean body mass; LTTT, liver-targeted testosterone therapy; PSA, prostate specific antigen; TSH, thyroid stimulating hormone.
*$P < 0.05$.

treatment. The mean urea level fell by 0.4 mmol/L (95% CI −0.9 to −0.1) during LTTT, but the change was not statistically significant compared to that observed during placebo treatment.

Mean body weight did not change significantly between placebo and LTTT treatments. We observed a trend toward an increase of LBM during LTTT and toward a fall during placebo treatment resulting in a gain of 0.8 kg (1.3%, $P = 0.04$) compared to placebo treatment (Fig. 2). Mean BMC also increased during LTTT and fell during placebo treatment resulting in a significant gain (1.7%, $P < 0.02$) over placebo treatment (Fig. 2). Fat mass increased significantly by 0.7 kg (2.1%) in both groups.

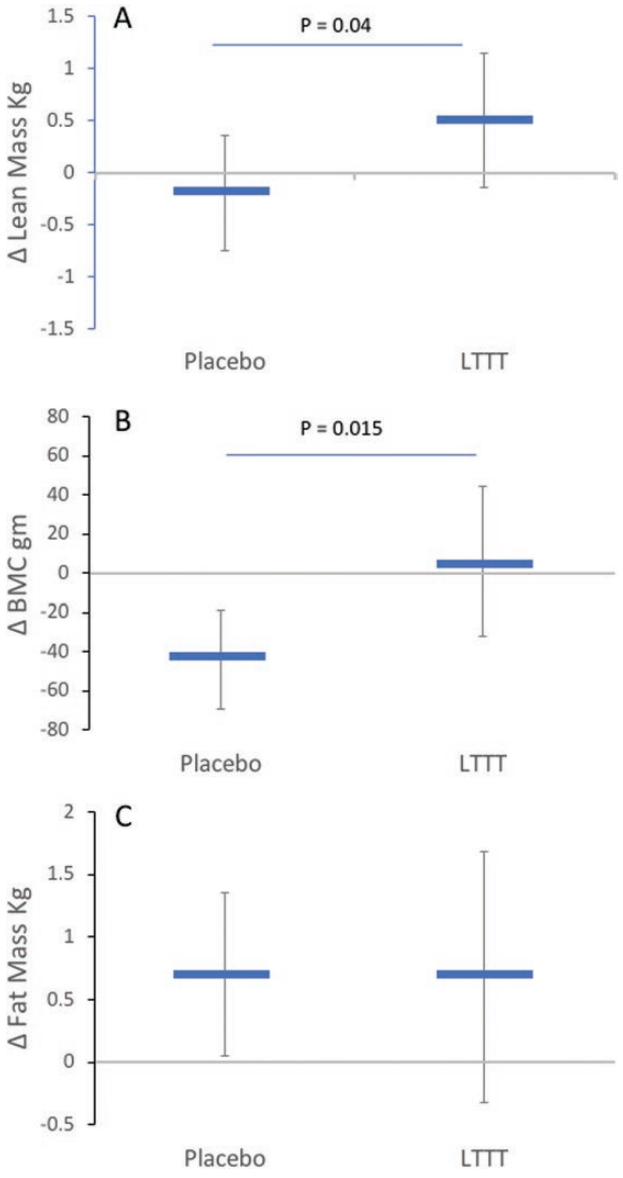

Figure 2. Changes lean body mass (A), bone mineral content (B), and fat mass (C) in patients with prostate cancer randomized to 6 months of liver-targeted testosterone therapy (LTTT) or placebo treatment. The figure shows means and 95% CIs.

The data were analyzed to ascertain whether there were differences in body compositional change between the acute and chronic ADT groups during placebo and LTTT. There was a trend toward a greater loss of LBM in the acute group during placebo treatment [−0.59 (−1.6 to 0.41) *vs* −0.04 (−0.83 to 0.75) kg chronic] and lesser gains in LBM during LTTT [0.38 (−0.61 to 1.37) *vs* 0.68 (−0.26 to 1.62) kg], although the differences did not reach statistical significance. During placebo treatment, BMC fell significantly in the acute [−77 (−122 to −31) g; $P = 0.04$] but not in the chronic group [−23 (−59 to 14) g]. During LTTT, there was a trend toward a lesser effect in the acute group [−11 (−57 to 34) *vs* 21 (−22 to 65) g], although the difference was not statistically significant. These trends were not evident for fat mass, which increased in both groups during placebo and LTTT.

Safety

During the treatment phase, 5 patients were withdrawn from the study because of rising PSA levels, and 2 patients withdrew for personal reasons (Fig. 1). Unblinding after the study revealed that all 5 patients with rising PSA had been allocated to LTTT, 1 patient was from the acute ADT subgroup and 4 from the chronic ADT subgroup. In 1 patient, the PSA concentration doubled from 4 to 7 nmol/L in parallel with a rise in testosterone concentration from 2 to 5 nmol/L. In another PSA rose from 6 to 13 nmol/L with testosterone concentrations increasing from 0.3 to 5.5 nmol/L. In another, PSA rose from 0.59 to 3 ng/mL without change in peripheral testosterone level. The complete data are shown in Table 4. The PSA concentrations in all 5 patients returned to baseline levels after withdrawal.

Discussion

We undertook a pilot evaluation of the anabolic effect and safety of LTTT in men with prostate cancer undergoing ADT administered 40 mg daily of testosterone in a double-blind placebo-controlled trial for 6 months. In the 42 patients completing the study, we observed a modest but significant increase in blood testosterone levels of about 2 nmol/L without a significant rise in PSA concentration in LTTT compared to placebo treatment. We observed a significant fall in blood urea concentration, with increases in BMC and LBM compared to placebo. In contrast, fat mass increased by a similar extent during LTTT and placebo treatments. We observed no difference in outcome measurements within the acute and chronic subgroups. LTTT did not affect blood count, electrolytes,

Table 4. PSA and testosterone levels at baseline, during and at follow-up in 7 patients who were withdrawn from the 6-month placebo-controlled trial of LTTT

			Baseline		At Withdrawal		Follow-up	
ID	Treatment group	Reason	PSA, ng/mL	Testosterone, nmol/L	PSA, ng/mL	Testosterone, nmol/L	PSA, ng/mL	Testosterone, nmol/L
2	Placebo	Travel	0.04	1.7	1.1	2.1	0.01	0.4
14	LTTT	PSA	0.22	0.3	8.2	2.5	0.42	NA
16	Placebo	Travel	0.77	0.3	0.62	NA	1.5	NA
22	LTTT	PSA	0.59	0.5	3.0	0.5	0.85	0.5
26	LTTT	PSA	6.8	0.3	13	5.5	1.0	NA
37	LTTT	PSA	2.6	0.4	11	1.9	1.1	NA
49	LTTT	PSA	4.2	2.0	15	5.0	8.5	0.6

Abbreviations: LTTT, liver-targeted testosterone therapy; PSA, prostate-specific antigen.

liver transaminases, and renal function. Five patients withdrew due to an increase in PSA, all occurring in patients taking LTTT, with levels returning to baseline after withdrawal. In short, LTTT induced biochemical and body compositional anabolic effects in men undergoing ADT. In 20% of patients on active treatment, LTTT reversibly increased PSA.

Prostate cancer incidence increases with age; over the age of 65 years, the incidence rate is as high as 60% [1]. ADT has a pivotal role in adjunctive therapy inducing remission. However, iatrogenic hypogonadism is invariably catabolic, impairing physical function, increasing fracture risk, and diminishing the quality of life. No established pharmacological therapies are available to prevent or reverse the catabolic consequences of ADT. Therefore, there is an unmet need for this large group of patients.

LTTT was developed from an understanding of how androgens regulate protein economy [16-18]. We demonstrated that selective androgenization of the liver by oral delivery induced a protein anabolic effect indistinguishable from systemic androgenization by transdermal delivery which normalized testosterone levels in peripheral blood of hypogonadal men [17]. Pharmaco-kinetic and -dynamic studies based on first-pass hepatic metabolism revealed that 40 mg of crystalline testosterone taken in 3 divided doses stimulated protein synthesis without increasing peripheral testosterone levels in the hypogonadal men [17,19]. In a proof-of-concept study, the same dose of crystalline testosterone stimulated whole-body protein anabolism in postmenopausal women of similar magnitude to hypogonadal men without causing peripheral androgen excess [17,18]. This information provided the rationale for selective hepatic targeting for preventing protein catabolism in male hypogonadism.

The hypothesis predicted that LTTT reduces urea production and increases protein accretion, leading to gains in lean and bone mass but not body fat. Indeed, we observed a fall in blood urea, an increase in LBM, and a trend toward fat mass gain in ADT-treated men with prostate cancer. There were no significant effects on liver transaminases or blood hemoglobin levels, which may increase in response to supraphysiologic systemic effects of testosterone. Thus, LTTT induced an anabolic effect reflected in biochemical and body compositional changes without hepatic dysfunction.

Although peripheral blood testosterone levels in ADT-treatment patients increased by up to an average of 2 nmol/L, this increase is unlikely to contribute to the anabolic effects. This is because we had previously observed that in hypogonadal men LTTT induced an anabolic effect of similar magnitude to that from systemic testosterone treatment without increasing testosterone concentration in peripheral blood [17]. The increase of 2 nmol/L contrasts with previous observations that the same oral dose had not affected blood testosterone concentration in hypogonadal men or had increased minimally by less than 0.5 nmol/L in postmenopausal women [17,18]. The ADT-treated patients were older and more obese and likely harbored more comorbidities than the hypogonadal men and menopausal women we had previously studied. It is likely that the pharmacokinetics of LTTT in men with ADT are different from younger hypogonadal men and postmenopausal women. Further work is required to explore a lower dose of testosterone that androgenizes the liver without spillover to peripheral blood in older men with prostate cancer.

The safety of LTTT is a critical consideration for men with prostate cancer. Among the LTTT-treated patients who completed the study, the mean plasma testosterone concentration rose by 2 nmol/L. This was accompanied by a slight rise in mean PSA concentration increase, which did not reach statistical significance. However, this this may be due to a type 2 error because of the small sample size. The observation suggest that a mild rise in testosterone levels may affect residual prostate tumor growth in some patients. Twenty

percent of LTTT-treated patients terminated the study because of a rise in PSA levels beyond the upper normal limit, all returning to baseline after withdrawal. LTTT for patients with prostate cancer must be closely monitored. However, the rapid return of PSA to baseline on withdrawal gives some reassurance that the effect is transient and reversible within the first months of therapy.

While the effect on prostate tissue from transient testosterone spillover is reversible, further work is required to optimize a LTTT dose in this population of older men with prostate cancer. PSA and testosterone are useful biochemical markers for tailoring and monitoring the long term safety of LTTT.

A strength of this study is the double-blind, placebo-controlled design and the conceptual novelty of liver targeting to prevent catabolism in a highly vulnerable group of patients subjected to long-term hypogonadism. Our observation that LBM and BMC rose with LTTT by 1.3% and 1.7%, respectively, is consistent with predictions of a preventative effect in patients initiating ADT at 6 months [6,7,21,22]. A larger sample size or longer duration of treatment may strengthen these findings. There were major challenges in recruiting larger numbers of frail elderly volunteers to undergo a trial over months with a medication that could risk prostate cancer progression. The body compositional changes did not differ significantly between those undergoing acute and chronic treatments, indicating LTTT benefits both groups. In summary, the collective biochemical and body compositional changes provide proof of therapeutic concept that LTTT prevents whole-body catabolism.

The potential anabolic application of testosterone has been explored across a range of catabolic conditions and in aging men to mitigate the loss of physical function. In older men with cardiometabolic comorbidities, testosterone treatment induced significant cardiac adverse events [23,24] even in low doses aimed at raising blood testosterone into the young physiological range. There is ongoing debate over potential cardiovascular adverse events related to testosterone therapy, particularly in older men with existing comorbidities. In one study of older men with mobility limitations, testosterone treatment was associated with adverse events [25] but not in another study of similarly aged men with frailty or intermediate frailty [26]. Nevertheless, these trials indicate possible risk associated with even modest elevations of systemic testosterone levels, a situation that does not occur with LTTT. The applicability of LTTT extends to women who would not be at risk of virilization.

We conclude that LTTT shows promise as simple therapy for preventing sarcopenia and bone loss during ADT in men with prostate cancer. Studies are required to optimize the dose, safety, and efficacy in older and frail prostate cancer patients and to explore potential application in other catabolic states in both sexes.

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