Effects of Testosterone Replacement on Metabolic and Inflammatory Markers in Men With Opioid-Induced Androgen Deficiency

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Abstract and Introduction

Abstract

Objective Symptomatic androgen deficiency is common in patients taking opioid analgesics, and testosterone replacement in these men improves libido, quality of life and body composition. However, the effects of testosterone replacement on metabolic and inflammatory markers in this setting have not been evaluated. This is important as opiate use itself has been associated with metabolic abnormalities. The objective of this investigation was to determine the effects of testosterone administration on metabolic and inflammatory markers in adult men with opioid-induced androgen deficiency.

Methods Sixty-four nondiabetic men aged 18 to 64 years using opioid analgesics for chronic noncancer pain with total testosterone levels <12 nmol/l were randomized to 14 weeks of transdermal testosterone gel or placebo gel daily. Total testosterone levels were measured by liquid chromatography mass spectrometry, and free testosterone was calculated using the law-of-mass-action equation. Metabolic parameters, inflammatory markers and oral glucose tolerance test (OGTT) were evaluated at baseline and 14 weeks.

Results Baseline characteristics were similar between the two groups. Testosterone concentrations increased from 7·7 ± 3·0 to 27 ± 19 nmol/l in the testosterone group, but did not meaningfully change in placebo group. Mean changes in metabolic and inflammatory markers during intervention did not differ significantly between groups and were not related to changes in on-treatment serum testosterone concentrations. Glucose and insulin response to the 75 g OGTT also did not differ between groups.

Conclusion In this 14-week trial, testosterone administration in men with opioid-induced androgen deficiency was not associated with worsening of metabolic and inflammatory markers.

Introduction

The use of opioid analgesics for the management of noncancer chronic pain has grown substantially over the last two decades.[1,2] Although efficacious as analgesics, opiates potently suppress the hypothalamic–pituitary–gonadal axis in both sexes.[3] Indeed, studies have demonstrated high prevalence of androgen deficiency in men on opioid analgesics, with some patients experiencing profound androgen deficiency with serum testosterone levels in the castrate range.[4] As a result, these men exhibit greater prevalence of decreased libido, erectile dysfunction and decreased quality of life.[5] Additionally, a growing body of evidence from laboratory and population studies suggests that testosterone modulates pain sensitivity and tolerance[6] and that testosterone replacement may enhance the potency of opioids in men with opioid-induced androgen deficiency. In a recent randomized-controlled trial, 14 weeks of testosterone replacement in men with opioid-induced androgen deficiency improved pain sensitivity, libido, body composition and quality of life.[7]

Testosterone replacement in hypogonadal men has been associated with improvement in sexual function, body composition and quality of life;[8] however, some recent reports have raised concerns regarding cardiovascular safety of testosterone therapy.[9–12] Although these findings have not been confirmed in other studies,[13,14] the cardiometabolic effects of testosterone replacement in men with opioid-induced androgen deficiency have not been evaluated. This is important as opiate use itself has been associated with metabolic abnormalities as well as coronary artery disease.[15–18] Opioid receptors are present on pancreatic beta cells, and laboratory studies have shown that opiates inhibit glucose-stimulated insulin release from the islets.[16] Several observational studies have also reported associations between opioid use and dyslipidaemia, impaired insulin release and type-2 diabetes.[2,19,20] In addition to the metabolic abnormalities, case–control studies in diabetic men undergoing coronary angiography have shown that recreational opiate use is associated with a higher risk for coronary artery disease compared to men not using opiates and that opiate use is associated with premature coronary artery disease.[21]

We recently reported the primary analysis from our Testosterone and Pain Trial (The TAP trial) which showed that testosterone replacement in men with opioid-induced androgen deficiency for 14 weeks improved pain sensitivity and pain tolerance.[7] Given
The evidence that male chronic opioid users have higher prevalence of cardiometabolic abnormalities along with the potential concerns of cardiovascular risk with testosterone therapy, it was also important to determine whether testosterone replacement can be administered to men with opioid-induced androgen deficiency without inducing worsening of cardiometabolic parameters. Accordingly, we investigated the effects of testosterone administration on serum metabolic and inflammatory markers in our original cohort of men with opioid-induced androgen deficiency.

Methods

Study Design

The eligibility criteria and design of The Testosterone and Pain (TAP) Trial have been published[7] and are described here briefly. This single-centre, parallel group, placebo-controlled, double-blind randomized trial was approved by the institutional review boards of Boston University Medical Center (BUMC). All participants provided written informed consent. For this study, a subset of 64 nondiabetic participants from the original cohort were evaluated.

Eligibility

The participants were community-dwelling men, 18 to 64 years of age, who were using opioid analgesics for chronic noncancer pain and had a morning total testosterone less than 12 nmol/l as measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS). Participants were also required to have been taking at least 20 mg of hydrocodone (or morphine equivalent dose of another opioid) daily for at least 4 weeks. Participants who had androgen deficiency as a result of known hypothalamic, pituitary or testicular disease were excluded. Each participant further underwent an extensive review of medical history, review of current medications and a thorough physical examination by a study clinician to exclude any underlying organic cause of androgen deficiency. These comprehensive measures ensured that only those participants were enrolled in the trial who had androgen deficiency as a result of opioid use. In the TAP Trial, we also excluded men with any malignancy, severe lower urinary tract symptoms, prostate-specific antigen >4 μg/l, diabetes, congestive heart failure, myocardial infarction within 3 months, unstable angina, uncontrolled congestive heart failure, uncontrolled hypertension, peripheral vascular disease and oxygen-requiring chronic obstructive pulmonary disease. Men using testosterone, growth hormone or any anabolic therapy or drugs that affect gonadal function were excluded.

Randomization and Study Intervention

Eligible participants were randomized to either a placebo or testosterone gel using a concealed computer-generated randomization table. The participants and outcome assessors were blinded to the randomized assignment. The participants applied daily transdermal gel containing either placebo or 5 g of transdermal testosterone gel (Androgel 1%; Abbvie Pharmaceuticals, North Chicago, IL, USA) once daily for 3 months. Two weeks after randomization, the dose of testosterone gel was adjusted by an unblinded study physician if the serum total testosterone level was <17 nmol/l, in which case the dose was increased to 7·5 g daily. For any participant in the testosterone group requiring a dose increase, a placebo participant was chosen at random by the unblinded physician and was assigned a (simulated) dose increase, thus maintaining blinding of the study team to participants' treatment assignment.

Hormone Measurements

Serum total testosterone levels were measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS) with sensitivity of 0·07 nmol/l.[22] The cross-reactivity of DHEA, DHEAS, DHT, androstenedione and oestradiol in the testosterone assay was negligible at ten times the circulating concentrations of these hormones. The interassay coefficient of variation was 15·8% at 0·42 nmol/l, 10·6% at 0·81 nmol/l, 7·9% at 1·68 nmol/l, 7·7% at 8·4 nmol/l, 4·4% at 18·4 nmol/l and 3·3% at 35·2 nmol/l, respectively. As part of the Centers for Disease Control's (CDC) Testosterone Assay Harmonization Initiative, quality control samples provided by the CDC were run every 3 months; the bias in quality control samples in the 3·47–to–34·7 nmol/l (100 to 1000 ng/dl) range was <6·2%. Free testosterone was calculated using a published law-of-mass-action equation.[9] Sex hormone-binding globulin levels were measured using an immunofluorometric assay with sensitivity 2·5 nmol/l.[9]

Metabolic Parameters

Plasma glucose was quantified using Beckman Glucose Analyzer 2 (Beckman Instruments, Inc., Fullerton, CA, USA). Fasting insulin (Alpco Diagnostics, Salem, NH, USA) was measured using high-sensitivity sandwich ELISA. Insulin resistance was calculated using the homeostatic model assessment (HOMA) index.[23] All participants underwent 75-g oral glucose tolerance
test (OGTT) after a 12-h fast. The plasma glucose and insulin levels were analysed at baseline and at 60 and 120 min after glucose loading. Serum total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol levels were measured by enzymatic assays and standardized to the CDC using the Lipid Research Clinic protocol. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. The interassay coefficient of variation (CV) for glucose, insulin, HbA1c and lipids was 2%.

Inflammatory Markers and Adipokines

We measured leptin levels using ELISA with an interassay CV of 2·6% to 6·2% and an intra-assay CV of 2·6% to 4·6% (Millipore, Billerica, MA, USA). Total adiponectin was measured using an RIA kit with an interassay CV of 6·9–9·3% and an intra-assay CV of 1·8–6·2% (Millipore). High-sensitivity C-reactive protein (Alpc0 Diagnostics) was measured using a high-sensitivity sandwich ELISA with an intra-assay CV of 5·6%.

Statistical Analysis

Exploratory analyses were employed to assess distributional properties of outcomes variables. Summary statistics were generated according to randomization, and graphical depictions generated to assess empirical evidence in favour of differences and associations. Mean change in outcomes for each group was estimated using mean sample differences and associated 95% confidence intervals obtained from a nonparametric bootstrap using 10 000 resamplings with replacement. Statistical significance of differences was additionally assessed using Student's $t$-tests permitting unequal variances in groups. Association between change in testosterone levels and change in outcomes was assessed using scatterplots, with smoothing by generalized additive models (GAM). Multiple linear regression analysis was used to assess the magnitude and statistical significance of these relationships adjusting for age, BMI and baseline outcomes levels. The sample size was sufficient to provide 80% power to detect standardized differences (ratio of mean difference to standard deviation of difference) between testosterone and placebo of approximately 0·70.

Results

Baseline Characteristics

A description of the analytic sample is provided in . Mean (SD) age at baseline was 49 (8) years. The mean (SD) total and free testosterone concentrations were 7·7 (3) nmol/l and 153 (78) pmol/l and 8·2 (3·4) nmol/l and 149 (67) pmol/l in the testosterone and placebo groups, respectively. The mean (SD) morphine equivalent opioid dose at baseline was 114 (176) mg in the testosterone arm and 77 (141) mg in the placebo arm. Baseline age, BMI, metabolic and inflammatory markers were similar in the two arms. Only a handful of participants were on lipid medications (eight in the testosterone arm and 10 in the placebo arm); hence, the numbers were balanced between the two groups. Only one subject in the placebo arm discontinued his lipid medication during the course of the study. All other participants remained on their lipid medications at the same dose throughout the course of the trial.

Table 1. Baseline characteristics of the study participants by treatment group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Testosterone ($n = 36$)</th>
<th>Placebo ($n = 28$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>48 ± 9</td>
<td>50 ± 6</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>32 ± 7</td>
<td>34 ± 8·0</td>
</tr>
<tr>
<td>Opioid dose (morphine equivalent), mg</td>
<td>114 ± 176</td>
<td>77 ± 141</td>
</tr>
<tr>
<td>Time on opioids, months</td>
<td>54 ± 48</td>
<td>40 ± 54</td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total testosterone (nmol/l)</td>
<td>7·7 ± 3·0</td>
<td>8·2 ± 3·4</td>
</tr>
<tr>
<td>Free testosterone (pmol/l)</td>
<td>153 ± 78</td>
<td>149 ± 67</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>39 ± 31</td>
<td>38 ± 15</td>
</tr>
<tr>
<td>Metabolic parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4·6 ± 1·1</td>
<td>5·2 ± 1·2</td>
</tr>
<tr>
<td></td>
<td>LDL (mmol/l)</td>
<td>HDL (mmol/l)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>2·8 ± 1·0</td>
<td>1·0 ± 0·3</td>
</tr>
<tr>
<td></td>
<td>3·2 ± 0·9</td>
<td>1·1 ± 0·4</td>
</tr>
</tbody>
</table>

Inflammatory cytokines and adipokines

<table>
<thead>
<tr>
<th>Adiponectin (μg/ml)</th>
<th>4·9 ± 2·7</th>
<th>4·5 ± 1·6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin (μg/l)</td>
<td>16 ± 12</td>
<td>18 ± 17</td>
</tr>
<tr>
<td>C-reactive protein (nmol/l)</td>
<td>29 ± 33</td>
<td>27 ± 22</td>
</tr>
</tbody>
</table>

Data represent mean ± SD or N (%).

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycosylated haemoglobin; HOMA<sub>IR</sub>, homeostatic model assessment for insulin resistance; SHBG, sex hormone-binding globulin; OGTT, oral glucose tolerance test.

Hormone Levels

Mean (SD) serum total testosterone concentrations increased from 7·7 ± 3·0 to 27 ± 19 nmol/l in the testosterone group, but did not change significantly in the placebo group. Similarly, mean on-treatment free testosterone concentrations increased from 153 (78) to 656 (525) pmol/l in the testosterone arm. Of the 36 men randomized to the testosterone arm, 24 required a testosterone dose increase from 5 to 7·5 g daily to achieve target range serum testosterone levels between 17 and 34·7 nmol/l. As reported previously, men in the testosterone group experienced greater improvements in pain sensitivity, sexual desire and in some quality-of-life domains compared to men in the placebo arm.[7]

Effect of Testosterone on Metabolic Parameters

Change in metabolic parameters is depicted by treatment arm in Fig. 1. Changes in lipid profile, fasting glucose and insulin, HOMA<sub>IR</sub> and C-reactive protein from baseline to the end of treatment were similar in testosterone and placebo. Figure 2 depicts the change in glucose and insulin measurements 1 and 2 h after a 75 g oral glucose challenge performed at baseline and end of treatment. There was little effect of randomization on changes in circulating glucose or insulin following glucose load. Figure 2 also provides a depiction of mean within-participant change in glucose and insulin over the course of OGTT both at baseline and follow-up. Inspection of these plots indicates similar differences (end of intervention minus baseline) in the two randomized arms, supporting the finding of no meaningful difference between them in 14 week changes.
Figure 1.

Fourteen-week change in cardiometabolic parameters, by randomized assignment. Means and standard error bars are shown. Sample mean differences (testosterone minus placebo) are given in text, along with 95% confidence intervals obtained by nonparametric bootstrap and *P*-values by Student's *t*-test.
Figure 2.

At left, 14-week change in insulin and glucose at one and 2 h following administration of 75 g glucose solution. Means and standard error bars are shown. At right, baseline and 14-week glucose and insulin levels during OGTT; means and 95% confidence intervals are shown.

Relationships between change in serum testosterone concentrations and metabolic parameters restricted to individuals randomized to testosterone, as estimated in linear regression analyses, are depicted in . Changes in lipid profile, fasting glucose, fasting insulin, HOMAIR and glucose tolerance were not related to increases in testosterone concentrations. There was a statistically significant 0.04 decrease in mean HbA1c for every 100 ng/dl increase in total testosterone levels, (β = −0.04; 95% CI: −0.06 to −0.01); however, the effects were very small and perhaps not clinically meaningful.

Table 2. Linear model for change in metabolic parameter vs change in serum testosterone (N = 36)

<table>
<thead>
<tr>
<th>Change in outcomes</th>
<th>Δ Total testosterone, 100 ng/dl</th>
<th>Δ Free testosterone, 10 pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>β (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.45 (−2.1, 3.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.46 (−1.2, 0.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.1 (−1.2, 3.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.1 (−3.7, 8.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>HbA1c</td>
<td>−0.04 (−0.06, −0.01)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
β Coefficients represent change in metabolic parameters adjusting for age, BMI and baseline metabolic parameter as a function of every 100 ng/dl (3.5 nmol/l) change in total and every 10 pg/ml (35 pmol/l) change in free testosterone levels, respectively.

Mean overall change in BMI during the intervention phase was only 0.4 kg/m², and there was little difference between the arms [mean difference, testosterone minus placebo: −0.11 kg/m² (95% CI: −0.67, 0.44)].

Effect of Testosterone on Inflammatory Markers and Adipokines

Changes in inflammatory markers and adipokines are depicted by treatment arm in Fig. 1. There were no significant changes in leptin, C-reactive protein and adiponectin levels from baseline to the end of treatment when compared to placebo. These changes were not significantly related to increases in testosterone concentrations ().

Table 2. Linear model for change in metabolic parameter vs change in serum testosterone (N = 36)
β Coefficients represent change in metabolic parameters adjusting for age, BMI and baseline metabolic parameter as a function of every 100 ng/dl (3·5 nmol/l) change in total and every 10 pg/ml (35 pmol/l) change in free testosterone levels, respectively.

Adverse Events

There were no significant differences in cardiovascular-related adverse events between testosterone and placebo groups.[7] Elevation in PSA level to >4 μg/l occurred in two participants, one in each group. Erythrocytosis did not occur in either group.

Discussion

In this first randomized-controlled trial of men with opioid-induced androgen deficiency, testosterone replacement for 14 weeks was not associated with worsening of metabolic and inflammatory markers. This is reassuring as testosterone replacement in this patient population has shown efficacy in improving libido, quality of life, body composition and pain perception.[7] Data from previous observational and experimental studies have suggested that chronic use of opioids may potentially impact cardiovascular disease risk. Men on opiates have been shown to have higher HbA1c and higher incidence of type 2 diabetes compared to controls,[2,17,20] and administration of naltrexone, an opioid antagonist, improves these metabolic parameters.[24,25] Additionally, opioid use in men with diabetes has been associated with premature coronary artery disease.[15,21] Taken together with the potential concerns recently raised in some studies regarding cardiovascular side effects of testosterone therapy,[9] it was important to evaluate the effects of testosterone administration on cardiometabolic markers in this population.

The increasing use of opioids for both cancer and noncancer pain has raised concerns regarding the potential long-term safety of opioid exposure on cardiovascular risk. Both animal and human studies have demonstrated that opioid administration leads to hyperglycaemia by multiple mechanisms.[17,26–28] Indeed, opioid receptors have been identified on pancreatic islets and laboratory studies have shown that opiates inhibit glucose-stimulated insulin release from the beta cells.[26] Damage to the beta cells and desensitization of insulin receptor signalling by opiates have been posited as potential mechanisms.[26,28] In addition to their effects in causing metabolic dysregulation, recent studies in men have also implicated opioid use as a risk factor for coronary artery disease.[21,30,31] Whether this effect of opiates is a direct effect on the arterial wall or via their influence on metabolic and inflammatory mediators remains unclear and requires further investigation.

It is well known that exogenous opioids potently suppress the hypothalamic–pituitary–gonadal axis leading to profound androgen deficiency in men.[17] As a result, these men have sexual dysfunction, decreased quality of life and low bone mass.[4,32] We have previously shown that testosterone replacement in men with opioid-induced androgen deficiency is efficacious as it improved sexual desire, quality of life, body composition and pain sensitivity.[7] Furthermore, the frequency of adverse events, including cardiovascular-related adverse events, was not different between the testosterone and the placebo arms. The fact that we also did not observe worsening of cardiometabolic parameters in this study is further reassuring. However, this study was not powered to detect differences in CVD risk, and the duration of testosterone intervention was limited to 14 weeks. Thus, long-term studies are needed to confirm our findings.

Testosterone deficiency has been associated with decreased lean mass and increased fat mass.[8] We previously demonstrated improvement in lean mass and reduction in fat mass with testosterone replacement in men with opioid-induced androgen deficiency.[7] In other trials, testosterone replacement in hypogonadal men has also been reported to reduce whole body and visceral fat and some components of the metabolic syndrome.[33–35] Given that men on opioids are susceptible to developing cardiometabolic abnormalities, the beneficial effects of testosterone replacement on body composition in these men might contribute in attenuating CVD risk. In this study, the improvement in body composition with testosterone replacement possibly contributed in preventing the worsening of their cardiometabolic parameters. This is important as the majority of participants at study entry were obese.

Our study has notable strengths and some limitations. The trial had many features of exemplary trial design: concealed randomization, placebo-control, blinding, parallel group design and oversight by an independent DSMB. Testosterone dose was adjusted in a blinded manner to maintain testosterone levels in the target range. Total testosterone was measured using liquid chromatography–tandem mass spectrometry, widely considered the reference method with the highest sensitivity and specificity. The effects of testosterone administration on cardiometabolic parameters in men with opioid-induced androgen deficiency have not been previously studied in the setting of clinical trials. However, measurement of metabolic and inflammatory markers was not the primary outcome of the trial, and the trial was not powered to detect a difference in changes in these parameters. Most participants in each group at study entry were obese. However, controlling for baseline BMI did not alter the results. It is also true that even though this is the first trial of its kind, it is not sufficiently powered to preclude subtle effects (see 'Methods') and
requires replication. Finally, the 14-week intervention duration may not have been long enough to demonstrate a significant change in metabolic and inflammatory parameters.

In conclusion, testosterone administration for 14 weeks in men on chronic opioids with low testosterone levels was not associated with worsening of metabolic and inflammatory markers. The cardiovascular safety of testosterone therapy in men with opioid-induced androgen deficiency needs further investigation in long-term, adequately powered trials. The findings from this study do not discourage short-term use of testosterone in men with opioid-induced androgen deficiency.

References


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