Effects of Exogenous Testosterone Replacement Therapy on Time to ST Segment Depression and Myocardial Ischemia in Men With Chronic Stable Angina

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Abstract

Background: Testosterone levels in men decline with age and low testosterone levels or hypogonadism can cause multiple negative effects and symptoms. Studies have shown that exogenous testosterone replacement therapy at physiological levels has a number of beneficial and protective effects on mood, libido, strength, lean body mass, bone health and cardiovascular health. One of the many cardiovascular benefits of testosterone therapy is its action as a vasodilator and effect on angina and exercise induced myocardial ischemia. This purpose of this paper is to review the effects of exogenous testosterone therapy in eugonadal and hypogonadal men with chronic stable angina. All evidence will be evaluated using the GRADE method.

Method: An exhaustive search of available medical literature was conducted through Medline, EBM, and CINHAL databases.

Results: Two randomized controlled trials were reviewed along with the outcome of time to 1mm ST segment depression on treadmill exercise testing. Both studies showed statistically relevant improvements in time to 1mm ST segment depression as well as improvements in total exercise time. Impact on overall quality of life also showed significant improvement verses placebo. Both studies showed an insiginificant increase in Hematocrit and PSA levels but all within normal physiologic ranges. No other adverse effects were seen.

Conclusion: Exogenous testosterone replacement therapy improves overall exercise time and time to 1mm ST segment depression in male eugonadal and hypogonadal patients with angina and myocardial ischemia. Overall GRADE of evidence was considered to be moderate.

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A course paper presented to the College of Health Professions in partial fulfillment of the requirements of the degree of Master of Science

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INTRODUCTION

Background

Hypogonadism, also called androgen deficiency, is defined as a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone, a major androgenic hormone synthesized and secreted by the Leydig cells of the testes (Costanzo, 2006). There are two causes of hypogonadism with primary hypogonadism being usually age related and due to Leydig cell dysfunction where the testicles fail to produce adequate amounts of testosterone resulting in low serum testosterone levels and increased production of luteinizing hormone and follicle-stimulating hormone by the anterior pituitary gland and secondary hypogonadism which is a failure of the hypothalamic–pituitary unit to produce sufficient levels of LH/FSH resulting in low testosterone levels with low LH/FSH. LH and FSH are produced by the anterior pituitary and signal the testis to produce testosterone. (Calof, Singh, Lee, Kenny, Urban, Tenover & Bhasin, 2005)

Symptoms of hypogonadism include: incomplete or delayed sexual development, decreased sexual desire/libido, decreased spontaneous erections, breast discomfort, gynecomastia, loss of axillary and pubic hair, very small or shrinking testes (< 5cm), low or zero sperm count, height loss, low trauma fractures, low bone mineral density, hot flushes and sweats, decreased energy, motivation, initiative and self confidence, feeling sad, blue and depressed mood, poor concentration and memory, sleep disturbances, increased sleepiness, mild anemia, decreased bulk and strength, increased body fat and body mass index, decreased physical or work performance (Stanworth & Jones, 2008).
Physiologic levels of total testosterone according to reference laboratory levels are between 300ng/dL and 1000ng/dL. Bhasin, Cunningham, Hayes, Matsumoto, Snyder & Montori (2006) identify levels below 300ng/dL as the threshold for defining hypogonadism. The conventional testosterone unit used in the United States is measured in ng/dl. The international system of units (SI Units) used abroad are measured in nmol/L and normal testosterone levels are between 7.5-37 nmol/L. Recent studies have shown that 5.5% of a random sample of men age 30-79 had testosterone levels below 300ng/dL and at least one symptom of hypogonadism (Hall, Esche, Araujo, Travisim, Clarek & McKinlay, 2008). According to the Baltimore Longitudinal Study on Aging (2006), the prevalence of hypogonadism increases with age rising from less than 10% in men under 49 years old to 12% of men in their 50’s to 19% of men in their 60’s, 28% of men in their 70’s and 49% of men in their 80’s. There is a diurnal variation in serum testosterone levels with peak levels seen in the morning following sleep. Samples measuring testosterone levels should always be taken in the morning before 11am to allow for standardization. (Stanworth, Jones, 2008).

Other conditions causing hypogonadism include radiation therapy, use of medications with antiandrogen properties such as glucocorticoids, ketoconazole, opioids, and marijuana, end stage renal disease, maintenance dialysis, moderate to severe chronic obstructive pulmonary disease, HIV related weight loss, infertility, osteoporosis, dyslipidemia, hereditary hemochromatosis, Type II Diabetes Mellitus, metabolic syndrome, tobacco use and obesity (Wald, Meacham, Ross, & Niederberger, 2006).
Exogenous testosterone therapy with low dose physiological replacement to stabilize testosterone levels within the physiological range has become a focus as of late because of its postulated anti-inflammatory and vasodilatory properties as well as ability to decrease cardiac afterload and increase angina threshold in patients with chronic stable angina. Stable angina is a dull aching retrosternal chest pain aggravated by exercise and relieved by rest which has been linked to the narrowing of the arteries in the heart caused by coronary artery disease. (Choi, McLaughlin, 2007). Narrow arteries reduce the availability of blood to the heart, this reduced blood flow to the heart is also known as myocardial ischemia. Ischemia becomes a problem during exercise, when extra blood and oxygen are needed by the body. When patients with angina exercise they can experience severe pain in the vessels supplying the heart (Cornoldi, Caminiti, Marazzi, Vitale, Patrizi, Volterrani & Rosano, 2010). Myocardial Ischemia can be identified by horizontal ST segment depression on the electrocardiogram during exercise treadmill testing.

Other benefits of exogenous testosterone therapy include improvement in sexual function, libido, increased sense of well being, improved mood, increased energy, better sleep, antidepressant effect, increase in muscle mass, strength, and bone mineral density (Bhasin, 2006).

Side effects of physiological dose exogenous testosterone therapy can include polycythemia, increased hemoglobin and hematocrit, detection of subclinical prostate cancer, growth of metastatic prostate cancer, as well as increased acne and hair growth (Morales, 2001).

Purpose of the Study
The purpose of this paper is to perform a systematic review of the literature on the use of exogenous testosterone replacement therapy for improvements in cardiovascular outcomes in the adult male using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group. (Guyatt, Oxman, Vist, Kunz, Falck-Ytter, Alonso-Coello & Scheunemann, 2008)

METHODS

An extensive literature search was performed using EBM, Medline, and CINHAL. These databases were accessed through the Pacific University Library system. The following keywords were searched individually and in combination: hypogonadism, testosterone, testosterone replacement therapy, angina, and myocardial ischemia. The search was limited to human subjects, males, the English language, and articles published since 2000. The initial results included 52 articles. Men with low or low normal testosterone levels and treated with any testosterone formulation were included as were comorbidities of hypertension, diabetes, and hypercholesterolemia. Articles that did not investigate the cardiovascular effects of testosterone and time to ST segment depression on ECG treadmill testing were excluded. Review articles, and systematic reviews were excluded. Also excluded were any studies examining patients with secondary causes of hypogonadism purely as a result of surgery or radiation treatment due to prostate cancer. This resulted in two randomized controlled trial studies for the final systematic review.

RESULTS

A total of two randomized control studies were analyzed for this review. A total of 60 patients were recruited for both studies. The first study reviewed, (English, Steeds,
Jones, Diver & Channer, 2000) included 50 eugonadal adult males with average age of 62 and average testosterone level of 13.55 nmol/L. This study examined the clinical effects of long term low dose androgens in men with angina. The second study reviewed, (Malkin, Pugh, Morris, Kerry, Jones & Channer, 2003) included 10 hypogonadal adult males with an average age of 60.8 with an average testosterone level of 4.2 nmol/L. This study measured the effects of testosterone replacement on ischaemic threshold in hypogonadal men with angina. Patients in both studies were on antianginal medications during the trial but were not allowed to make medication changes 4 weeks prior to treadmill testing. They were also asked not to use glyceryl trinitrate six hours prior to treadmill testing. Patients were included in both studies if they had confirmed coronary artery disease (>70% stenosis of a major coronary artery at coronary angiography), previous proven myocardial infarction, symptoms of angina pectoris, male sex and age greater than 18. Malkin et al., (2003) included only patients with a clinical indication for testosterone therapy, eg. hypogonadal males. Both studies included patients with various co-morbid conditions of hypertension, diabetes mellitus, family history of myocardial ischemia, current smokers, and hypercholesteremia in both the testosterone and placebo groups at presentation. Exclusion criteria for both studies were prostate specific antigen concentration above normal range or any other contraindication to androgen therapy. They were also excluded if they had left main stem artery stenosis, a coronary or cerebrovascular event or taking other trial drugs within the preceding three months, severe hypertension (BP > 180/114mg/Hg), significant arrhythmias or ECG abnormalities precluding ST-segment analysis on a treadmill. Patients in both studies had their baseline total testosterone levels measured
between 8am and 9:30 am which are peak testosterone levels for the adult male as testosterone levels follow a circadian rhythm (Caminiti et al., 2009)

Interventions for English et al., (2000) included 5mg of transdermal testosterone via two 2.5mg patches placed nightly, Andropatch. Malkin et al., (2003) included 100mg intramuscular testosterone given by deep intramuscular injection to the buttock every two weeks. Comparison for both groups was placebo without active testosterone. Final outcome and primary endpoint for both groups was time to 1-mm ST-segment depression with treadmill testing. Quality of life was also measured in both studies. English et al., (2000) measured total testosterone as well as time to 1-mm ST-segment depression for both the active and placebo groups in at baseline, week 6, and week 14. Malkin et al., (2003) only measured outcomes at baseline and after 4 weeks for the active and placebo groups. English et al., (2000) revealed total testosterone levels of 13.55 nmol/L at baseline, 22.34 nmol/L at week 6 and 18.57 nmol/L at week 14. Mean time to 1mm ST-segment depression in the testosterone group was 309 seconds at baseline, 343 seconds at week 6 and significantly greater by week 14 (P < 0.05) at 361 seconds. Mean time to 1mm ST-segment depression increased in both the placebo and testosterone groups but the increase in the active testosterone group was greater than the placebo group. Results in Malkin et al., (2003) revealed total testosterone levels of 4.39 nmol/L at baseline and 9.19 nmol/L at 4 weeks. Mean time to 1mm ST-segment depression in the testosterone group was 318 seconds at baseline and 399 seconds at 4 weeks (P< 0.0001) Compared with placebo, the testosterone group had a greater increase in mean time to 1mm ST-segment depression by 81 seconds vs 7.2 seconds in the placebo group.
Limitations for both studies included the eugonadal population in English et al., (2000) vs. hypogonadal population in Malkin et al., (2003). Measurements were not performed during the same weeks of therapy and therapy length was also different between both studies as well as variation in types of testosterone, delivery and dosing. The sample size in Malkin et al., (2003) was small at only 10 patients.

English et al., (2000) concluded that low dose supplemental testosterone treatment in men with chronic stable angina reduced exercise induced myocardial ischemia and time to ST segment depression. Adverse effects showed no significant change in hemoglobin or PSA in either the active or placebo groups.

Malkin et al., (2003) concluded that testosterone replacement therapy in hypogonadal men delayed the time to ischemia as measured by ST segment depression. Adverse effects included a slight but insignificant rise in PSA levels in the active group. Both studies showed improvements in mood and quality of life.
DISCUSSION

These studies both demonstrate that exogenous testosterone supplementation in men with chronic stable angina improves time to myocardial ischemia over placebo. In both studies by Malkin et al. (2003) and English et al. (2000) improvements in time to ischemic threshold improved by 14% and 22% respectively compared with placebo. Numerous other studies have attributed this improvement in ischemia to the vasodilatory effects of testosterone (Webb, Elkington, Draidly, Keenan, Pennell & Collins, 2008) and (Pugh, Jones & Channer, 2003)

Testosterone was also associated with major improvements in mood and quality of life. The Malkin et al. (2003) study measured this by scores on the ADAM test which stands for androgen deficiency in the adult male. This test consists of 10 true/false questions regarding current health status. Lower scores indicate better quality of life. Malkin, 2003 showed major improvements in mood and hypogonadal symptoms with ADAM decreasing by 3 points vs 0 points with placebo. English et al., (2000) measured quality of life through the Raw SF-36 test. This test looks at 8 domains covering functional status, well-being and overall evaluation of health. Each domain is given a numerical score. A high numerical score, or positive change in score indicates an improvement in well being or overall quality of life. Patients showed an improvement in all 8 domains after 14 weeks of testosterone therapy. The greatest improvements were in pain perception and role limitation resulting from physical problems.

There were no serious side effects in either studies. Studies have shown than testosterone therapy can cause an overall increase in both PSA and hematocrit levels.
Although there was an increase in PSA levels in both studies, there was no evidence of increase in prostate symptoms such as difficulty or frequency of urination. Studies have shown that this is a benign and clinically insignificant elevation of PSA levels and could correlate with the advanced age of the study participants and the fact that PSA levels do increase with age (Legros et al., 2009). Despite the clinically insignificant elevations in PSA levels, Nieschlat (2005), recommends all patients being treated with testosterone therapy be screened with both PSA and digital rectal exam every 3 months while on testosterone therapy. The increase in hematocrit seen in both studies is due to testosterone’s effect on elevating red blood cell mass and stimulation of bone marrow hematopoiesis causing polycythemia. (Basaria, 2007). The average increase in hematocrit among men treated with testosterone therapy is 7%. (Tenover, 1999). The elevation in hematocrit in both studies was still under the cutoff of 54% which is the point that testosterone therapy should be discontinued. (Bhasin et al., 2006).

Both studies had limitations which were evaluated using the GRADE system. GRADE stands for Grading of Recommendations assessment, development and evaluation. This system is used to determine the quality of evidence presented in studies. There are four grade categories according to Guyatt, (2008).

1) High= further research is very unlikely to change our confidence in the estimate of effect.
2) Moderate= further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
3) Low= further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4) Very low= any estimate of effect is very uncertain. The studies were given an overall grade of moderate. GRADE was decreased from high to moderate due to the quality of the Malkin et al., (2003) study. He had a small sample size of only 10 participants, it was a single blind study and he only measured testosterone therapy for a short period of only four weeks compared to fourteen weeks in the English et al., (2000) study. The researchers were not blinded to the treatment and placebo groups. Malkin et al., (2003) states this was accounted for by use of the Marquette ECG data recording software that eliminated observer bias of the ECG results during treadmill testing.

Study limitations include different active treatment time lengths, different routes of testosterone administration and different baseline levels of testosterone between both studies. Previous studies have shown the effects of testosterone therapy on ischemic symptoms are greater in hypogonadal men versus eugonadal men. (Mathur et al., 2009). I believe these differences are only limitations and do not effect the overall GRADE of the studies.

Conclusion

The effects of testosterone therapy have shown promising evidence in the anti-ischemic and vasodilatory effects on myocardial tissue and overall cardiovascular health (Caminiti et al., 2009). Both studies showed improvements in time to ST segment depression with exercise and overall increased exercise time as well as quality of life improvement with no significant side effects identified in either study. Based on these studies I feel that testosterone therapy would improve overall health and well being in the adult male population and exogenous testosterone therapy administered in
the physiologic range would be beneficial for older adult males with hypogonadal symptoms and low serum total testosterone levels. Additional randomized controlled studies with a larger study population are needed to provide higher quality evidence of the effects of testosterone therapy in hypogonadal males.
REFERENCES


Rosano, G.M.C., Sheiban, I., Massaro, R., Pagnotta, P., Marazzi, G., Vitale, C., … Fini, M. (2007). Low testosterone levels are associated with coronary artery disease
in male patients with angina. *International Journal of Impotence Research, 19*, 176-182.


APPENDICES
## APPENDIX A

### Table 1: GRADE Table/Strength of Evidence

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Findings</th>
<th>Decrease GRADE</th>
<th>Increase GRADE</th>
<th>Grade of Evidence for Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous testosterone therapy vs. Placebo in anginal patients.</td>
<td>Time to Angina threshold/ 1 mm ST-segment depression on treadmill testing</td>
<td>2 RCT (60)</td>
<td>Increase in time to 1mm ST segment depression</td>
<td>Study Quality</td>
<td>Consistency</td>
<td>Directness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Overall GRADE of Evidence: Moderate**
APPENDIX B

Table 1: Malkin et al., (2003) Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>pValue</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>60.8 +/-4.6</td>
<td></td>
<td></td>
<td>60.8 +/- 4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to 1mm ST depression (seconds)</td>
<td>345</td>
<td>352</td>
<td>0.492</td>
<td>318</td>
<td>399</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prostate Specific Antigen (ug/l)</td>
<td>1.01 +/- 1.3</td>
<td></td>
<td></td>
<td>1.01 +/- 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/l)</td>
<td>148</td>
<td>149</td>
<td>0.81</td>
<td>147</td>
<td>150</td>
<td>0.02</td>
</tr>
<tr>
<td>Total Testosterone (nmol/l)</td>
<td>5.55</td>
<td>5.5</td>
<td>0.94</td>
<td>4.39</td>
<td>9.19</td>
<td>0.02</td>
</tr>
<tr>
<td>ADAM Score</td>
<td>6</td>
<td>6</td>
<td>0.5</td>
<td>7</td>
<td>4</td>
<td>0.007</td>
</tr>
</tbody>
</table>

ADAM-androgen deficiency in the adult male screen score. (Negative change in score = improvement in health perception.)
APPENDIX C

Table 2: English et al., (2000) Low Dose Transdermal Testosterone Therapy Improves Angina Threshold in Men with Chronic Stable Angina: A Randomized, Double-Blind, Placebo- Controlled Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Baseline</th>
<th>6 weeks</th>
<th>14 weeks</th>
<th>Placebo</th>
<th>Baseline</th>
<th>6 weeks</th>
<th>14 weeks</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 +/- 2</td>
<td>62 +/- 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to 1mm ST depression (seconds)</td>
<td>267 +/- 25</td>
<td>284 +/- 23</td>
<td>292 +/- 24</td>
<td>309 +/- 27</td>
<td>343 +/- 26</td>
<td>361 +/- 22</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Testosterone (nmol/l)</td>
<td>12.38 +/- 0.72</td>
<td>11.35 +/- 0.76</td>
<td>12.23 +/- 0.89</td>
<td>13.55 +/- 0.78</td>
<td>22.34 +/- 1.19</td>
<td>18.57 +/- 1.6</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw SF-36 Score</td>
<td></td>
<td>50.6 +/- 4</td>
<td>53.8 +/- 5.5</td>
<td>53.1 +/- 5.2</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SF-36 Short Form quality of life questionnaire (positive change in score = improvement in health perception.)