

PRO

High Serum Testosterone Is Associated With Reduced Risk of Cardiovascular Events in Elderly Men

The MrOS (Osteoporotic Fractures in Men) Study in Sweden

Claes Ohlsson, MD, PhD,* Elizabeth Barrett-Connor, MD,‡ Shalender Bhasin, MD, PhD,§ Eric Orwoll, MD, PhD,¶ Fernand Labrie, MD, PhD,¶|| Magnus K. Karlsson, MD, PhD,# Östen Ljunggren, MD, PhD,** Liesbeth Vandenput, PHARM.D, PhD,* Dan Mellström, MD, PhD,* Åsa Tivesten, MD, PhD†

Gothenburg, Malmö, and Uppsala, Sweden; La Jolla, California; Boston, Massachusetts; Portland, Oregon; and Québec, Canada

Objectives We tested the hypothesis that serum total testosterone and sex hormone-binding globulin (SHBG) levels predict cardiovascular (CV) events in community-dwelling elderly men.

Background Low serum testosterone is associated with increased adiposity, an adverse metabolic risk profile, and atherosclerosis. However, few prospective studies have demonstrated a protective link between endogenous testosterone and CV events. Polymorphisms in the SHBG gene are associated with risk of type 2 diabetes, but few studies have addressed SHBG as a predictor of CV events.

Methods We used gas chromatography/mass spectrometry to analyze baseline levels of testosterone in the prospective population-based MrOS (Osteoporotic Fractures in Men) Sweden study (2,416 men, age 69 to 81 years). SHBG was measured by immunoradiometric assay. CV clinical outcomes were obtained from central Swedish registers.

Results During a median 5-year follow-up, 485 CV events occurred. Both total testosterone and SHBG levels were inversely associated with the risk of CV events (trend over quartiles: $p = 0.009$ and $p = 0.012$, respectively). Men in the highest quartile of testosterone (≥ 550 ng/dl) had a lower risk of CV events compared with men in the 3 lower quartiles (hazard ratio: 0.70, 95% confidence interval: 0.56 to 0.88). This association remained after adjustment for traditional CV risk factors and was not materially changed in analyses excluding men with known CV disease at baseline (hazard ratio: 0.71, 95% confidence interval: 0.53 to 0.95). In models that included both testosterone and SHBG, testosterone but not SHBG predicted CV risk.

Conclusions High serum testosterone predicted a reduced 5-year risk of CV events in elderly men.

Acute Anti-Ischemic Effect of Testosterone in Men With Coronary Artery Disease

Giuseppe M.C. Rosano, MD, PhD; Filippo Leonardo, MD; Paolo Pagnotta, MD; Francesco Pelliccia, MD; Gaia Panina, MD; Elena Cerquetani, MD; Paola Lilla della Monica, MD; Bruno Bonfigli, MD; Massimo Volpe, MD; Sergio L. Chierchia, MD

Background—The role of testosterone on the development of coronary artery disease in men is controversial. The evidence that men have a greater incidence of coronary artery disease than women of a similar age suggests a possible causal role of testosterone. Conversely, recent studies have shown that the hormone improves endothelium-dependent relaxation of coronary arteries in men. Accordingly, the aim of the present study was to evaluate the effect of acute administration of testosterone on exercise-induced myocardial ischemia in men.

Methods and Results—After withdrawal of antianginal therapy, 14 men (mean age, 58.64 years) with coronary artery disease underwent 3 exercise tests according to the modified Bruce protocol on 3 different days (baseline and either testosterone or placebo given in a random order). The exercise tests were performed 30 minutes after administration of testosterone (2.5 mg IV in 5 minutes) or placebo. All patients showed at least 1-mm ST-segment depression during the baseline exercise test and after placebo, whereas only 10 patients had a positive exercise test after testosterone. Chest pain during exercise was reported by 12 patients during baseline and placebo exercise tests and by 8 patients after testosterone. Compared with placebo, testosterone increased time to 1-mm ST-segment depression (579.6204 versus 471.6210 seconds; $P,0.01$) and total exercise time (631.6180 versus 541.6204 seconds; $P,0.01$). Testosterone significantly increased heart rate at the onset of 1-mm ST-segment depression (135.612 versus 123.614 bpm; $P,0.01$) and at peak exercise (140.612 versus 132.612 bpm; $P,0.01$) and the rate-pressure product at the onset of 1-mm ST-segment depression (24 213.63750 versus 21 619.63542 mm Hg3bpm; $P,0.05$) and at peak exercise (26 746.63109 versus 22 527.65443 mm Hg3bpm; $P,0.05$).

Conclusions—Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary artery disease. This effect may be related to a direct coronary-relaxing effect. (*Circulation*. 1999;99:1666-1670.)

Testosterone as a protective factor against atherosclerosis – immunomodulation and influence upon plaque development and stability

C J Malkin, P J Pugh, R D Jones¹, T H Jones^{1,2} and K S Channer

Department of Cardiology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK

¹Academic Unit of Endocrinology, Division of Genomic Medicine, University of Sheffield Medical School S10 2RX, UK

²Centre for Diabetes and Endocrinology, Barnsley District General Hospital, Barnsley

(Requests for offprints should be addressed to K S Channer, M131, Cardiology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK; Email:

Kevin.Channer@sth.nhs.uk)

Abstract

Inflammation plays a central pathogenic role in the initiation and progression of coronary atheroma and its clinical consequences. Cytokines are the mediators of cellular inflammation and promote local inflammation in the arterial wall, which may lead to vascular smooth muscle apoptosis, degradation of the fibrin cap and plaque rupture. Platelet adhesion and thrombus formation then occur, resulting clinically in unstable angina or myocardial infarction. Recent studies have suggested that cytokines are pathogenic, contributing directly to the disease process. ‘Anti-cytokine’ therapy may, therefore, be of benefit in preventing or slowing the progression of cardiovascular disease.

Both oestrogens and testosterone have been shown to have immune-modulating effects;

testosterone in particular appears to suppress activation of pro-inflammatory cytokines. Men with low testosterone levels are at increased risk of coronary artery disease. An anti-inflammatory effect of normal physiological levels of sex hormones may, therefore, be important in atheroprotection.

In this article, we discuss some of the mechanisms involved in atherosclerotic coronary artery disease and the putative link between testosterone deficiency and atheroma formation. We present the hypothesis that the immune-modulating properties of testosterone may be important in inhibiting atheroma formation and progression to acute coronary syndrome.

SUBCUTANEOUS TESTOSTERONE IMPLANT THERAPY IMPROVES ENDOTHELIUM-DEPENDENT AND INDEPENDENT VASODILATION IN POSTMENOPAUSAL WOMEN ALREADY RECEIVING OESTROGEN

Worboys S, Kotso-wulos D, Teede H

The Jean Hailes Foundation and Monash University Dept of Medicine, Monash Medical Centre, Clayton, Vic, Australia

The gender difference in cardiovascular disease has been partly attributed to higher androgenic hormone levels. Although testosterone in women may not affect lipids, it remains unknown whether it negates favourable oestrogenic effects on endothelial function. We have investigated the effects of testosterone implant therapy on endothelial function [flow mediated vasodilation (FMD)] in women using hormone replacement therapy (HRT). B-mode ultrasound measurements of resting brachial artery diameter, following reactive hyperaemia (endothelium-dependent) and following glyceryl trinitrate (GTN) (endothelium-independent) dilatation were recorded in 33 postmenopausal women stabilised on HRT (> 6 months), at baseline and 6 weeks after a testosterone implant (50mg), with 15 postmenopausal non-users of HRT serving as controls. In the brachial artery baseline resting diameter was similar (0.40 ± 0.01 vs 0.41 ± 0.01 cm, $p = 0.5$). In the treated group, testosterone levels increased (0.99 ± 0.08 to 4.99 ± 0.3 nmol/L, $p < 0.001$), associated with a mean 42% increase in FMD (6.4 ± 0.7 to 9.1 ± 1.1 , $p = 0.03$). The control group did not change (8.1 ± 1.4 to 5.6 ± 1.0 , $p = 0.4$). There was significantly greater improvement in FMD in the testosterone-treated compared to control group ($p = 0.04$). GTN induced vasodilatation increased with testosterone treatment (14.9 ± 0.9 to 17.8 ± 21.2 , $p = 0.03$).

Conclusion: Exogenous testosterone implants improve both endothelial dependent (flow mediated) and endothelium-independent (GTN mediated) brachial artery vasodilation in postmenopausal women, using long-term oestrogen therapy. The mechanisms underlying these potentially beneficial cardiovascular effects require further investigation.

Review

The effects of testosterone on risk factors for, and the mediators of, the atherosclerotic process

T. Hugh Jones^{a,b}, Farid Saad^{c,d,*}

a Academic Unit of Diabetes, Endocrinology & Metabolism, University of Sheffield, Sheffield, UK

b Centre for Diabetes & Endocrinology, Barnsley Hospital NHS Foundation Trust, Barnsley, UK

c Scientific Affairs Men's Healthcare, Bayer Schering Pharma, Berlin, Germany

d Gulf Medical University School of Medicine, Ajman, United Arab Emirates

abstract

It is becoming increasingly evident that the low serum levels of testosterone experienced by aging men are associated with increased all-cause mortality from CHD and other vascular disorders. Achieving a normal physiological testosterone concentration through the administration of testosterone therapy has been shown to provide beneficial effects on the pathophysiological markers and clinical symptoms of CHD. Many of the factors involved in the atherosclerotic process are interlinked with other, increasingly prevalent pathological conditions such as obesity, the metabolic syndrome (MetS), type 2 diabetes and erectile dysfunction, suggesting that testosterone therapy has potentially wide-ranging health benefits. As the number and scope of testosterone substitution and androgen deprivation studies increases and evidence accumulates, it is timely to assess available data and this review summarizes the current understanding of the effects of testosterone on cardiovascular risk factors with particular emphasis on the relevance of testosterone treatment.

© 2009 Elsevier Ireland Ltd. All rights reserved.

Testosterone and the aging male: To treat or not to treat?

Jerald Bain

a Department of Medicine, University of Toronto, Canada

b Division of Endocrinology and Metabolism, Mount Sinai Hospital, Toronto, Canada

c Department of Obstetrics and Gynecology, University of Toronto, Canada

abstract

It is well-established that total testosterone (TT) in men decreases with age and that bioavailable testosterone (bio-T) falls to an even greater extent. The clinical relevance of declining androgens in the aging male and use of testosterone replacement therapy (TRT) in this situation is controversial. Most studies have been short term and there are no large randomized placebo-controlled trials. Testosterone has many physiological actions in: muscles, bones, hematopoietic system, brain, reproductive and sexual organs, adipose tissue. Within these areas it stimulates: muscle growth and maintenance, bone development while inhibiting bone resorption, the production of red blood cells to increase hemoglobin, libido, enhanced mood and cognition, erectile function and lipolysis. Anabolic deficits in aging men can induce: frailty, sarcopenia, poor muscle quality, muscle weakness, hypertrophy of adipose tissue and impaired neurotransmission. The aging male with reduced testosterone availability may present with a wide variety of symptoms which in addition to frailty and weakness include: fatigue, decreased energy, decreased motivation, cognitive impairment, decreased self-confidence, depression,

irritability, osteoporotic pain and the lethargy of anemia. In addition, testosterone deficiency is also associated with type-2 diabetes, the metabolic syndrome, coronary artery disease, stroke and transient ischemic attacks, and cardiovascular disease in general. Furthermore, there are early studies to suggest that TRT in men with low testosterone levels may improve metabolic status by: lowering blood sugar and HbA1C in men with type-2 diabetes, reducing abdominal girth, ameliorating features of the metabolic syndrome, all of which may be protective of the cardiovascular system. The major safety issue is prostate cancer but there is no evidence that supports the idea that testosterone causes the development of a de novo cancer. So on balance in a man with symptoms of hygonadism and low or lowish levels of testosterone with no evidence of prostate cancer such as a normal PSA a therapeutic (4–6 months) trial of TRT is justified. Treatment and monitoring of this duration will determine whether the patient is responsive.

© 2010 Elsevier

Original Article

Testosterone Supplementation in Heart Failure: A Meta-Analysis

Mustafa Toma¹, Finlay A. McAlister², Erin E. Coglianese³, Venketesan Vidi⁴, Samip Vasaiwala⁴, Jeffrey A. Bakal², Paul W. Armstrong² and Justin A. Ezekowitz^{2*}

Author Affiliations

* Corresponding author; email: jae2@ualberta.ca

Abstract

Background—Low testosterone is an independent predictor of reduced exercise capacity and poor clinical outcomes in patients with heart failure (HF). We sought to determine if testosterone therapy improves exercise capacity in patients with stable chronic HF.

Methods and Results—We searched MEDLINE, EMBASE, Web of Science and Cochrane CENTRAL (1980 to 2010). Eligible studies included randomized trials reporting the effects of testosterone on exercise capacity in HF patients. Reviewers determined the methodological quality of studies and collected descriptive, quality, and outcome data. Four trials (n=198 patients, 84% male, mean age 67 years) were identified reporting the 6-minute walk test (6MWT, 2 RCT), incremental shuttle walk test (ISWT, 2 RCT) or peak VO₂ (2 RCT) to assess exercise capacity after up to 52 weeks of treatment. Testosterone therapy was associated with a significant improvement in exercise capacity compared to placebo. The mean increase in the 6MWT, ISWT, and peak VO₂ between the testosterone and placebo groups were 54.0 m (95% CI 43.0-65.0m), 46.7m (95% CI 12.6-80.9m), and 2.70 ml/kg/min (95% CI 2.68-2.72 ml/kg/min), respectively. Testosterone therapy was associated with a significant increase in exercise capacity as measured by units of pooled standard deviations (net effect 0.52 SD, 95% CI 0.10-0.94). No significant adverse cardiovascular events were noted.

Conclusions—Given the unmet clinical needs, testosterone appears to be a promising therapy to improve functional capacity in HF patients. Adequately powered RCT are required to assess the benefits of testosterone in this high-risk population assessing quality of life, clinical events and safety.

Heart. 2010 Nov;96(22):1821-5. Epub 2010 Oct 19.

Low serum testosterone and increased mortality in men with coronary heart disease.

Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS.

Source

Department of Cardiology, Royal Hallamshire Hospital, Sheffield, UK

Abstract

BACKGROUND:

To examine the effect of serum testosterone levels on survival in a consecutive series of men with confirmed coronary disease and calculate the prevalence of testosterone deficiency.

DESIGN:

Longitudinal follow-up study.

SETTING:

Tertiary referral cardiothoracic centre. Patients 930 consecutive men with coronary disease referred for diagnostic angiography recruited between June 2000 and June 2002 and followed up for a mean of 6.9 ± 2.1 years.

OUTCOME:

All-cause mortality and vascular mortality. Prevalence of testosterone deficiency.

RESULTS:

The overall prevalence of biochemical testosterone deficiency in the coronary disease cohort using bio-available testosterone (bio-T) < 2.6 nmol/l was 20.9%, using total testosterone < 8.1 nmol/l was 16.9% and using either was 24%. Excess mortality was noted in the androgen-deficient group compared with normal (41 (21%) vs 88 (12%), $p=0.002$). The only parameters found to influence time to all-cause and vascular mortality (HR \pm 95% CI) in multivariate analyses were the presence of left ventricular dysfunction (3.85; 1.72 to 8.33), aspirin therapy (0.63; 0.38 to 1.0), β -blocker therapy (0.45; 0.31 to 0.67) and low serum bio-T (2.27; 1.45 to 3.6).

CONCLUSIONS:

In patients with coronary disease testosterone deficiency is common and impacts significantly negatively on survival. Prospective trials of testosterone replacement are needed to assess the effect of treatment on survival.

Curr Opin Endocrinol Diabetes Obes. 2010 Jun;17(3):262-8.

Testosterone and heart failure.

Malkin CJ, [Channer KS](#), [Jones TH](#).

Source

Department of Cardiology Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.

Abstract

PURPOSE OF REVIEW:

Chronic heart failure (CHF) is a common condition with significant morbidity despite optimal medical therapy. Standard therapy involves inhibiting the maladaptive changes of metabolism and neuro-hormones that characterize the syndrome of CHF. Anabolic deficiency is a major component of the CHF syndrome and testosterone replacement therapy has been subject to recent trials.

RECENT FINDINGS:

The recent literature shows that physiological testosterone replacement therapy leads to modest improvements in voluntary muscle strength, lean muscle mass, endurance and positive effects on neuro-muscular and baro-receptor reflexes. Long-term efficacy and safety remain unstudied at present.

SUMMARY:

Testosterone replacement therapy appears to improve metabolism and endurance in patients with CHF; further trials will be necessary before widespread use. Physicians who regularly treat patients with CHF may consider testosterone therapy but it is likely that they will require the advice and support from endocrine specialists.

PMID: 20404724 [PubMed - indexed for MEDLINE]

Low Serum Testosterone and Mortality in Older Men

Gail A. Laughlin, Elizabeth Barrett-Connor, and Jaclyn Bergstrom

Department of Family and Preventive Medicine, School of Medicine, University of California, San Diego, La Jolla, California 92093

Context: Declining testosterone levels in elderly men are thought to underlie many of the symptoms and diseases of aging; however, studies demonstrating associations of low testosterone with clinical outcomes are few.

Objective: The objective of the study was to examine the association of endogenous testosterone levels with mortality in older community-dwelling men.

Design, Setting, and Participants: This was a prospective, population-based study of 794 men, aged 50–91 (median 73.6) yr who had serum testosterone measurements at

baseline (1984–1987) and were followed for mortality through July 2004.

Main Outcome Measure: All-cause mortality by serum testosterone level was measured.

Results: During an average 11.8-yr follow-up, 538 deaths occurred. Men whose total testosterone levels were in the lowest quartile (< 241 ng/dl) were 40% [hazards ratio (HR) 1.40; 95% confidence interval (CI) 1.14–1.71] more likely to die than those with higher levels, independent of age, adiposity, and lifestyle. Additional adjustment for health status markers, lipids, lipoproteins, blood pressure, glycemia, adipocytokines, and estradiol levels had minimal effect on results. The low testosterone-mortality association was also independent of the metabolic syndrome, diabetes, and prevalent cardiovascular disease but was attenuated by adjustment for IL-6 and C-reactive protein. In cause-specific analyses, low testosterone predicted increased risk of cardiovascular (HR 1.38; 95% CI 1.02–1.85) and respiratory disease (HR 2.29; 95% CI 1.25–4.20) mortality but was not significantly related to cancer death (HR 1.34; 95% CI 0.89–2.00). Results were similar for bioavailable testosterone.

Conclusions: Testosterone insufficiency in older men is associated with increased risk of death over the following 20 yr, independent of multiple risk factors and several preexisting health conditions.

(J Clin Endocrinol Metab 93: 68–75, 2008)

Clin Sci (Lond). 2006 Oct;111(4):265-74.

Effect of testosterone on ex vivo vascular reactivity in man.

Malkin CJ, Jones RD, Jones TH, Channer KS.

Source

Department of Cardiology Research, Royal Hallamshire Hospital Sheffield, Sheffield S10 2JF, UK.

Abstract

Testosterone is reported to have an acute vasodilating action in vitro, an effect that may impart a favourable haemodynamic response in patients with chronic heart failure. However, the effect of chronic testosterone exposure on general vascular reactivity is poorly described. In the present study, fresh subcutaneous resistance arteries were obtained from patients with heart failure (n=10), healthy controls (n=9) and men with androgen-deficiency (n=17). All arteries were studied using a wire myograph to examine the effect of cumulative additions of testosterone (1 nmol/l-100 micromol/l) compared with vehicle control following maximal pre-constriction with KCl (1-100 micromol/l). The vascular reactivity of arteries from androgen-deficient patients was examined further by recording tension concentration curves to cumulative additions of noradrenaline (1

nmol/l-100 micromol/l) and U46619 (1-300 nmol/l), followed by relaxation concentration curves to additions of ACh (acetylcholine; 10 nmol/l-30 micromol/l) and SNP (sodium nitroprusside; 10 nmol-30 micromol/l) respectively. In all cases, statistical analysis was performed by ANOVA. Patients with proven androgen-deficiency were treated according to clinical recommendations for a minimum of 3 months and further arteries (n=19) were taken for experimentation using the same protocol. In all groups, testosterone was confirmed to be an acute concentration-dependent vasodilator at concentrations ≥ 1 micromol/l ($P=0.0001$). The dilating effect of testosterone was augmented in patients with androgen-deficiency prior to treatment, and this effect was abrogated following appropriate testosterone replacement. Testosterone therapy significantly reduced the normal vascular dilating response to ACh and SNP ($P<0.01$) and significantly increased the contractile response to noradrenaline ($P<0.01$), but not U46619. Testosterone is an acute dose-dependent vasodilator of resistance arteries. Physiological testosterone replacement attenuates general vascular reactivity in androgen-deficient subjects. The numerous perceived benefits of testosterone replacement may be offset by a decline in vascular reactivity and, therefore, further studies and careful monitoring of patients is recommended.

Eur Heart J. 2006 Jan;27(1):57-64. Epub 2005 Aug 10.

Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial.

Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH, Channer KS.

Source

Department of Cardiology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK.

Abstract

AIMS:

Chronic heart failure is associated with maladaptive and prolonged neurohormonal and pro-inflammatory cytokine activation causing a metabolic shift favouring catabolism, vasodilator incapacity, and loss of skeletal muscle bulk and function. In men, androgens are important determinants of anabolic function and physical strength and also possess anti-inflammatory and vasodilatory properties.

METHODS AND RESULTS:

We conducted a randomized, double-blind, placebo-controlled parallel trial of testosterone replacement therapy (5 mg Androderm) at physiological doses in 76 men (mean \pm -SD, age 64 \pm -9.9) with heart failure (ejection

fraction 32.5+/-11%) over a maximum follow-up period of 12 months. The primary endpoint was functional capacity as assessed by the incremental shuttle walk test (ISWT). At baseline, 18 (24%) had serum testosterone below the normal range and bioavailable testosterone correlated with distance walked on the initial ISWT ($r=0.3$, $P=0.01$). Exercise capacity significantly improved with testosterone therapy compared with placebo over the full study period (mean change +25+/-15 m) corresponding to a 15+/-11% improvement from baseline ($P=0.006$ ANOVA). Symptoms improved by at least one functional class on testosterone in 13 (35%) vs. 3 (8%) on placebo ($P=0.01$). No significant changes were found in handgrip strength, skeletal muscle bulk by cross-sectional computed tomography, or in tumour necrosis factor levels. Testosterone therapy was safe with no excess of adverse events although the patch preparation was not well tolerated by the study patients.

CONCLUSION:

Testosterone replacement therapy improves functional capacity and symptoms in men with moderately severe heart failure.

[Clin Endocrinol \(Oxf\)](#). 2005 Sep;63(3):239-50.

Androgens, insulin resistance and vascular disease in men.

Kapoor D, Malkin CJ, Channer KS, Jones TH.

Source

Centre for Diabetes and Endocrinology, Barnsley NHS Foundation Trust Hospital, Barnsley, UK.

Abstract

Type 2 diabetes mellitus is increasing globally and is an established risk factor for the development of atherosclerotic vascular disease. Insulin resistance is the hallmark feature of type 2 diabetes and is also an important component of the metabolic syndrome. There is evidence to suggest that testosterone is an important regulator of insulin sensitivity in men. Observational studies have shown that testosterone levels are low in men with diabetes, visceral obesity (which is strongly associated with insulin resistance), coronary artery disease and metabolic syndrome. Short-term interventional studies have also demonstrated that testosterone replacement therapy produces an improvement in insulin sensitivity in men. Thus hypotestosteronaemia may have a role in the pathogenesis of insulin-resistant states and androgen replacement therapy could be a potential treatment that could be offered for improvements in glycaemic control and reduction in cardiovascular risk, particularly in diabetic men.

Heart. 2004 Aug;90(8):871-6.

Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life.

Malkin CJ, Pugh PJ, Morris PD, Kerry KE, Jones RD, Jones TH, Channer KS.
Source

Department of Cardiology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK.

Abstract

BACKGROUND:

Low serum testosterone is associated with several cardiovascular risk factors including dyslipidaemia, adverse clotting profiles, obesity, and insulin resistance. Testosterone has been reported to improve symptoms of angina and delay time to ischaemic threshold in unselected men with coronary disease.

OBJECTIVE:

This randomised single blind placebo controlled crossover study compared testosterone replacement therapy (Sustanon 100) with placebo in 10 men with ischaemic heart disease and hypogonadism.

RESULTS:

Baseline total testosterone and bioavailable testosterone were respectively 4.2 (0.5) nmol/l and 1.7 (0.4) nmol/l. After a month of testosterone, delta value analysis between testosterone and placebo phase showed that mean (SD) trough testosterone concentrations increased significantly by 4.8 (6.6) nmol/l (total testosterone) ($p = 0.05$) and 3.8 (4.5) nmol/l (bioavailable testosterone) ($p = 0.025$), time to 1 mm ST segment depression assessed by Bruce protocol exercise treadmill testing increased by 74 (54) seconds ($p = 0.002$), and mood scores assessed with validated questionnaires all improved. Compared with placebo, testosterone therapy was also associated with a significant reduction of total cholesterol and serum tumour necrosis factor alpha with delta values of -0.41 (0.54) mmol/l ($p = 0.04$) and -1.8 (2.4) pg/ml ($p = 0.05$) respectively.

CONCLUSION:

Testosterone replacement therapy in hypogonadal men delays time to ischaemia, improves mood, and is associated with potentially beneficial reductions of total cholesterol and serum tumour necrosis factor alpha.

J Clin Endocrinol Metab. 2004 Jul;89(7):3313-8.

The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men.

Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH.

Source

Cardiology Department, Royal Hallamshire Hospital, Sheffield, United Kingdom S10 2JF.
chris.malkin@sth.nhs.uk

Abstract

Testosterone has immune-modulating properties, and current in vitro evidence suggests that testosterone may suppress the expression of the proinflammatory cytokines TNFalpha, IL-1beta, and IL-6 and potentiate the expression of the antiinflammatory cytokine IL-10. We report a randomized, single-blind, placebo-controlled, crossover study of testosterone replacement (Sustanon 100) vs. placebo in 27 men (age, 62 +/- 9 yr) with symptomatic androgen deficiency (total testosterone, 4.4 +/- 1.2 nmol/liter; bioavailable testosterone, 2.4 +/- 1.1 nmol/liter). Compared with placebo, testosterone induced reductions in TNFalpha (-3.1 +/- 8.3 vs. 1.3 +/- 5.2 pg/ml; P = 0.01) and IL-1beta (-0.14 +/- 0.32 vs. 0.18 +/- 0.55 pg/ml; P = 0.08) and an increase in IL-10 (0.33 +/- 1.8 vs. -1.1 +/- 3.0 pg/ml; P = 0.01); the reductions of TNFalpha and IL-1beta were positively correlated ($r(S) = 0.588$; P = 0.003). In addition, a significant reduction in total cholesterol was recorded with testosterone therapy (-0.25 +/- 0.4 vs. -0.004 +/- 0.4 mmol/liter; P = 0.04). In conclusion, testosterone replacement shifts the cytokine balance to a state of reduced inflammation and lowers total cholesterol. Twenty of these men had established coronary disease, and because total cholesterol is a cardiovascular risk factor, and proinflammatory cytokines mediate the development and complications associated with atheromatous plaque, these properties may have particular relevance in men with overt vascular disease.

PMID: 15240608 [PubMed - indexed for MEDLINE]

Eur J Endocrinol. 2007 May;156(5):595-602.

The effect of testosterone replacement therapy on adipocytokines and C-reactive protein in hypogonadal men with type 2 diabetes.

Kapoor D, Clarke S, Stanworth R, Channer KS, Jones TH.

Source

Centre for Diabetes and Endocrinology, Barnsley NHS Foundation Trust Hospital,

Barnsley, United Kingdom.

Abstract

OBJECTIVE:

Serum testosterone levels are known to inversely correlate with insulin sensitivity and obesity in men. Furthermore, there is evidence to suggest that testosterone replacement therapy reduces insulin resistance and visceral adiposity in type 2 diabetic men. Adipocytokines are hormones secreted by adipose tissue and contribute to insulin resistance. We examined the effects of testosterone replacement treatment on various adipocytokines and C-reactive protein (CRP) in type 2 diabetic men.

DESIGN:

Double-blinded placebo-controlled crossover study in 20 hypogonadal type 2 diabetic men. Patients were treated with testosterone (sustanon 200 mg) or placebo intramuscularly every 2 weeks for 3 months in random order followed by a washout period of 1 month before the alternate treatment phase.

METHODS:

Leptin, adiponectin, resistin, tumour necrosis factor-alpha (TNF-alpha), interleukin (IL)-6 and CRP levels were measured before and after each treatment phase. Body mass index (BMI) and waist circumference were also recorded.

RESULTS:

At baseline, leptin levels significantly correlated with BMI and waist circumference. There was a significant inverse correlation between baseline IL-6 and total testosterone ($r=-0.68$; $P=0.002$) and bioavailable testosterone levels ($r=-0.73$; $P=0.007$). CRP levels also correlated significantly with total testosterone levels ($r=-0.59$; $P=0.01$). Testosterone treatment reduced leptin (-7141.9 ± 1461.8 pg/ml; $P=0.0001$) and adiponectin levels (-2075.8 ± 852.3 ng/ml; $P=0.02$). There was a significant reduction in waist circumference. No significant effects of testosterone therapy on resistin, TNF-alpha, IL-6 or CRP levels were observed.

CONCLUSION:

Testosterone replacement treatment decreases leptin and adiponectin levels in type 2 diabetic men. Moreover, low levels of testosterone in men are associated with pro-inflammatory profile, though testosterone treatment over 3 months had no effect on inflammatory markers.

PMID: 17468196 [PubMed - indexed for MEDLINE]

Adverse events associated with testosterone administration.

Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, Bhasin S.

Source

Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts 02118, USA.

Abstract

BACKGROUND:

Testosterone supplementation has been shown to increase muscle mass and strength in healthy older men. The safety and efficacy of testosterone treatment in older men who have limitations in mobility have not been studied.

METHODS:

Community-dwelling men, 65 years of age or older, with limitations in mobility and a total serum testosterone level of 100 to 350 ng per deciliter (3.5 to 12.1 nmol per liter) or a free serum testosterone level of less than 50 pg per milliliter (173 pmol per liter) were randomly assigned to receive placebo gel or testosterone gel, to be applied daily for 6 months. Adverse events were categorized with the use of the Medical Dictionary for Regulatory Activities classification. The data and safety monitoring board recommended that the trial be discontinued early because there was a significantly higher rate of adverse cardiovascular events in the testosterone group than in the placebo group.

RESULTS:

A total of 209 men (mean age, 74 years) were enrolled at the time the trial was terminated. At baseline, there was a high prevalence of hypertension, diabetes, hyperlipidemia, and obesity among the participants. During the course of the study, the testosterone group had higher rates of cardiac, respiratory, and dermatologic events than did the placebo group. A total of 23 subjects in the testosterone group, as compared with 5 in the placebo group, had cardiovascular-related adverse events. The relative risk of a cardiovascular-related adverse event remained constant throughout the 6-month treatment period. As compared with the placebo group, the testosterone group had significantly greater improvements in leg-press and

chest-press strength and in stair climbing while carrying a load.

CONCLUSIONS:

In this population of older men with limitations in mobility and a high prevalence of chronic disease, the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events. The small size of the trial and the unique population prevent broader inferences from being made about the safety of testosterone therapy. (ClinicalTrials.gov number, NCT00240981.)

NOTE: there were more co-authors than adverse events (30 vs. 28). Edema (swelling) was the major adverse event. Estradiol (causes edema) was not measured. Many researches have criticized the study:

Comment in

Reproductive endocrinology: Testosterone-replacement therapy in older men with limited mobility: is it safe? [Nat Rev Endocrinol. 2010]

Testosterone deficiency and replacement in older men. [N Engl J Med. 2010]

Adverse events associated with testosterone administration. [N Engl J Med. 2010]

ACP Journal Club. Testosterone increased risk for adverse events in older men with mobility limitations. [Ann Intern Med. 2010]

Adverse events associated with testosterone administration. [N Engl J Med. 2010]

Adverse events associated with testosterone administration. [N Engl J Med. 2010]

Words of wisdom. Re: Adverse events associated with testosterone administration. [Eur Urol. 2011]

Adverse events associated with testosterone administration. [N Engl J Med. 2010]