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, 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 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 Patients were withdrawn if PSA exceeded 4 ng/mL.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 – 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 – -0.1] mmol/L) during LTTT but not placebo (Δ 0.05 [-0.8 – 0.9] mmol/L). BMC (Δ 49 [5 – 93] gm, p<0.02) and lean mass (Δ 0.8 [-0.1 – 1.7] kg; p=0.04) increased compared to placebo. Five patients on LTTT withdrew from increased PSA levels, all returning to baseline levels.

Conclusion: LTTT shows promise as 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
Introduction

Prostate cancer is the second most frequent cancer diagnosis made in men and the fifth leading cause of death worldwide. 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. Because ADT is often prescribed for extended times, these patients suffer from long-term catabolic consequences of hypogonadism. 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. The ensuing sarcopenia reduces muscle strength and physical function, diminishing quality of life (QoL). Up to 2.5% of lean mass is lost within the first 6 to 12 months, continuing at a lower rate thereafter. The annualized loss of lean body mass is about 10 times that occurs with ageing. Similarly, there is parallel rapid and progressive loss of bone amounting to 2-3% within 6-12 months, increasing the risk of fracture. 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. 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 three divided doses. This regimen did not increase testosterone levels in peripheral blood of hypogonadal men indicating complete first-pass hepatic degradation 19. In post-menopausal 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 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 multi-disciplinary 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 40mg 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; commencing or receiving ADT. Exclusion criteria were: non-prostatic metastatic disease, coexisting conditions that affect lean body mass such as liver disease, renal insufficiency, 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 a further 30 excluded based on blood screening eligibility, leaving 50 for participation (Figure 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.
Randomisation and Masking

Patients were randomised in a 1:1 ratio using a 4 by 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 (YS); 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 anytime 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.

Outcome measures

We tested the hypothesis that LTTT increases lean and bone mass. The primary outcome measures were lean body mass (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 three capsules daily approximately 8 hours apart, totaling 40 mg/day. Matching placebo capsules were prepared and taken in an identical manner.

Assays

Testosterone, PSA, 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 CV of 5.7%. The PSA assay had a detection limit of 0.08 µg/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%

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, BMI, renal function, thyroid function (TSH and fT4) as covariates. We calculated least-squares mean estimates with 95% CIs of treatment 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 one-tailed test.
Sample size estimates were drawn from studies reporting body compositional change after ADT. The primary outcome measures were LBM and BMC. The average loss over 6-9 months for LBM was 1 – 2.6% with a SD of 1.7 – 3.4 %, and for BMD 1.9 – 2.4% with an SD of 1.5 – 2.5%. We considered that LTTT treatment prevent a decline of 1% in LBM and of 2.0 % 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% drop out.

Results

Fifty patients were enrolled into the study (Figure 1). One withdrew after enrolment after reconsidering participation. The remaining 49 comprised 19 ADT-naive (acute) and 30 ADT-treated (chronic) patients treated for a median duration of 420 days (range 135 – 3020 days). All ADT-naive 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, five patients withdrew from the study in the LTTT group due to a rising
PSA and two from the placebo group for personal reasons. Thus 42 patients completed the
study, 19 of 24 in the LTTT and 23 of 25 in the placebo group (Figure 1).

Results of Intervention (Table 2 and 3)
There was no significant change in hemoglobin, electrolytes, liver transaminases, creatinine,
TSH and fT4 levels in both placebo and LTTT groups during the study.
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 treatment. The mean urea level fell by 0.4 mmol/L (95% CI -0.9 - -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 towards an increase of LBM during LTTT and towards a fall during placebo
treatment resulting in a gain of 0.8 kg (1.3%, p=0.04) compared to placebo treatment
(Figure 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 (Figure 2). Fat mass increased significantly by 0.7 kg (2.1%) in both groups.

The data were analysed 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 towards a greater loss of LBM in the acute group during placebo treatment (-0.59 [-1.6 – 0.41] vs -0.04 [-0.83 - 0.75] kg chronic) and lesser gains in LBM during LTTT (0.38 [-0.61 – 1.37] vs 0.68 [-0.26 – 1.62] kg although the differences did not reach statistical significance. During placebo treatment, BMC fell significantly in the acute (-77[-122 - -31] gms, P=0.04) but not in the chronic group (-23[-59 – 14] gms). During LTTT, there was a trend towards a lesser effect in the acute group (-11[-57 – 34] vs 21[-22 – 65] gms) 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, five patients were withdrawn from the study because of rising PSA levels and two for personal reasons (Figure 1). Unblinding after the study revealed that all five patients with rising PSA had been allocated to LTTT. One patient was from the acute while 4 was from the chronic ADT subgroup. In one, 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 five returned to baseline levels after withdrawal. Two patients in the placebo group withdrew for personal reasons.
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 six 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, 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 androgenisation of the liver by oral delivery induced a protein anabolic effect indistinguishable from systemic androgenisation by transdermal
delivery which normalised testosterone levels in peripheral blood of hypogonadal men.\textsuperscript{17} Pharmaco-kinetic and -dynamic studies based on first-pass hepatic metabolism revealed that 40 mg of crystalline testosterone taken in three divided doses stimulated protein synthesis without increasing peripheral testosterone levels in the hypogonadal men.\textsuperscript{17,19} In a proof-of-concept study, the same dose of crystalline testosterone stimulated whole body protein anabolism in post-menopausal women of similar magnitude to hypogonadal men without causing peripheral androgen excess.\textsuperscript{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, 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 towards fat mass gain in ADT-treated men with prostate cancer. There were no significant effects on liver transaminases nor on 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.\textsuperscript{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 post-menopausal women.\textsuperscript{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 post-menopausal 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 lean body mass 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\textsuperscript{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 ageing men to mitigate the loss of physical function. In older men with cardio-metabolic co-morbidities, testosterone treatment induced significant cardiac adverse events\textsuperscript{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\textsuperscript{25}, but not in another study of similarly aged men with frailty or intermediate frailty\textsuperscript{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 extend 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.
Contributions

RH and AN contributed equally to design, recruitment, data collection, interpretation and writing. IR contributed to recruitment and data collection. DG contributed to recruitment, data collection and writing. YS contributed to study design and writing. PH contributed to recruitment. TN contributed to data analysis, interpretation and writing. SW contributed to design, recruitment and interpretation. KH contributed to study design, data analysis, interpretation and writing.

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Disclosure

We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.
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Consort diagram showing the flow of patient numbers through the phases of recruitment, randomization, treatment and analysis. Patients with prostate cancer comprised two groups, an acute group initiating androgen deprivation therapy (ADT) and a chronic group on stable ADT with controlled disease for at least 4 months.

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 figures show mean and 95% confidence intervals.
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   | 24      | 19    | 30      |
| Mean (95% CI)      |      |         |       |         |
| Age yr             | 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) |

LTTT = liver-targeted testosterone therapy, PSA = prostate specific antigen, TSH = thyroid stimulating hormone, fT4 = free thyroxine, Hb = hemoglobin, LBM = lean body mass, FM = fat mass, BMC = bone mineral content
Table 2

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

|                          | Placebo         | LTTT            |
|--------------------------|-----------------|-----------------|
|                          | Baseline Mean (95% CI) | 6 months Mean (95% CI) | Baseline Mean (95% CI) | 6 months Mean (95% CI) |
| Weight Kg                | 90.0 (80.2 – 99.8) | 90.6 (80.9 – 100.2) | 91.3 (79.3 – 103.3) | 92.4 (80.5 – 104.3) |
| Hb g/L                   | 134 (128 – 139) | 131 (125 – 138) | 134 (126 – 140) | 135 (127 – 143) |
| PSA nmol/L               | 0.99 (0.16 – 1.83) | 0.78 (-0.36 – 1.59) | 0.29 (-0.73 – 1.32) | 1.22 (0.23 – 2.22) |
| Testosterone nmol/L      | 1.40 (0.67 – 2.1) | 0.71 (0.03 – 1.38) | 0.66 (-0.24 – 1.56) | 3.1 (2.28 – 3.9) |
| Urea mmol/L              | 6.5 (5.8 – 7.3) | 6.7 (5.9 – 7.5) | 7.4 (6.5 – 8.3) | 6.8 (5.8 – 7.7) |
| Creatinine mmol/L        | 82 (75 – 90) | 81 (72 – 90) | 85 (76 – 94) | 80 (69 – 91) |
| ALT IU/L                 | 27 (21 – 33) | 26 (20 – 32) | 27 (20 – 35) | 26 (19 – 33) |
| AST IU/L                 | 20 (17 – 22) | 19 (16 – 22) | 20 (17 – 23) | 20 (16 – 23) |
| TSH IU/L                 | 1.4 (1.0 – 1.8) | 2.0 (1.4 – 2.5) | 1.6 (1.1 – 2.0) | 1.6 (0.8 – 2.2) |
| Free T4 pmol/L           | 10.7 (9.8 – 11.6) | 11.1 (10.2 – 12.0) | 10.9 (9.9 – 12.0) | 10.7 (9.6 – 11.8) |
| Lean mass Kg             | 52.3 (49.0 – 55.7) | 52.1 (48.6 – 55.6) | 55.8 (52.1 – 59.4) | 56.3 (52.4 – 60.2) |
| BMC gm                   | 2.89 (2.70 – 3.09) | 2.85 (2.64 – 3.05) | 3.02 (2.80 – 3.23) | 3.03 (2.80 – 3.25) |
| Fat mass Kg              | 33.0 (28.0 – 38.0) | 33.8 (28.5 – 39.0) | 32.1 (26.5 – 37.7) | 32.8 (27.1 – 38.6) |
Table 3

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

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

LTTT = liver-targeted testosterone therapy, PSA = prostate specific antigen, TSH = thyroid stimulating hormone, fT4 = free thyroxine, Hb = hemoglobin, LBM = lean body mass, FM = fat mass, BMC = bone mineral content

*P < 0.05
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 liver-targeted testosterone therapy (LTTT).

| ID | Treatment Group | Reason | Baseline | At Withdrawal | Follow-up |
|----|-----------------|--------|----------|---------------|-----------|
|    |                 |        | 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               |
Figure 2

A

\[
\begin{align*}
\Delta \text{Lean Mass Kg} &: \\
\text{Placebo} &: 0.5 \\
\text{LTTT} &: -0.5 \\
P &= 0.04
\end{align*}
\]

B

\[
\begin{align*}
\Delta \text{BMC gm} &: \\
\text{Placebo} &: -0.5 \\
\text{LTTT} &: 0.5 \\
P &= 0.015
\end{align*}
\]

C

\[
\begin{align*}
\Delta \text{Fat Mass Kg} &: \\
\text{Placebo} &: 0.5 \\
\text{LTTT} &: 1.0
\end{align*}
\]