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Muscle function following testosterone replacement in men on opioid therapy for chronic non-cancer pain - a randomized controlled trial

Running Title: Testosterone and muscle function in chronic pain

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Abstract

**Background:** Chronic pain and opioid treatment are associated with increased risk of male hypogonadism and subsequently decreased muscle function. A diagnosis of hypogonadism is based on the presence of low total testosterone (TT) and associated symptoms. The effect of testosterone replacement therapy (TRT) on muscle function in men with chronic pain and low TT remains to be investigated.

**Objectives:** To investigate effects of TRT on muscle function and gait performance in men treated with opioids for chronic non-cancer pain.

**Materials and methods:** Double-blind, placebo-controlled study. 41 men (>18 years) with opioid-treated chronic pain and serum total testosterone <12 nmol/L were randomized to 24 weeks TRT (Testosterone undecanoate injection three times/6 months, n =20) or placebo injections (n =21). Muscle function was measured as leg press maximal voluntary contraction (LP-MVC), leg extension power using the Nottingham power rig and handgrip strength using a handheld dynameter. Gait performance was measured at usual and maximal gait speed on a 10-m track. Body composition (lean body mass and fat mass) was determined by Dual-energy X-ray Absorptiometry. Mann-Whitney tests were performed on Δ-values (24–0 weeks) between TRT and placebo.

**Results:** At baseline, median (interquartile range) age was 55 ± 13 years and BMI was 30.7 ± 5.2 kg/m². Δ-muscle function and Δ-gait performance were similar between TRT and placebo. Median Δ-LP-MVC was 174.2 ± 406.7 Newton following TRT and 7.6 ± 419.1 Newton after placebo, p =0.091. Δ-lean body mass was significantly higher following TRT compared to placebo, 3.6 ± 2.7 vs 0.1 ± 3.5 kg, respectively (p <0.001).

**Discussion:** TRT, compared to placebo, did not improve muscle function or gait performance despite increased lean body mass. Changes in body composition did not infer any changes in muscle function.

**Conclusion:** 24 weeks TRT in opioid treated men with pain-related male hypogonadism did not improve muscle function.

Key words: hypogonadism, testosterone, chronic pain, muscle function, gait speed, opioids
The aim of the present study was to examine changes in muscle functions and gait performance following six months intramuscular TRT in men with chronic pain and opioid-induced hypogonadism.
Materials and Methods

Study design
The full trial protocol has been published by Glintborg et al.25 In brief, men aged >18 years, treated with opioids for non-cancer pain for at least 3 months at an opioid dosage corresponding to at least 50 mg morphine/day were eligible for inclusion if TT was <12 nmol/L and luteinizing hormone and prolactin were within reference range. Participants were randomly assigned to receive injections containing 1,000 mg testosterone undecanoate (Nebido) (n=20) or placebo (n=21). Injections were applied at time of randomization and again after 6 and 18 weeks. Study investigators and participants were blinded to treatment allocation. Participants were examined before and after 24 weeks of intervention. Assessment included tests of muscle function, gait performance, test-related pain ratings, clinical examinations, fasting blood samples, and dual-energy X-ray absorptiometry (DXA) scans. Data on body composition and hormonal profile have been published previously.25 All participants gave written informed consent. The study was approved by The Regional Scientific Ethical Committees for Southern Denmark (S-20150004) and the Danish Health and Medicines Agency (EudraCT: 2014-004729-42). Monitoring was performed according to good clinical practice (GCP) by the GCP unit at Odense University Hospital and all procedures were carried out in accordance with the revised (2013) Helsinki Declaration. The trial was registered at www.clinicaltrials.gov (NCT02433730). Reporting in this article was aligned with the Consolidated Standards of Reporting Trials (CONSORT) guideline.

Study outcome measures
Muscle function was assessed as muscle power and muscle strength. Muscle power (force*velocity) was assessed as leg extension power (LEP) on a Nottingham Power rig27 with participants seated, arms crossed, leaning slightly forward, with their pelvis supported at their back. Subjects were instructed to push a footplate as forcefully and as fast as possible with their dominant leg until fully extended. Visual feedback was provided on a PC screen after each trial. Eight trials were performed with 30-45 s rest intervals. Muscle strength was measured as i) maximal isometric voluntary leg press contraction (LP-MVC) in a custom-built leg press device,28 and ii) handgrip strength (HGS) of the dominant hand with a handheld dynamometer (Smedley, S Dynamometer, TTM, Tokyo, 100 kg).

For the LP-MVC test, participants were seated with a knee angle of approximately 120 degrees on the device and asked to push as hard and fast as possible for approximately 5 s with their dominant leg against a fixed footplate. Strong verbal encouragement was provided while on-line visual feedback of the force produced was available to the

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participant. The force signals from the piezoelectric force transducers (Kistler 9367/8 B) embedded in the footplate were digitally sampled at 1 kHz. Five trials were performed with 2-min rest intervals between trials. HGS measures were taken in the standing position, palm facing the thigh. Participants were asked to squeeze the dynamometer as hard as possible while strong verbal encouragement was provided. Three trials were performed with 1-min rest intervals between trials. In case of injury/disease of the dominant limb (e.g., causing inability to fully extend the leg), the non-dominant limb was used for testing during both baseline and follow up testing.

For all muscle function measurements, if the two highest recordings differed >5%, within the minimum allotted trials for each test, additional trials were performed until this criterion was fulfilled. The order of muscle function testing was standardized, and it is presented chronologically. The highest recorded values were used for statistical analyses in all muscle function tests.

Gait performance
The time required to walk 10 m was measured with a stopwatch with participants walking in a straight line. The test was performed in two conditions: (1) with usual (UGS) and (2) maximal gait speed (MGS). For both protocols time was measured as the time between the points of contact of forwardmost heel on the floor when crossing the start and finish line. Participants were instructed to walk a total of 12 m during each trial to allow for a 2 m deceleration phase. Two trials were performed for UGS and MGS. The fastest recorded time during each test was used for analysis.

Acute pain-rating
We previously reported that laboratory-tested experimental pain in the resting condition was unchanged following TRT. To supplement this finding, we obtained measures of acute pain during physical strain i.e., pain experienced during tests of muscle function and gait performance. Acute pain was assessed using a visual analogue scale ranging from 0 (no pain) to 10 (worst possible pain). Participants were asked to rate their pain immediately following each trial during UGS, MGS, HGS and LP-MVC tests as well as before and after the first and last LEP trial. The highest recorded value for each trial was used for statistical analyses.

Hormonal assays
Testosterone was measured two times between 0800 h and 1000 h in the fasting state by liquid chromatography tandem mass spectrometry. For testosterone measurements the intra-assay coefficient of variation was 10% for TT >0.2 nmol/l and 30% in the range between 0.1- 0.2 nmol/l.25
Body composition
Lean body mass (LBM), Leg lean mass (LLM) and total fat mass (TFM) were measured by whole body DXA scans using a Hologic Discovery device (Waltham, MA, USA). LLM is presented for the dominant leg. Coefficient of Variation for LBM and TFM was earlier reported as 0.6 and 0.8% respectively. Clinical examination included measures of height, weight, and waist circumference.

Statistical analyses
The sample size of the original study was calculated using the effect of TRT on LBM based on a meta-analysis by Isidori. Inter-group differences were compared using Mann Whitney U statistics as described by Altman. Δ-values for clinical and biochemical markers were calculated as follow-up treatment level minus pretreatment level. Treatment effects within groups were examined using Wilcoxon signed-rank statistics. Bivariate correlations between multiple study outcomes were investigated using Spearmann’s Rho correlational analyses. The potential confounding effect of pain on muscle function was tested comparing Δ-values from each test with the Δ-pain score recorded for that specific test. The association between significant changes in LLM and lower limb muscle function was investigated comparing Δ-LLM and Δ-values on LP-MVC and LEP. Additionally, associations between significant changes in body composition and TT was investigated comparing Δ-TT and Δ-LBM. All statistics were performed using SPSS 17.0 (SPSS Inc, Chicago, USA). A p-value of <0.05 was considered significant. All data are presented as median ± interquartile range.

Results
A total of 41 men were included and 38 men (TRT =18, placebo =20) completed the trial. At baseline, median age was 55 ± 13 years, BMI was 30.7 ± 5.2 kg/m². Baseline characteristics were comparable between TRT and placebo groups (Table 1). Six participants (TRT =4, placebo =2) were unable to complete all tests of muscle function (3 unable to provide valid test measures and 3 refused). These participants were similar to complete cases regarding all other available study outcomes (all p >0.05). Partial cases were included in all analyses. In the TRT group, one participant had serious pneumonia, which led to treatment at intensive care unit and death. This participant received opioid treatment due to pancreatitis and chronic abdominal pain. One participant started anti-depressive treatment due to depression. Both cases were found to be unrelated to TRT treatment.

Muscle function and gait performance
No between groups differences in Δ-muscle function and Δ-gait performance were observed after the intervention (fig. 2). The TRT group increased significantly in LP-MVC, while no change occurred in the placebo group (Table 2).
Pain experienced during muscle function testing

Δ-values of pain experienced during muscle function testing were comparable between TRT vs. placebo (Table 2).

Testosterone levels and body composition

Significant between-group changes for testosterone levels and body composition were observed following intervention with TRT vs. placebo (Table 1). LBM, LLM, body weight and TT increased significantly within the TRT group along with a decline in total fat mass (Table 1). No changes were observed in testosterone and body composition for the placebo group.

Bivariate correlations

Association between Δ-lower limb muscle function and Δ-pain

Association between Δ-LEP and Δ-pain (LEP) was significant for the placebo group (r = -0.76, p =0.005). No other significant associations were identified between Δ-muscle function and Δ-pain in TRT or placebo groups.

Association between Δ-TT and Δ-LBM and Δ-LLM

In the TRT group, Δ-TT was associated with Δ-LBM (r =0.826) and Δ-LLM (r =0.826), both p <0.001.

Association between Δ-LLM and Δ-lower limb muscle function

In the TRT group, Δ-LLM was not associated with any changes in lower limb muscle function (Δ-LP-MVC or Δ-LEP).

Discussion

This is the first randomized double-blinded placebo-controlled trial examining the effect of TRT on muscle function in men with chronic non-cancer pain treated with opioids. The main study finding was, that TRT did not result in changes in muscle function and gait performance superior to placebo treatment. Furthermore, increased LBM during TRT was not significantly associated with changes in muscle function.

Several previous studies examined the effect of TRT on muscle function in men with hypogonadism unrelated to opioid therapy.24,32,33 Our findings of unchanged muscle function during TRT are in line with two previous placebo-controlled RCTs in healthy older (≥60 years)
men with hypogonadism. In addition, a recent systematic review evaluating the impact of TRT on muscle function in older men without opioid treatment found no effect of TRT on muscle function. However, this review is not aligned with a meta-analysis indicating an average 10.3% increase in lower extremity strength following TRT in older men (≥60 years). In the present study, LP-MVC increased by ~10% in the TRT group, which is similar to the average change reported in the meta-analysis. However, present changes in muscle function following TRT were not different from the placebo group. Furthermore, TRT increased LBM and LLM. Nevertheless, changes in body composition were not associated with changes in muscle function. Findings of concurrent improvement in LBM and muscle function are frequently reported. However, the relationship between change in muscle mass and muscle function (e.g., muscle strength) in patients has been debated. In patients with chronic obstructive pulmonary disease (COPD), testosterone treatment increased muscle mass without changes in muscle function. In contrast, in men with chronic heart failure, testosterone treatment did not increase muscle mass while muscle function increased. Therefore, the magnitude by which TRT independently affect muscle mass and function may depend on the target population. People with chronic pain are prone to exhibit sedentary behavior and are unlikely to voluntarily engage in high-intensity activities, thus providing little stimulation to elicit neuromuscular growth or maintain neuromuscular level (e.g., muscle strength). In the present study, participants were not encouraged to exercise. Lack of exercise/high intensity daily physical activity may therefore explain the lack of association between body composition and muscle function following study intervention. In accordance, interventions combining TRT with physical exercise showed larger increase in muscle strength and muscle function compared to TRT alone. This was earlier demonstrated in healthy subjects, COPD patients and men with hypogonadism. The combined effect of TRT and physical exercise on muscle function in men with chronic pain should be investigated in future studies.

Serum TT increased 12.3 ± 12.9 nmol/L following TRT (range: -3.17; 41.63 nmol/L), and this change was associated with improvement in both LLM and LBM. Sattler et al found that a supraphysiologica increase of TT by 1046 ng/dL (36.3 nmol/L) was necessary to achieve a median increase in LBM of 1.5 kg, which was required to significantly improve muscle strength (1-repetition max). In clinical practice, the target range for TT in men treated with TRT is to achieve values in the mid-normal range for young men, not a supraphysiological increase. Only one participant in present sample achieved an increase in TT >36.3 nmol/L. Nevertheless, just three participants in the TRT group achieved less than 1.5 kg increase in total LBM. Excluding these three participants from analyses had no effect on the presented findings (data not shown). Pain was not an inclusion criterion in Sattler et al. and median baseline TT-levels were 16.4 nmol/L, indicating most participants were not hypogonadal. Given the comparatively large increase in LBM, the lack of improved muscle function in present study is unlikely to be the cause of insufficient treatment dose or duration but more likely related to demographic characteristics specific to present sample e.g., lack of physical activity in chronic pain.
Pain experienced during assessment of muscle function (table 2) as well as laboratory tested pain in the resting condition were unchanged following TRT in the present study. Intense pain reduces muscle function and people with chronic pain may experience day-to-day variation in pain severity, which may affect muscle function testing. The present double-blinded trial showed no between-group differences in pain severity. However, unchanged pain status could also have influenced our results (i.e., pain inhibits muscle function and if pain is unchanged, similar inhibitory effects on muscle function would be present at baseline and follow-up, which would limit potential improvements in muscle function). In a prospective study on physical exercise in people with chronic low back pain, decreased pain at follow-up was closely associated with improved muscle function, whereas changes in muscle function were not associated with changes in muscle volume. In present study, we expected that if pain increased between baseline and follow-up, this would decrease muscle function and vice versa, resulting in a negative association between muscle function and pain. However, this hypothesis was only confirmed regarding LEP, which was performed with participants pushing against the footplate as forcefully and fast as possible. This suggests that rapid force generation may be more affected by day-to-day variation in pain severity than maximal force capacities. In addition, we observed a decrease in pain during LP-MVC in the placebo group, which however, was not associated with changes in muscle function. Whether decreased pain may facilitate better muscle function in men with chronic pain remains to be investigated.

The present study included all forms of non-cancer pain and the study population had nonuniform symptomatology and diverse etiological origins of pain conditions. The origin of pain may be important to consider in relation to clinical applications. Poor muscle function is prevalent in some patient groups with chronic pain. In some patients, the pathology causing pain may simultaneously cause muscle weakness (e.g. altered Ca²⁺ and free radical signaling with rheumatoid arthritis). However, not all clinical populations with chronic pain exhibit poor muscle function. Therefore, the impact of pain on muscle function is likely dependent on the pain’s specific etiology. Potential benefits of TRT for specific sub-groups of men with chronic pain conditions should be investigated in future studies.

A major strength of the present study was the study design (double blinded RCT). However, the primary study outcome was LBM. While we did report a significant treatment effect on LBM, the study may have been underpowered to detect between-group differences in muscle function. Three participants dropped out and 6 (~15 %) participants were unable or unwilling to perform all tests of muscle function. According to recent guidelines, TRT is indicated in patients with TT <8 nmol/L, whereas TRT may be indicated in patients with TT <12 nmol/L, based on symptoms. All men in the present study cohort were treated with opioids of considerable dosage (≥50 mg morphine/day), which in all cases would imply signs and symptoms suggestive of male hypogonadism (fatigue, decreased energy, mood, hot flushes etc.). In addition, more specific sexual symptoms of male hypogonadism were present in 23/35 of participants (12/18 in the TRT group). To investigate whether TRT effects depended on baseline TT, we did a post-hoc stratified analysis excluding...
participants with TT ≥8 nmol/L (n = 15). The result of this analysis (n = 23) was in agreement with presented results.

Conclusion

Our findings indicate that TRT, compared to placebo, provides no superior improvements in muscle function or gait performance in men with chronic non-cancer pain. In addition, Changes in body composition did not infer any changes in muscle function.

Acknowledgement

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Conflict of interest

The authors declare no conflicts of interest.
References


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FIGURE 1: Mechanisms for chronic pain and reduced muscle function. See text for details.

HPG = hypothalamic-pituitary-gonadal. Chronic pain can result in low testosterone, which leads to muscle atrophy and poor muscle function. Painful movement or fear-avoidance behavior may reduce physical activity causing further atrophy. The resulting reduction in muscle function may further limit movement and decrease physical activity, thus, making the patient susceptible to further disability and pain.
FIGURE 2: Changes in muscle function and functional performance.

LP MVC = Leg press maximal voluntary contraction, LEP = Leg extension power, HGS = Hand grip strength, MGS = Maximal gait speed, UGS = Usual gait speed. Black bars are median values. Colored bars indicate interquartile ranges.
<table>
<thead>
<tr>
<th></th>
<th>TESTOSTERONE (n= 18)</th>
<th>PLACEBO (n= 20)</th>
<th>Within-group effect</th>
<th>Within-group effect</th>
<th>Between-group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline 6 months Δ-change p-value</td>
<td>Baseline 6 months Δ-change p-value</td>
<td>p-value</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 10</td>
<td>55 ± 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.2 ± 5.0</td>
<td>30.7 ± 5.6</td>
<td>0.9 ± 1.2</td>
<td>0.001</td>
<td>32.4 ± 6.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>97.8 ± 15.9</td>
<td>102.0 ± 14.2</td>
<td>2.7 ± 3.6</td>
<td>&lt;0.001</td>
<td>98.8 ± 21.9</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>6.8 ± 4.1</td>
<td>19.3 ± 12.8</td>
<td>12.3 ± 12.9</td>
<td>&lt;0.001</td>
<td>7.4 ± 4.4</td>
</tr>
<tr>
<td>(nmol/L)</td>
<td>0.12 ± 0.08</td>
<td>0.37 ± 0.17</td>
<td>0.26 ± 0.25</td>
<td>&lt;0.001</td>
<td>0.15 ± 0.10</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>41.5 ± 28.3</td>
<td>36.6 ± 21.8</td>
<td>-2.9 ± 9.5</td>
<td>0.006</td>
<td>32.2 ± 20.0</td>
</tr>
<tr>
<td>Total lean body mass</td>
<td>60.5 ± 12.1</td>
<td>63.5 ± 8.2</td>
<td>3.6 ± 2.8</td>
<td>&lt;0.001</td>
<td>58.6 ± 9.8</td>
</tr>
<tr>
<td>(kg)</td>
<td>9.8 ± 1.7</td>
<td>10.3 ± 1.4</td>
<td>0.4 ± 0.3</td>
<td>0.006</td>
<td>9.6 ± 1.0</td>
</tr>
<tr>
<td>Lean leg mass (kg)</td>
<td>32.6 ± 10.5</td>
<td>29.6 ± 9.4</td>
<td>-1.2 ± 3.2</td>
<td>0.015</td>
<td>33.7 ± 10.4</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as median ± interquartile range. BMI = Body mass index. SHBG = Sex hormone binding globulin. The highest recorded pain score associated with any test is presented directly below the test result for that test, respectively. There were no between-group differences at baseline (p>0.05). Within-group effect denotes the p-value associated with the change from baseline to follow-up. Between-group effects denotes the placebo-controlled p-value comparing Δ-values between groups.
Table 2 – Changes in muscle function, gait performance and test associated pain from baseline to follow-up.

<table>
<thead>
<tr>
<th></th>
<th>TESTOSTERONE (n= 14)</th>
<th>PLACEBO (n= 19)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Within-group effect</td>
<td>Within-group effect</td>
<td>Between-group effect</td>
<td></td>
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<tr>
<td><strong>Muscle Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Baseline</strong></td>
<td>Baseline</td>
<td>6 months</td>
<td>Δ-change</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Leg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extension power (Watts)</strong></td>
<td>263.5 ± 143.7</td>
<td>299.5 ± 177.7</td>
<td>23.0 ± 74.8</td>
<td>0.509</td>
</tr>
<tr>
<td><strong>Highest pain score during test</strong></td>
<td>5.5 ± 3.5</td>
<td>5.5 ± 3.8</td>
<td>0.0 ± 4.0</td>
<td>0.384</td>
</tr>
<tr>
<td><strong>Leg Press MVC (Newton)</strong></td>
<td>1843 ± 1261</td>
<td>2102 ± 1134</td>
<td>174 ± 407</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td><strong>Highest pain score during test</strong></td>
<td>6.0 ± 3.0</td>
<td>7.0 ± 3.0</td>
<td>0.0 ± 3.0</td>
<td>0.589</td>
</tr>
<tr>
<td><strong>Handgrip Strength (kg)</strong></td>
<td>41.8 ± 12.2</td>
<td>47.0 ± 12.6</td>
<td>3.0 ± 6.3</td>
<td>0.345</td>
</tr>
<tr>
<td><strong>Highest pain score during test</strong></td>
<td>6.5 ± 5.5</td>
<td>7.0 ± 4.5</td>
<td>0.0 ± 3.0</td>
<td>0.321</td>
</tr>
<tr>
<td><strong>Gait Performance (gait speed)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Normal 10-m walk (m/s)</strong></td>
<td>1.2 ± 0.5</td>
<td>1.3 ± 0.2</td>
<td>0.0 ± 0.1</td>
<td>0.530</td>
</tr>
<tr>
<td><strong>Highest pain score during test</strong></td>
<td>5.5 ± 3.0</td>
<td>5.0 ± 5.2</td>
<td>0.0 ± 4.0</td>
<td>0.561</td>
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<tr>
<td><strong>Maximum 10-m walk (m/s)</strong></td>
<td>1.7 ± 0.6</td>
<td>1.8 ± 0.5</td>
<td>0.0 ± 0.1</td>
<td>0.975</td>
</tr>
<tr>
<td><strong>Highest pain score during test</strong></td>
<td>5 ± 5.5</td>
<td>5.5 ± 5.5</td>
<td>0 ± 3</td>
<td>0.572</td>
</tr>
</tbody>
</table>

Data presented as median ± interquartile range. The highest recorded pain score associated with any test is presented directly below the test result for that test, respectively. Within-group effect denotes the p-value associated with the change from baseline to follow-up. Between-group effects denotes the placebo-controlled p-value comparing Δ-values between groups.