PRO

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

The MrOS (Osteoporotic Fractures in Men) Study in Sweden

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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

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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, 5864 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 (5796204 versus 4716210 seconds; *P*,0.01) and total exercise time (6316180 versus 5416204 seconds; *P*,0.01). Testosterone significantly increased heart rate at the onset of 1-mm ST-segment depression (135612 versus 123614 bpm; *P*,0.01) and at peak exercise (140612 versus 132612 bpm; *P*,0.01) and the rate-pressure product at the onset of 1-mm ST-segment depression (24 21363750 versus 21 61963542 mm Hg3bpm; *P*,0.05) and at peak exercise (26 74663109 versus 22 52765443 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

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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 TRSTOSTRRONE IMPLANT THERAPY IMPROVES END0 THELIUM-DEPENDENT AND INDEPENDENT VASODILATION IN POSIMENOPAUSAL WOMEN ALREADY RECEIVING OESTROGEN

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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 testostemne implant (SOmg), 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 2 0.3 mnol/L, p<O.OOl), associated with a mean 42% increase in FMD (6.4% 5 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

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a b s t r a c t

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.

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

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a b s t r a c t
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.

Original Article

Testosterone Supplementation in Heart Failure: A Meta-Analysis

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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.

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Source

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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 ± 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

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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.

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Low Serum Testosterone and Mortality in Older Men

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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.

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Source

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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 > or =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

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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+/-SD, age 64+/-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.

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Source

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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.

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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

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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.

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Source

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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

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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]

J Gerontol A Biol Sci Med Sci. 2005 Nov;60(11):1451-7.
Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials.

Calof OM1, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S.
Author information

Abstract

BACKGROUND:
We performed a meta-analysis of randomized clinical trials to determine the risks of adverse events associated with testosterone replacement in older men.

METHODS:
The MEDLINE database was searched from 1966 to April 2004, using testosterone as the indexing term; limits included human, male, > or =45 years old, and randomized controlled trial. Of the 417 studies thus identified, 19 met the inclusion criteria: testosterone replacement for at least 90 days, men > or =45 years old with low or low-normal testosterone level, randomized controlled trial, and medically stable men. Odds ratios (ORs) were pooled using a random effects model, assuming heterogeneous results across studies, and were weighted for sample size.

RESULTS:
In the 19 studies that met eligibility criteria, 651 men were treated with testosterone and 433 with placebo. The combined rate of all prostate events was significantly greater in testosterone-treated men than in placebo-treated men (OR = 1.78, 95% confidence interval [CI], 1.07-2.95). Rates of prostate cancer, prostate-specific antigen (PSA) >4 ng/ml, and prostate biopsies were numerically higher in the testosterone group than in the placebo group, although differences between the groups were not individually statistically significant. Testosterone-treated men were nearly four times as likely to have hematocrit >50% as placebo-treated men (OR = 3.69, 95% CI, 1.82-7.51). The

frequency of cardiovascular events, sleep apnea or death was not significantly different between the two groups.

CONCLUSIONS:
Testosterone replacement in older men was associated with a significantly higher risk of detection of prostate events and of hematocrit >50% than was placebo; hematocrit increase was the most frequent adverse event associated with testosterone replacement. These data reaffirm the need to monitor hematocrit, PSA, and digital examination of the prostate during testosterone replacement in older men.

PMID: 16339333 [PubMed - indexed for MEDLINE]

J Clin Endocrinol Metab. 2010 Jun;95(6):2560-75. doi: 10.1210/jc.2009-2575.
Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis.

Fernández-Balsells MM1, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, Agrwal N, Elamin MB, Gallegos-Orozco JF, Wang AT, Erwin PJ, Bhasin S, Montori VM.
Author information

Abstract

CONTEXT:
The risks of testosterone therapy in men remain poorly understood.

OBJECTIVE:
The aim of this study was to conduct a systematic review and meta-analyses of testosterone trials to evaluate the adverse effects of testosterone treatment in men.

DATA SOURCES:
We searched MEDLINE, EMBASE, and Cochrane CENTRAL from 2003 through August 2008. Review of reference lists and contact with experts further identified candidate studies.

STUDY SELECTION:
Eligible studies were comparative, randomized, and nonrandomized and reported the effects of testosterone on outcomes of interest (death, cardiovascular events and risk factors, prostate outcomes, and erythrocytosis). Reviewers, working independently and in duplicate, determined study eligibility.

DATA EXTRACTION:
Reviewers working independently and in duplicate determined the methodological quality of studies and collected descriptive, quality, and outcome data.

DATA SYNTHESIS:
The methodological quality of the 51 included studies varied from low to medium, and follow-up duration ranged from 3 months to 3 yr. Testosterone treatment was associated with a significant increase in hemoglobin [weighted mean difference (WMD), 0.80 g/dl; 95% confidence interval (CI), 0.45 to 1.14] and hematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01), and a decrease in high-density lipoprotein cholesterol (WMD, -0.49 mg/dl; 95% CI, -0.85 to -0.13). There was no significant effect on mortality, prostate, or cardiovascular outcomes.

CONCLUSIONS:
The adverse effects of testosterone therapy include an increase in hemoglobin and hematocrit and a small decrease in high-density lipoprotein cholesterol. These findings are of unknown clinical significance. Current evidence about the safety of testosterone treatment in men in terms of patient-important outcomes is of low quality and is hampered by the brief study follow-up.

PMID: 20525906 [PubMed - indexed for MEDLINE]

CON

N Engl J Med. 2010 Jul 8;363(2):109-22. Epub 2010 Jun 30.
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. Edema (swelling) was the major adverse event. Estradiol (causes edema) was not measured. Many researches have criticized the study.

CON and rebuttal.

JAMA. 2013 Nov 6;310(17):1829-36. doi: 10.1001/jama.2013.280386.

Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels.

Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi A, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS, Ho PM.

Source

The University of Texas at Southwestern Medical Center, Dallas.

Abstract

IMPORTANCE:

Rates of testosterone therapy are increasing and the effects of testosterone therapy on cardiovascular outcomes and mortality are unknown. A recent randomized clinical trial of testosterone therapy in men with a high prevalence of cardiovascular diseases was stopped prematurely due to adverse cardiovascular events raising concerns about testosterone therapy safety.

OBJECTIVES:

To assess the association between testosterone therapy and all-cause mortality, myocardial infarction (MI), or stroke among male veterans and to determine whether this association is modified by underlying coronary artery disease.

DESIGN, SETTING, AND PATIENTS:

A retrospective national cohort study of men with low testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011.

MAIN OUTCOMES AND MEASURES:

Primary outcome was a composite of all-cause mortality, MI, and ischemic stroke.

RESULTS:

Of the 8709 men with a total testosterone level lower than 300 ng/dL, 1223 patients started testosterone therapy after a median of 531 days following coronary angiography. Of the 1710 outcome events, 748 men died, 443 had MIs, and 519 had strokes. Of 7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Among 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. The absolute rate of events were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group, with an absolute risk difference of 5.8% (95% CI, -1.4% to 13.1%) at 3 years after coronary angiography. In Cox proportional hazards

models adjusting for the presence of coronary artery disease, testosterone therapy use as a time-varying covariate was associated with increased risk of adverse outcomes (hazard ratio, 1.29; 95% CI, 1.04 to 1.58). There was no significant difference in the effect size of testosterone therapy among those with and without coronary artery disease (test for interaction, P = .41).

CONCLUSIONS AND RELEVANCE:
Among a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes. These findings may inform the discussion about the potential risks of testosterone therapy.

The rebuttal

Is Testosterone Therapy Dangerous? Dr. Mark Richards in Washington, DC Debunks the Myth

Hormone Specialist Dr. Mark Richards says a recent study on the dangers of testosterone therapy uses statistical manipulation to skew the results.

Washington, DC -- Recently, a study was published in the Journal of the American Medical Association (JAMA) with a conclusion suggesting that men who had received testosterone therapy had a higher risk of myocardial infarction (MI), stroke, and death. According to Dr. Mark Richards, a hormone specialist and plastic surgeon in Washington, DC, the JAMA study used misleading statistical methodology to provide these conclusions. The study, entitled "Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels" was a retrospective chart review of men with low testosterone levels who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011. Dr. Richards notes that the men who were receiving "Testosterone treatment" had measured post treatment levels that averaged (~330ng/dl) which, according to the Washington, DC plastic surgeon, is "about 40% under the minimum suggested for heart health as defined in the recent cardiology science literature."

Dr. Richards noted that when the data the authors collected was presented, they claimed the rates of heart attack, death and stroke were approximately *30%* higher in the group treated with testosterone. Yet, the study's own reported numbers presented in the Results section of the Abstract reveal that of the 1223 men who received some form of testosterone therapy, there was a 5% mortality rate, a 1.8% heart attack rate, and a 2.7% stroke rate. Conversely, of the 7486 men who did not receive testosterone therapy, there was a 9% mortality rate, a 5.6% heart attack rate, and a 6.5% stroke rate. This meant that in reality, the data suggests that the mortality rate was nearly double in the group that did NOT receive testosterone! Additionally, heart attacks were more than 3 times more common in the group that did NOT receive testosterone. Dr. Richards says the data obtained from the chart review appears to have been statistically manipulated in order to support a false conclusion. He further explains, "[the authors] used a method called inverse probability treatment, weighting to adjust for differences in demographics and prior risk factors such as for stroke or heart attack to theoretically account for potential confounding variables that might affect the patients' outcome. In this case, they used over 50 variables to compute this weighting and change the data. By selecting the

weighting of variables as they did, the authors changed the raw data that clearly supported the beneficial effects of even sub-therapeutic levels of testosterone to an opposite conclusion. This should cause anyone to question the integrity of their conclusion that flies in the face of decades of more soundly performed research."

Arguing in support of the known benefits of testosterone therapy, Dr. Richards highlights some key information, noting that "decades of high quality prospective epidemiologic studies have shown a strong correlation between low testosterone levels in *both sexes* and disease and death rates. In particular, strong correlations exist between low testosterone and heart disease, diabetes/metabolic syndrome, breast and prostate cancers, atherosclerosis, depression, fatigue, loss of muscle mass, increased intra-abdominal fat, cognitive failures including Alzheimer's disease, loss of mobility, loss of libido, decreased sexual function, and menopausal symptoms." He stresses that many of these diseases have actually been prevented, improved, or cured with bio-identical human testosterone supplementation.

Dr. Richards is concerned that the JAMA study's conclusion will be misleading and confusing to physicians as well as the public, possibly resulting in the denial of treatment for those for whom this therapy might be lifesaving. Molecularly identical human testosterone modalities such as patches, injections, or gels, though not ideal, have been scientifically proven to be very helpful in treating disease states common in aging populations. He believes the best hormone treatment uses highly compressed, sterile hormone pellets placed within the body's superficial fat layers. Dr. Richards explains these pellets are placed while using local anesthesia, and dissolve completely, usually over a period of three to five months. He says this treatment has been used in the US since 1939, but because the testosterone pellets cannot be patented, they are not considered to be commercially profitable, and thus are not widely known or marketed.

Dr. Richards advises patients and physicians alike to be cautious when reviewing medical studies such as the one published in JAMA, stating, "The misleading conclusions in the JAMA article highlighted by many news articles and broadcasts serves to remind us that news headlines must always be tempered by the scientific reality of the data. One must not accept any study's conclusion without first considering the data, the statistical analysis used, and the existing body of literature on the subject that would speak to the reproducibility of the findings and soundness of the conclusions."

About Mark E. Richards, MD

Dr. Mark Richards is a board-certified plastic surgeon in Washington, DC. He is also a practitioner in hormone therapy, using time-released bio-identical hormone pellets to improve effects of aging that cannot be treated with cosmetic surgery, such as energy levels and psychological and physiological health. Dr. Richards also offers his knowledge on the topic to assist physicians interested in offering hormone therapy to help their patients. **He is available for interview upon request.**

BMC Med. 2013 Apr 18;11:108. doi: 10.1186/1741-7015-11-108.
Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials.

Xu L1, Freeman G, Cowling BJ, Schooling CM.

Abstract

BACKGROUND:
Testosterone therapy is increasingly promoted. No randomized placebo-controlled trial has been implemented to assess the effect of testosterone therapy on cardiovascular events, although very high levels of androgens are thought to promote cardiovascular disease.

METHODS:
A systematic review and meta-analysis was conducted of placebo-controlled randomized trials of testosterone therapy among men lasting 12+ weeks reporting cardiovascular-related events. We searched PubMed through the end of 2012 using "("testosterone" or "androgen") and trial and ("random*")" with the selection limited to studies of men in English, supplemented by a bibliographic search of the World Health Organization trial registry. Two reviewers independently searched, selected and assessed study quality with differences resolved by consensus. Two statisticians independently abstracted and analyzed data, using random or fixed effects models, as appropriate, with inverse variance weighting.

RESULTS:
Of 1,882 studies identified 27 trials were eligible including 2,994, mainly older, men who experienced 180 cardiovascular-related events. Testosterone therapy increased the risk of a cardiovascular-related event (odds ratio (OR) 1.54, 95% confidence interval (CI) 1.09 to 2.18). The effect of testosterone therapy varied with source of funding (P-value for interaction 0.03), but not with baseline testosterone level (P-value for interaction 0.70). In trials not funded by the pharmaceutical industry the risk of a cardiovascular-related event on testosterone therapy was greater (OR 2.06, 95% CI 1.34 to 3.17) than in pharmaceutical industry funded trials (OR 0.89, 95% CI 0.50 to 1.60).

CONCLUSIONS:
The effects of testosterone on cardiovascular-related events varied with source of funding. Nevertheless, overall and particularly in trials not funded by the pharmaceutical industry, exogenous testosterone increased the risk of cardiovascular-related events, with corresponding implications for the use of testosterone therapy.

PMID: 23597181 [PubMed - indexed for MEDLINE] PMCID: PMC3648456 **Free PMC Article**

PLoS One. 2014 Jan 29;9(1):e85805. doi: 10.1371/journal.pone.0085805. eCollection 2014.

Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men.

Finkle WD1, Greenland S2, Ridgeway GK1, Adams JL1, Frasco MA1, Cook MB3, Fraumeni JF Jr3, Hoover RN3.
Author information

Abstract

BACKGROUND:
An association between testosterone therapy (TT) and cardiovascular disease has been reported and TT use is increasing rapidly.

METHODS:
We conducted a cohort study of the risk of acute non-fatal myocardial infarction (MI) following an initial TT prescription (N = 55,593) in a large health-care database. We compared the incidence rate of MI in the 90 days following the initial prescription (post-prescription interval) with the rate in the one year prior to the initial prescription (pre-prescription interval) (post/pre). We also compared post/pre rates in a cohort of men prescribed phosphodiesterase type 5 inhibitors (PDE5I; sildenafil or tadalafil, N = 167,279), and compared TT prescription post/pre rates with the PDE5I post/pre rates, adjusting for potential confounders using doubly robust estimation.

RESULTS:
In all subjects, the post/pre-prescription rate ratio (RR) for TT prescription was 1.36 (1.03, 1.81). In men aged 65 years and older, the RR was 2.19 (1.27, 3.77) for TT prescription and 1.15 (0.83, 1.59) for PDE5I, and the ratio of the rate ratios (RRR) for TT prescription relative to PDE5I was 1.90 (1.04, 3.49). The RR for TT prescription increased with age from 0.95 (0.54, 1.67) for men under age 55 years to 3.43 (1.54, 7.56) for those aged ≥75 years (ptrend = 0.03), while no trend was seen for PDE5I (ptrend = 0.18). In men under age 65 years, excess risk was confined to those with a prior history of heart disease, with RRs of 2.90 (1.49, 5.62) for TT prescription and 1.40 (0.91, 2.14) for PDE5I, and a RRR of 2.07 (1.05, 4.11).

DISCUSSION:
In older men, and in younger men with pre-existing diagnosed heart disease, the risk of MI following initiation of TT prescription is substantially increased.

PMID: 24489673 [PubMed - in process] PMCID: PMC3905977 **Free PMC Article**

COMMENTS

Comment: Improperly drawn casual inferences, unmatched cohorts, lack of biological plausibility

In the January 29, 2014 PLoS One article, "Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men," the authors improperly draw causal inferences from retrospective, observational connections between testosterone therapy and non-fatal myocardial infarctions in unmatched cohorts [1]. Comparing cardiac risks in a group of men with low testosterone, a known major risk factor for heart disease, to men on Cialis® or Viagra® is incommensurate. This "cohort" study should be considered associative at best.

What is disturbing is all the sensationalism surrounding these findings by "medical staff writers" who have reported findings as though definitive. Their lack of medical knowledge and skills to interpret the data is obvious and leads to very subjective and biased reporting.

Clearly ignored in these recent "news" articles are the documented benefits of testosterone therapy including cardiac protection as well as a lack of cardiovascular events documented in two well-designed meta-analyses of prospective, controlled trials [2,3].

Furthermore, over 80% of published epidemiologic studies are later disproven or shown to be false [4]. The known physiologic effects of testosterone at the androgen receptor and the lack of biologic plausibility make this a likely outcome in this case. Most importantly, many higher

quality studies and trials have supported the benefits and safety of testosterone therapy in both men and women.

Is there another way to explain the purported 'finding' in the unlikely case that is was valid?

Aromatization of testosterone to estradiol is rarely addressed in studies on testosterone and was not addressed in this study, even though patients with heart disease have many risk factors for increased aromatase activity: age, obesity, sedentary life style, insulin resistance and medications (statins, cardiac and anti-hypertensive medications) [5]. Side effects from increased local aromatization to estradiol (which is immeasurable in serum), including fluid retention, weight gain and edema, may potentially have adverse cardiovascular effects [6,7,8]. However, these are easily prevented with the use of low dose aromatase inhibitors [9,10]. Interestingly, some, albeit not all, studies in men have shown an increased risk of myocardial infarction with elevated estradiol or a high estradiol/testosterone ratio; this is not necessarily causal and should be approached with caution [11-18]. The confounders (e.g., age, obesity, sedentary life style, insulin resistance and medications), associated with low testosterone and increased aromatization to estradiol, are most likely causative.

As with many cohort studies there are severe methodical limitations including selection bias and lack of a suitable control group. As physicians and scientists, we should not ignore these results but rather keep them in perspective and, as suggested by the FDA, investigate them further with properly designed studies that also address signs and symptoms of aromatization as well as confounding variables.
R. Glaser

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Open Letter to the FDA Concerning the 1/31/2014 Safety Announcement entitled: FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products

As concerned physicians and scientists, we must be mindful of false positives, false negatives, poor study design, selection bias, failure to adequately address confounding conditions, statistical manipulation, and, most importantly, improperly drawn causal inference – all of which can result in a false conclusion being published. The Economist magazine review on this topic (October 19th, 2013 edition – "Problems with Scientific Research") cites the independent findings from multiple distinguished institutions that less than 25% of scientific published studies are in fact reproducible. Unfortunately, while there is much yet to be learned about testosterone therapy, the two studies cited by the FDA (due in part to the headline grabbing nature of their titles) are of very inferior quality.

Poor quality medical articles such as these have the potential to create significant population health risks, as often has happened in the past. For example, an article published in 1941 by Drs. Huggins and Hodges purported to prove that testosterone caused prostate cancer genesis and growth, with much of their conclusions based upon only one patient. This led to 60 years of castration and androgen deprivation therapy in men unfortunate enough to be diagnosed with prostate cancer. These treatments caused decades of untold suffering due to the morbidity and mortality of the "cures". The 1941 "study" by Huggins et al was false and invalid from the start; and its conclusions were close to the opposite of the truth. Seventy years later, we now know from validated biochemical research that the testosterone-albumin complex initiates prostate cell apoptosis, thus giving us a possible avenue for cure. So as to avoid repeating similar travesties of the past, this peer reviewed letter is being sent to the FDA with the hope that we will not focus on the headline grabbing false conclusions of the two studies cited with anything but skepticism.

The FDA Safety Announcement cites two articles that were terminally flawed and made conclusions that run counter to vast numbers of scientific articles on testosterone from the past 20 years. The JAMA study, entitled "Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels" was a retrospective

chart review of men with low testosterone levels who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011. Oddly, the study's findings as presented in the Results section of the Abstract are completely counter to the article's Conclusion. The Results section states that of the 1223 men who received some form of testosterone therapy, there was a 5% mortality rate, a 1.8% heart attack rate, and a 2.7% stroke rate. Conversely, of the 7486 men who did not receive testosterone therapy, there was a 9% mortality rate, a 5.6% heart attack rate, and a 6.5% stroke rate. The raw data the authors presented in the Results section of the JAMA article demonstrated that the group that had received some form of testosterone therapy had a 45% **reduction** in mortality, a 68% **reduction** in heart attacks, and a 58% **reduction** in strokes.

Additionally, the low quality JAMA data was gleaned from a retrospective chart review with undocumented testosterone treatment levels from multiple forms of T therapy in the "treatment cohort". Instead of submitting this poor quality data "as is", which would have weakly supported years of better published studies on the benefits of testosterone therapy, the authors choose to use inverse probability treatment weighting to "adjust" for differences in demographics and prior risk factors in order to *theoretically* account for potential confounding variables that might affect the patients' outcome. In this case, they used over 50 variables to compute this weighting and change the data. Strangely, the researchers did not include the use of hypertensive drugs as a possible confounding or mitigating factor affecting the outcome, though hypertension is a leading causative factor in heart attacks and strokes. By selecting the specific statistical variables as they did, it was possible for the authors to change their own data that clearly supported the beneficial effects of even sub-therapeutic levels of testosterone to an opposite conclusion.

The second article cited titled "Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men" is equally flawed and perhaps more scientifically outrageous. In this paper, the authors compared the myocardial infarction and mortality rates of men prescribed testosterone for low T versus men prescribed PDE inhibitors such as Cialis™ or Viagra™. The glaring errors in this study include that the authors did not measure or know the testosterone levels of the men in the PDE-I cohort, nor did they measure or know the baseline or post-treatment T levels in the testosterone treated group. The study extracted the data from a review of insurance submitted prescriptions and post-prescriptions insurance ICD diagnosis codes. In reality, what the authors compared in this paper was a group of men with presumably low testosterone (who may not have received adequate treatment for low T) against an unrelated cohort of men with unknown but presumed average testosterone. Amazingly, this PLOS article did not even measure the one variable they were supposedly studying – testosterone. Clearly, the two groups in this paper are not comparable; and, the study is of no value. If one assumes the men given T prescriptions had "low T", then these authors may have also inadvertently lent support to the more established findings across two decades of studies linking men with low testosterone levels to significantly higher levels of myocardial infarctions and mortality from all causes: the PLOS study's presumed low testosterone group had higher levels of MIs and mortality for the first 3 months of treatment, but not after 3 months of treatment. Unfortunately, it is impossible to draw any conclusion from this paper as the authors did not have scientifically valid comparable cohort groups or critically important patient data.

While much quality prospective, randomized, and double blind (when possible) research still needs to be done on the topic of testosterone supplementation in men and women, the studies that have qualified in this regard have shown dramatic benefits without health risk in men and women when molecularly human identical testosterone was appropriately delivered (compressed steady state release subcutaneous testosterone pellets being the ideal therapy option in my opinion). Furthermore, as the American Journal of Cardiovascular Drugs stated in 2005: "testosterone treatment is reported to reduce serum levels of the pro-inflammatory cytokines interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha, and to increase levels of the anti-inflammatory cytokine IL-10; to reduce vascular cell adhesion molecule (VCAM)-1 expression in aortic

endothelial cells; to promote vascular smooth muscle and endothelial cell proliferation; to induce vasodilatation and to improve vascular reactivity, to reduce serum levels of the pro-thrombotic factors plasminogen activator inhibitor (PAI)-1 and fibrinogen; to reduce low-density lipoprotein-cholesterol (LDL-C); to improve insulin sensitivity; and to reduce body mass index and visceral fat mass. These actions of testosterone may confer cardiovascular benefit since testosterone therapy reduces atheroma formation in cholesterol-fed animal models, and reduces myocardial ischemia in men with CHD." It is therefore most difficult to imagine a scenario where this human hormone (unadulterated) would increase cardiovascular risk.
Sincerely,
Mark Richards MD
Rockville, MD

EXCERPT from Glaser R, Dimitrakakis C. Testosterone therapy in women: Myths and misconceptions. Maturitas. 2013;74:230-234.

2.6. Myth: Testosterone has adverse effects on the heart

Men have higher levels of testosterone than women: men have a higher incidence of heart disease; however, it is illogical to assume that T causes or contributes to cardiovascular (CV) disease in either sex. Unlike anabolic and oral, synthetic steroids, there is no evidence that T has an adverse effect on the heart. In addition, it is not physiologically plausible.

There is overwhelming biological and clinical evidence that T is cardiac protective [23]. T has a beneficial effect on lean body mass, glucose metabolism and lipid profiles in men and women; and has been successfully used to treat and prevent CV disease and diabetes [24]. T acts as a vasodilatorin both sexes, has immune-modulating properties that inhibit atheromata, and has a beneficial effect on cardiac muscle [25–27].

Low T in men is associated with an increased risk of heart disease and mortality from all causes [28,29]. In addition, low T is an independent predictor of reduced exercise capacity and poor clinical outcomes in patients with heart failure. Similar to men, T supplementation has been shown to improve functional capacity, insulin resistance and muscle strength in women with congestive heart failure [30].

Testosterone is a diuretic. However, T can aromatize to E2, which can have adverse effects including edema, fluid retention, anxiety, and weight gain. Medications, including statins and anti-hypertensives, increase aromatase activity and elevate E2, indirectly causing side effects from T therapy.

Fact

There is substantial evidence that testosterone is cardiac protective and that adequate levels decrease the risk of cardiovascular disease.