Male Hypogonadism

Hormone Replacement Therapy – Part 1

Objectives:

1. To review the risks & benefits of testosterone therapy
2. To review alternatives to testosterone therapy
3. To review the available forms of testosterone therapy

Disclosures: none

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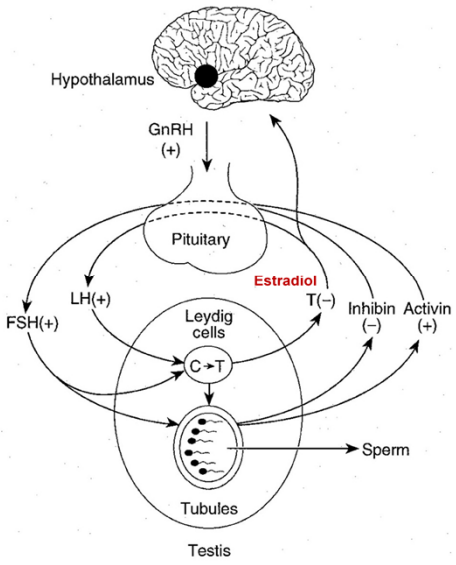
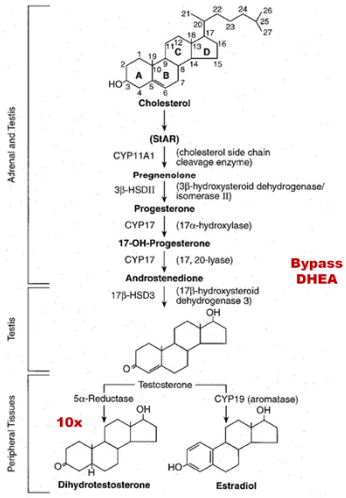
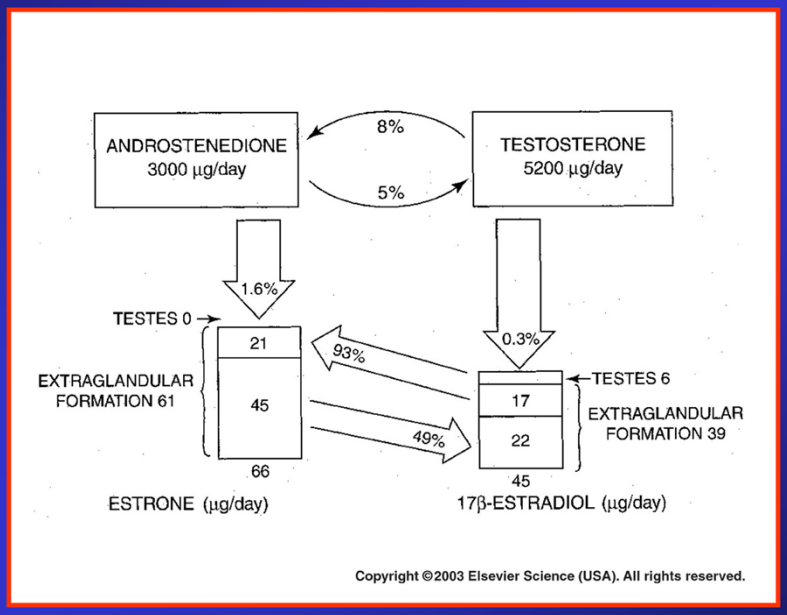
Testosterone: Normal Physiology





Testosterone – Estradiol Inter-conversion



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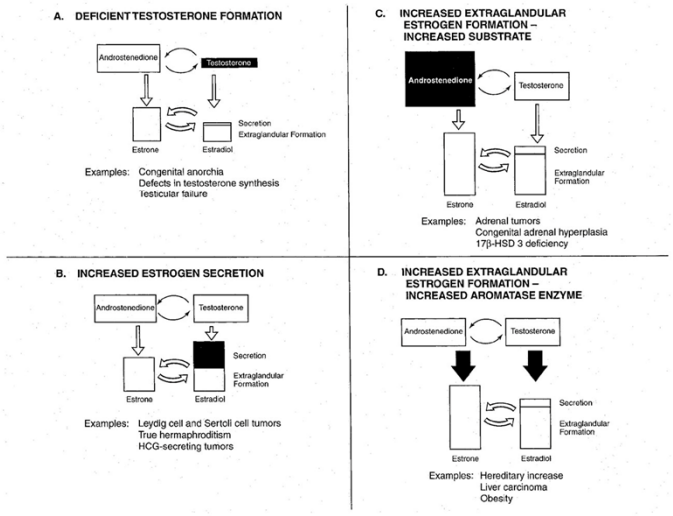
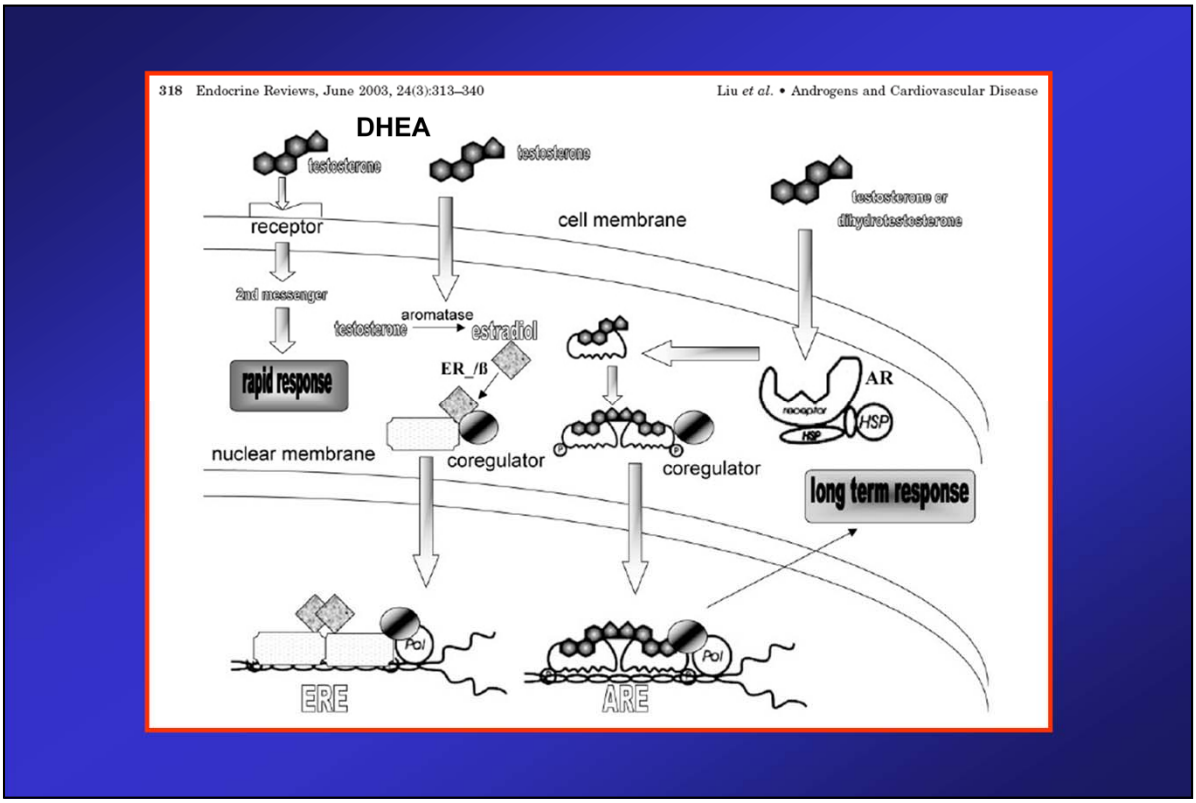
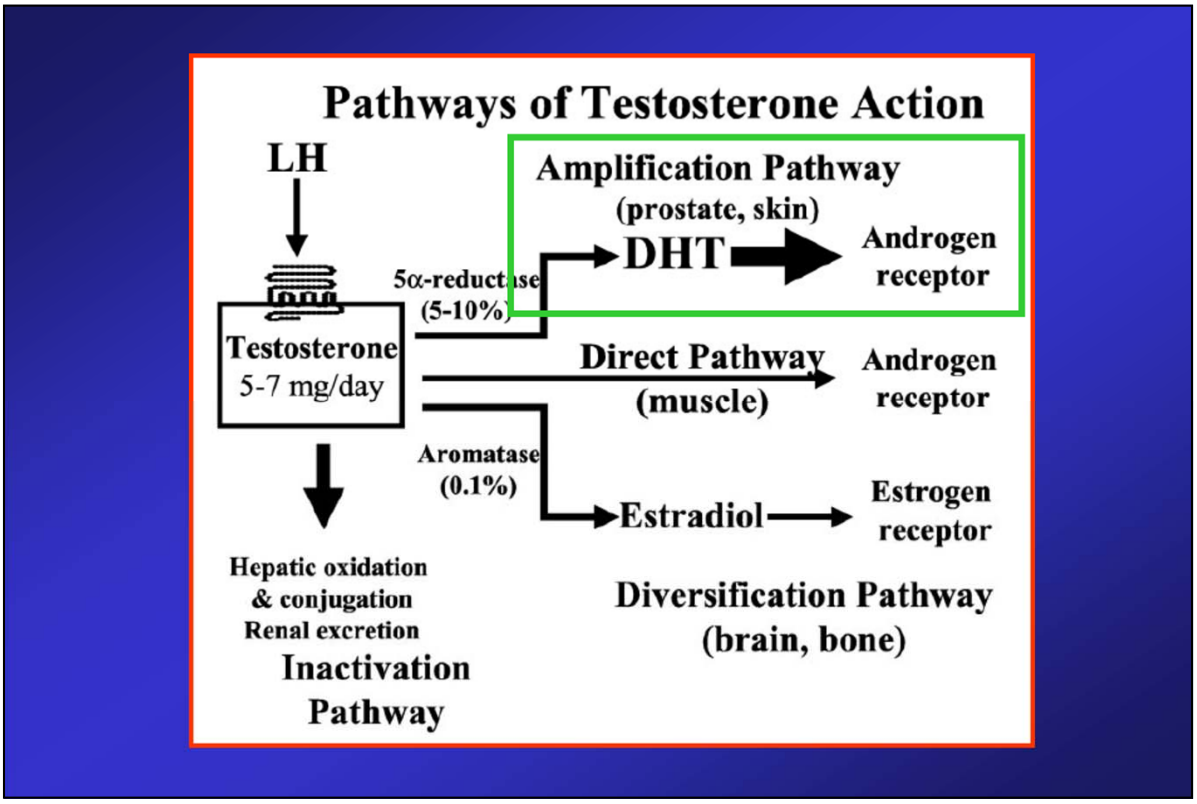


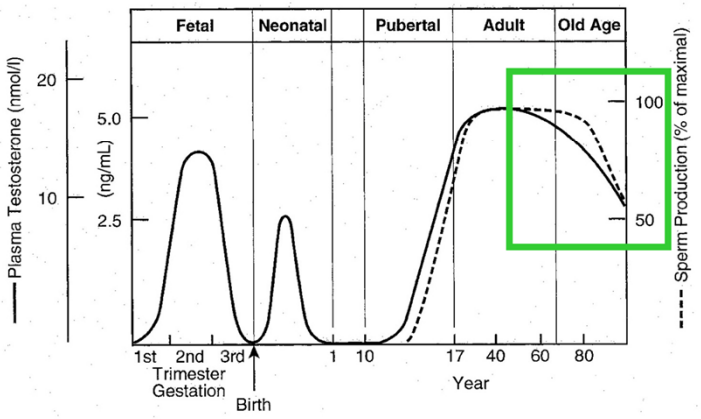


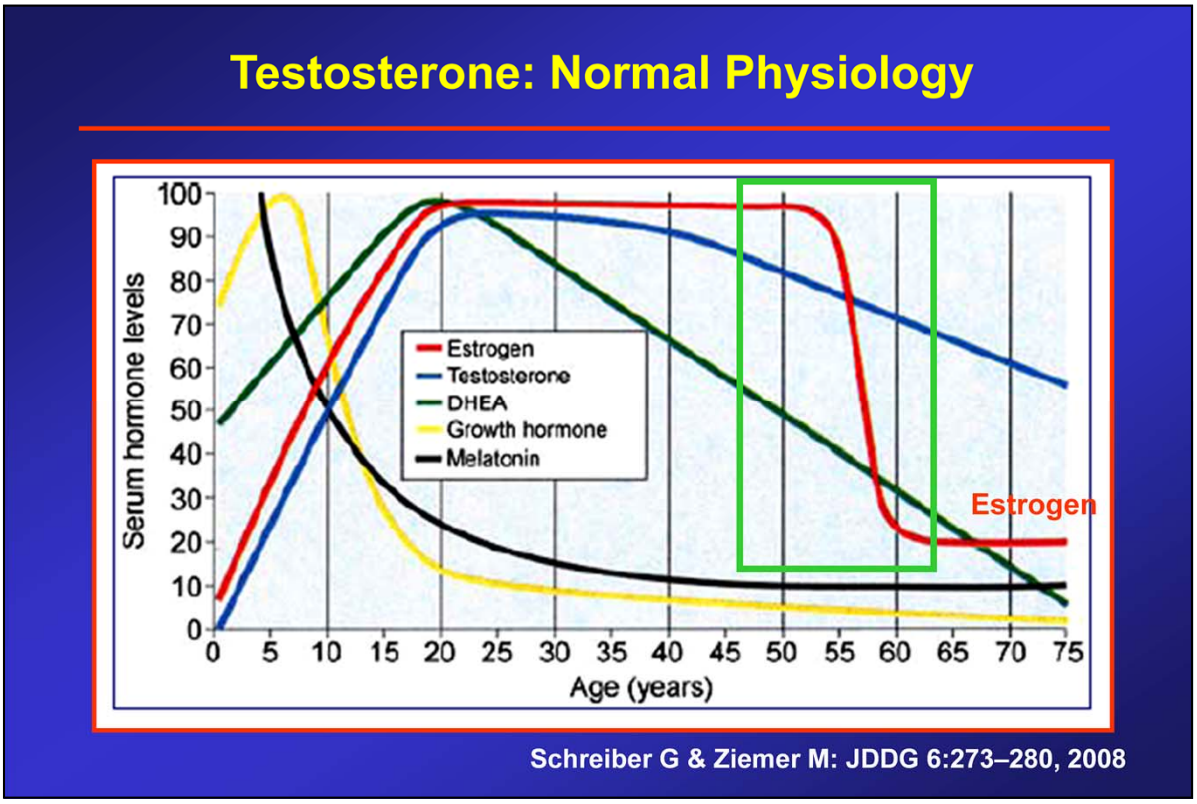
Globally, cardiovascular disease will continue causing most human deaths for the foreseeable future. The consistent gender gap in life span of approximately 5.6 yr in all advanced economies must derive from gender differences in age specific cardiovascular death rates, which rise steeply in parallel for both genders but 5–10 yr earlier in men. The lack of inflection point at modal age of menopause, contrasting with unequivocally estrogen-dependent biological markers like breast cancer or bone density, makes estrogen protection of premenopausal women an unlikely explanation. Limited human data suggest that testosterone exposure does not shorten life span in either gender, and oral estrogen treatment increases risk of cardiovascular death in men as it does in women. Alternatively, androgen exposure in early life (perinatal androgen imprinting) may predispose males to earlier onset of atherosclerosis. Following the recent reevaluation of the estrogen-protection orthodoxy, empirical research has flourished into the role of androgens in the progression of cardiovascular disease, highlighting the need to better understand androgen receptor (AR) coregulators, nongenomic androgen effects, tissue-specific metabolic activation of androgens, and androgen sensitivity. Novel therapeutic targets may arise from understanding how androgens enhance early plaque formation and cause vasodilatation via nongenomic androgen effects on vascular smooth muscle, and how tissue specific variations in androgen effects are modulated by AR coregulators as well as metabolic activation of testosterone to amplify (via 5-reductase to form dihydrotestosterone acting on AR) or diversify (via aromatization to estradiol acting upon estrogen receptor /) the biological effects of testosterone on the vasculature. Observational studies show that blood

testosterone concentrations are consistently lower among men with cardiovascular disease, suggesting a possible preventive role for testosterone therapy, which requires critical evaluation by further prospective studies. Short-term interventional studies show that testosterone produces a modest but consistent improvement in cardiac ischemia over placebo, comparable to the effects of existing anti-anginal drugs. By contrast, testosterone therapy has no beneficial effects in peripheral arterial disease but has not been evaluated in cerebrovascular disease. Erectile dysfunction is most frequently caused by pelvic arterial insufficiency due to atherosclerosis, and its sentinel relationship to generalized atherosclerosis is insufficiently appreciated. The commonality of risk factor patterns and mechanisms (including endothelial dysfunction) suggests that the efficacy of anti-atherogenic therapy is an important challenge with the potential to enhance men's motivation for prevention and treatment of cardiovascular diseases. (*Endocrine Reviews* 24: 313–340, 2003)


Pathways of Testosterone Action
LH
Amplification Pathway
(prostate, skin)
DHT
Androgen receptor
5α-reductase
(5-10%)
Testosterone
5-7 mg/day
Direct Pathway
(muscle)
Androgen receptor
Aromatase
(0.1%)
Estradiol
Estrogen receptor
Hepatic oxidation
& conjugation
Renal excretion
Inactivation Pathway
Diversification Pathway
(brain, bone)

Testosterone: Normal Physiology





Managing the clinical features of hormone insufficiency in aging men is an important field of activity for dermatologists and in particular for dermatologists specialized in andrology. Potential consequences of age-associated decrease in plasma testosterone levels include long-term changes in diverse organ systems including changes of bone architecture, body composition, muscular strength, cognitive functions, and mood as well as negative effects on skin and hair. Indications and contraindications for a hormone replacement therapy as well as therapy monitoring are well-defined. Replacement of testosterone in the case of late-onset hypogonadism is not a standardized therapy. Previous studies suggest that testosterone replacement therapy has positive clinical effects. Dermatologic effects of testosterone replacement therapy have not yet been investigated. Further research is required to identify potential benefits and risks of hormone replacement therapy in aging men.

Male Hypogonadism

- Sexual Function – Libido, erectile function
- Bone Metabolism
- Muscle Mass & Strength
- Body Composition, Obesity, Insulin Resistance
- Lipoproteins
- Vascular Disease & Atherosclerosis
- Cancer: Prostate, Breast
- Neuro-psychological
- Erythropoiesis
- Skin

Male Hypogonadism: Infertility

Low Testosterone

- Hypothalamic - Pituitary
  - Fasting, illness
  - LH deficiency or mutation
  - GnRH receptor mutation
  - High Cortisol or Prolactin
  - Hemochromatosis
- Testicular
  - LH Receptor mutation
  - Klinefelter's (XXY)
  - XX Male Syndrome
  - Viral, Trauma, Radiation
  - Drugs: spiron, ETOH, ketoconazole
  - Toxins
  - Autoimmune, Granulomatous D
  - Liver, Renal, Neurological Disease
  - SSD, HIV, RA

Normal Testosterone

- Hypothalamic - Pituitary
  - FSH deficiency or mutation
  - Congenital Adrenal Hyperplasia
  - Androgen administration
- Testicular
  - Germinal Cell Aplasia
  - FS Receptor mutations
  - AZF mutations of Y-chromosome
  - Cryptorchidism, Varicocele?
  - Mycoplasma, Radiation
  - Drugs: cyclophospho, sulfasalazine
  - Toxins
  - Autoimmune, febrile illness
  - Celiac Disease, Paraplegia
  - Obstruction

Male Hypogonadism: Infertility

Table 18–5. Relative Frequency of Causes and Associated Conditions in Men Who Present with Infertility

Cause or Condition	% in Study of Greenberg et al.[394] (n = 425)	% in Study of Baker et al.[440] (n = 1041)
Hypogonadotropic hypogonadism	0.9	0.6
Klinefelter's syndrome	1.6	1.9
Cryptorchidism	6.1	6.4
Varicocele	37.4	40.3
Immotile sperm	0.5	0.6
Viral orchitis	1.9	1.6
Radiation-chemotherapy	—	0.5
Obstruction of epididymis or vas deferens	6.1	4.1
Androgen resistance	—	0.1
Coital disorders	4.0	0.5
Idiopathic disorders	41.5*	43.4†

*Includes miscellaneous semen abnormalities, 10.2%, and undiagnosed primary testicular failure, 5.9.%

†Includes possible obstruction, 4.5%.

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- Skin

Male Hypogonadism

- Sexual Function – Libido, erectile dysfunction
  - Healthy, young men
    - Low level replacement effective
    - Higher levels not better
  - Older men w/ ED: ~10% low T; same as non-ED
    - Replacement improves libido
    - ED improved by T in 57%
      - Testicular 64% Pituitary 44%
      - Transdermal 81% IM 51%
    - Coexist: CVD, DM, HBP, CRI, psychological
    - T helps if FT <6.6 ng/ml (normal in young men: 9 – 12 ng/ml)
    - Not known whether T helps if borderline low

Male Hypogonadism

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Male Hypogonadism: Bone Metabolism

TABLE 2. Proportion and odds of osteoporosis at hip as a function of sex steroid category[a]

	Proportion osteoporotic at hip, % (n/N)	*P* value	Odds of osteoporosis at hip, OR (95% CI)[b]
Total testosterone category[c]			
Deficient	12.3 (9/73)	0.003	3.5 (1.5, 7.7)
Possibly deficient (200 – 400)	4.1 (44/1080)		0.9 (0.6, 1.4)
Normal	6.0 (77/1294)		1.0 (ref)
<200 ng/dl	12.3 (9/73)	0.002	3.1 (1.3, 7.0)
200 to <300 ng/dl	2.6 (9/340)		0.6 (0.3, 1.2)
300 to <400 ng/dl	4.7 (35/738)		0.9 (0.6, 1.5)
400 to <500 ng/dl	4.7 (29/618)		0.7 (0.5, 1.2)
≥500 ng/dl	7.1 (48/678)		1.0 (ref)

Testosterone

Only most T deficient had increased risk

TABLE 4. Proportion and odds of rapid hip bone loss as a function of baseline sex steroid category[a]

	Proportion with rapid hip bone loss, % (n/N)	*P* value	Odds of rapid hip bone loss, OR (95% CI)[b]
Total testosterone category[c]		0.007	
Deficient	22.5 (9/40)		3.2 (1.4, 7.3)
Possibly deficient	7.9 (41/522)		0.9 (0.6, 1.4)
Normal	8.6 (57/665)		1.0 (ref)
<200 ng/dl	22.5 (9/40)	0.03	3.0 (1.3, 7.0)
200 to <300 ng/dl	8.6 (14/163)		0.9 (0.5, 1.9)
300 to <400 ng/dl	7.5 (27/359)		0.8 (0.5, 1.4)
400 to <500 ng/dl	8.0 (25/314)		0.8 (0.5, 1.5)
≥500 ng/dl	9.1 (32/351)		1.0 (ref)

Testosterone

E_2 does not predict rapid bone loss

Context: The clinical value of measuring testosterone and estradiol in older men with osteoporosis and of measuring bone mineral density (BMD) in older men with testosterone or estradiol deficiency is uncertain.

Objective: The objective of the study was to examine the association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men.

Design: This study was a cross-sectional and longitudinal analysis.

Setting: The study was conducted at six U.S. centers of the Osteoporotic Fractures in Men study.

Participants: The study population consisted of 2447 community dwelling men aged 65 year or older.

Main Outcome Measures: Total testosterone deficiency was defined as less than 200 ng/dl. Total estradiol deficiency was defined as less than 10 pg/ml. Osteoporosis was defined as femoral neck or total hip BMD T-score of2.5 or less. Rapid bone loss was defined as 3%/year or more.

Results: Prevalence of osteoporosis in men with deficient and normal total testosterone was 12.3 and 6.0% (P <0.003) and 15.4 and 2.8% (P<0.0001) in those with deficient and normal total estradiol. Among osteoporotic men and those with normal BMD, prevalence of total testosterone deficiency was 6.9 and 3.2% (P 0.01), and prevalence of total estradiol deficiency was 9.2 and 2.4% (P <0.0001). Incidence of rapid hip bone loss in men with deficient and normal total testosterone was 22.5 and 8.6% (P 0.007) and in those with deficient and normal total estradiol was 14.3 and 6.3% (P <0.08).

Conclusions: Older men with total testosterone or estradiol deficiency were more likely to be osteoporotic. Those with osteoporosis were more likely to be total testosterone or estradiol deficient. Rapid hip bone loss was more likely in men with total testosterone deficiency. BMD testing of older men with sex steroid deficiency may be clinically warranted. **(*J Clin Endocrinol Metab* 91: 3908–3915, 2006)**

Male Hypogonadism: Bone Metabolism

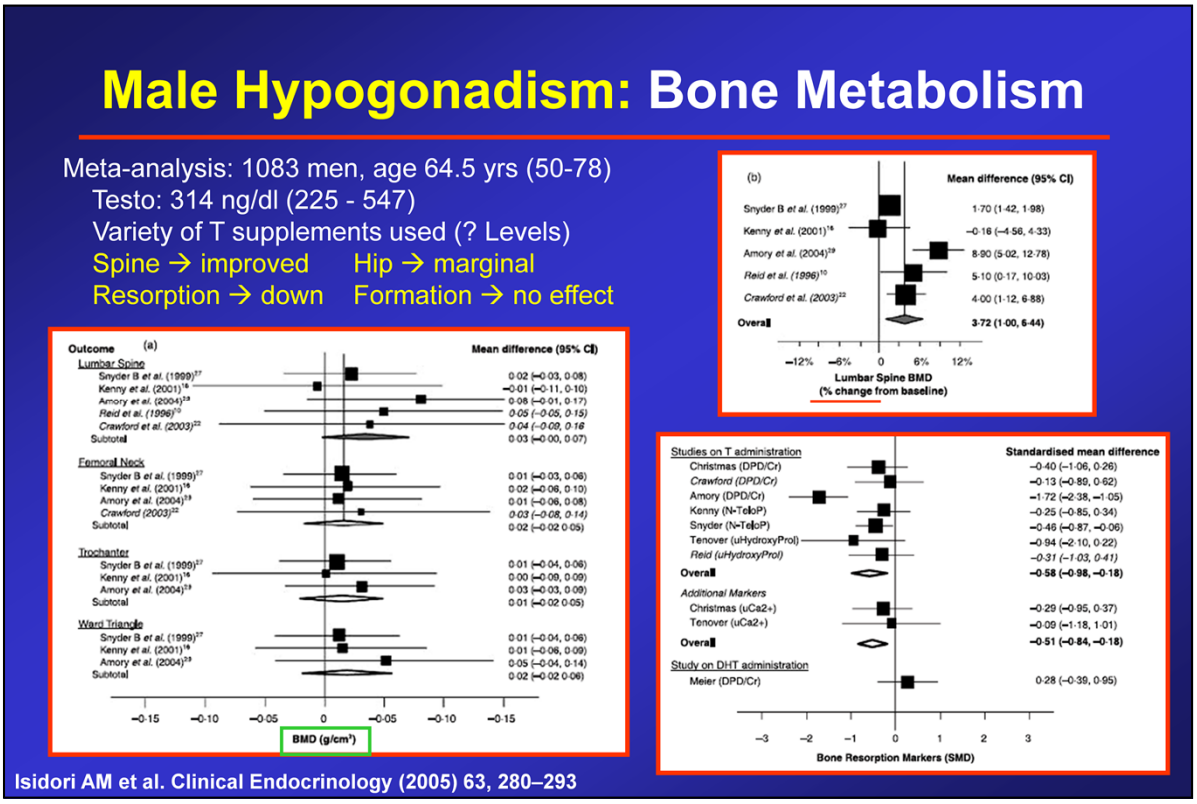
Total estradiol category[c]	% w/ Osteoporosis		OR (CI)
Deficient	15.4 (12/78)	<0.0001	4.8 (2.1, 10.6)
Possibly deficient (10 – 20)	5.9 (98/1653)		1.8 (1.1, 2.9)
Normal	2.8 (20/716)		1.0 (ref)
<10 pg/ml	15.4 (12/78)	<0.0001	5.4 (1.8, 16.6)
10 to <15 pg/ml	6.3 (42/668)		2.0 (0.8, 5.2)
15 to <20 pg/ml	5.7 (56/983)		2.0 (0.8, 5.2)
20 to <25 pg/ml	3.1 (15/491)		1.2 (0.4, 3.4)
≥25 pg/ml	2.2 (5/227)		1.0 (ref)

Estradiol

TABLE 3. Proportion and odds of sex steroid deficiency as a function of hip osteoporosis category[a]

	Proportion total testosterone deficient, % (n/N)[b]	*P* value	Odds of total testosterone deficiency, OR (95% CI)[c]
Hip osteoporosis category			
Normal	3.2 (34/1062)	0.01	1.0 (ref)
Low bone mass	2.4 (30/1255)		1.0 (0.6, 1.6)
Osteoporotic	6.9 (9/130)		3.7 (1.6, 8.3)
	Proportion total estradiol deficient, % (n/N)[d]	***P* value**	**Odds of total estradiol deficiency, OR (95% CI)[e]**
Hip osteoporosis category			
Normal	2.4 (25/1062)	0.0001	1.0 (ref)
Low bone mass	3.3 (41/1255)		1.4 (0.8, 2.3)
Osteoporotic	9.2 (12/130)		3.9 (1.8, 8.4)

Only very low T (<200) is significant but any E_2 loss important
Either hormone deficiency increases the risk of osteoporosis



Objectives Ageing in men is associated with a gradual decline in serum testosterone levels and a concomitant loss of muscle mass, accumulation of central adiposity, impaired mobility and increased risk of bone fractures. Whether androgen treatment might be beneficial in these subjects is still under debate. We have carried out a systematic review of randomized controlled trials (RCTs) evaluating the effects of testosterone (T) administration to middle-aged and ageing men on body composition, muscle strength, bone density, markers of bone metabolism and serum lipid profile.

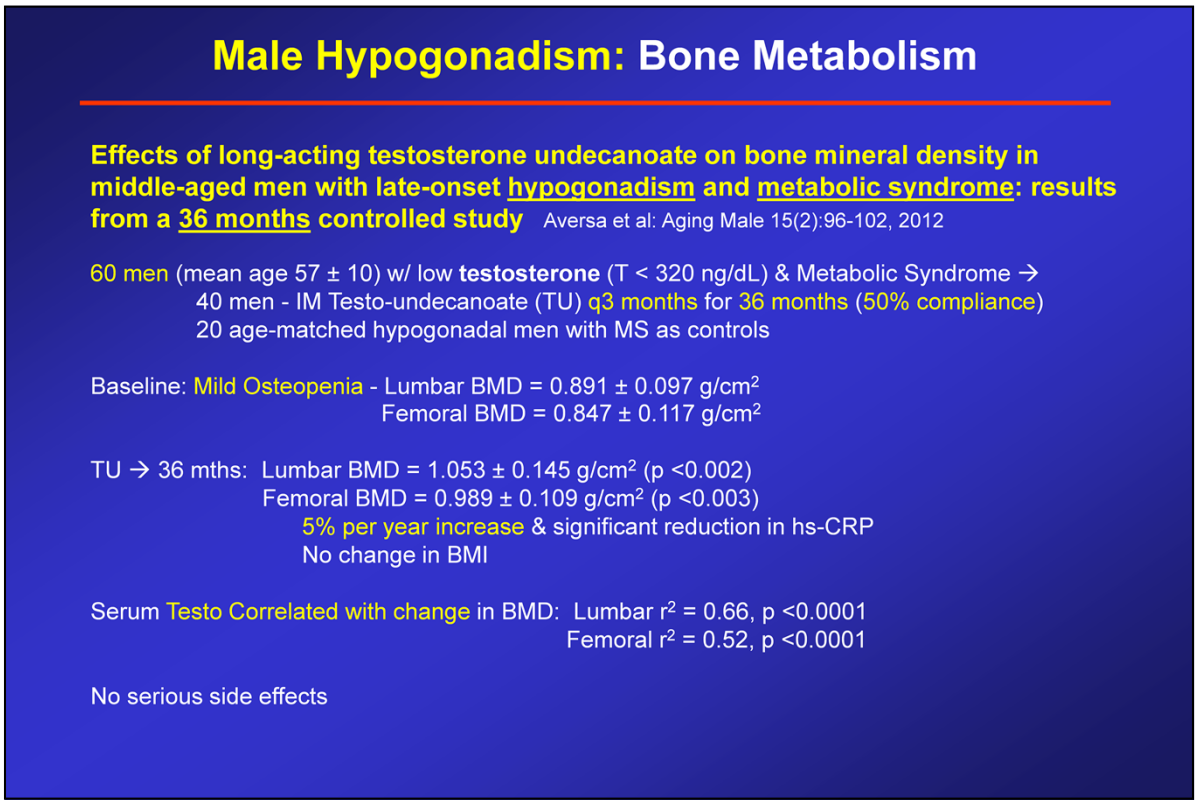
Data source A comprehensive search of all published randomized clinical trials was performed using the MEDLINE, Cochrane Library, EMBASE and *Current Contents* databases.

Review methods Guided by pre-specified criteria, software-assisted data abstraction and quality assessed by two independent reviewers, 29 RCTs were found to be eligible. For each investigated variable, we reported the results of pooled estimates of testosterone treatment using the random effect model of meta-analysis. Heterogeneity, reproducibility and consistency of the findings across studies were explored using sensitivity and meta-regression analysis.

Results Overall, 1083 subjects were evaluated, 625 randomized to T, 427 to

placebo and 31 to observation (control group). Weighted mean age was 64·5 years (range 49·9–77·6) and mean serum testosterone was 10·9 nmol/ l (range 7·8–19). Testosterone treatment produced: (i) a reduction of 1·6 kg (CI: 2·5–0·6) of total body fat, corresponding to −6·2% (CI: 9·2–3·3) variation of initial body fat, (ii) an increase in fat free mass of 1·6 kg (CI: 0·6–2·6), corresponding to +2·7% (CI: 1·1–4·4) increase over baseline and (iii) no change in body weight. The effects of T on muscle strength were heterogeneous, showing a tendency towards improvement only at the leg/knee extension and handgrip of the dominant arm (pooled effect size = 0·3 standard mean difference (SMD), CI:−0·0 to 0·6). Testosterone improved bone mineral density (BMD) at the lumbar spine by +3·7% (CI: 1·0–6·4%) compared to placebo, but not at the femoral neck, and produced a consistent reduction in bone resorption markers (pooled effect size = −0·6 SMD, CI: −1·0 to −0·2). Testosterone also reduced total cholesterol by 0·23 mmol/ l (CI: −0·37 to −0·10), especially in men with lower baseline T concentrations, with no change in low density lipoprotein (LDL)-cholesterol. A significant reduction of high density lipoprotein (HDL)-cholesterol was found only in studies with higher mean T-values at baseline (−0·085 mmol/l, CI: −0·017 to −0·003). Sensitivity and meta-regression analysis revealed that the dose / type of T used, in particular the possibility of aromatization, explained the heterogeneity in findings observed on bone density and HDL-cholesterol among studies.

Conclusion The present analysis provides an estimate of the average treatment effects of testosterone therapy in middle-aged men. Our findings are sufficiently strong to justify further interventional studies focused on alternative targets of androgenic treatment carrying more stringent clinical implications, in particular the cardiovascular, metabolic and neurological systems.



We evaluated the effects of long-term **testosterone replacement** therapy (TRT) on the bone mineral density (BMD) in obese patients with metabolic syndrome (MS) and late-onset hypogonadism (LOH).

Sixty men (mean age 57 ± 10) with low serum **testosterone** (T < 320 ng/dL) and MS regardless the presence of osteoporosis were enrolled. Forty men received intramuscular T-undecanoate (TU) four times/year for 36 months and 20 age-matched hypogonadal men with MS in whom T treatment was contraindicated were used as controls. Hormonal, biochemical markers, vertebral and femoral BMD by dual-energy x-ray absorptiometry were measured.

At baseline, overall patients had mild osteopenia (lumbar BMD= 0.891 ± 0.097 g/cm(2); femoral BMD= 0.847 ± 0.117 g/cm(2)). TU induced a significant improvement of bone mass after 36 months (lumbar BMD=1.053 ± 0.145 g/cm(2); p < 0.002; femoral BMD=0.989 ±0.109; p < 0.003 g/cm(2)) with a 5%/year increase and a significant reduction in hs-CRP without changes in body mass index. A direct relationship between serum T and BMD increments at the lumbar (r(2) = 0.66, p < 0.0001) and femoral (r(2) =0.52, p < 0.0001) sites was demonstrated. Study adherence was 50% without serious side effects.

Long-term TRT in middle-aged men with LOH and MS determines a significant

increase in both vertebral and femoral BMD related to increased serum T levels, probably independently from estradiol modifications.

Male Hypogonadism: Bone Metabolism

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Table 1 Characteristics and BMD in 167 AD men related to quality of prior testosterone treatment. Data expressed as means±S.E.M.

Variables	Never treated	Partially treated	Well treated	P
n	24	66	77	
Age (years)	43.8±2.7	47.9±1.6	45.7±1.5	0.42
Height (cm)	173.6±2.1	176.2±1.1	174.9±1.1	0.51
Weight (kg)	78.8±4.1	82.9±2.0	84.4±1.1	0.41
BMI (kg/m^2)	25.8±0.9	26.5±0.5	27.4±0.6	0.27
BSA (m^2)	1.9±0.06	2.0±0.03	2.0±0.03	0.42
L1–L4				
BMD	1.115±0.036	1.109±0.041	1.171±0.041	0.510
T-score	−0.78±0.26	−0.70±0.21	0.02±0.16	0.010
Z-score	−0.41±0.27	−0.55±0.13	0.23±0.16	0.022
Femoral neck				
BMD	0.943±0.058	0.905±0.030	0.971±0.018	0.234
T-score	−1.10±0.24	−0.66±0.14	−0.36±0.13	0.025
Z-score	−0.70±0.22	−0.41±0.13	−0.03±0.13	0.019
Ward's triangle				
BMD	0.847±0.092	0.744±0.036	1.019±0.063	0.050
T-score	−1.23±0.32	−0.95±0.20	−0.65±0.17	0.234
Z-score	−0.82±0.25	−0.50±0.16	−0.11±0.13	0.035
Trochanter				
BMD	0.803±0.084	0.755±0.029	0.850±0.026	0.129
T-score	−0.61±0.32	−0.77±0.16	−0.20±0.15	0.051
Z-score	−0.37±0.28	−0.66±0.15	−0.08±0.14	0.031

P values from a one-way ANOVA.

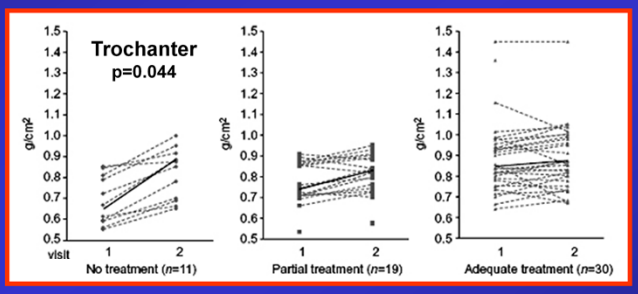


Table 2 Change in bone density between 1st and 2nd DEXA scan according to quality of treatment prior to 1st DEXA scan. Data expressed as means±S.E.M.

	Never treated (*n* = 11)	Partially treated (*n* = 19)	Well treated (*n* = 30)	P
L1–L4				
BMD (% change/year)	2.85±0.82	1.67±0.38	1.31±0.84	0.494
Z-score (% change/year)	−17.05±4.52	−0.30±3.64	−13.41±25.49	0.975
Z-score (final)	0.15±0.51	−0.78±0.28	−0.20±0.19	0.121
Femoral neck				
BMD (% change/year)	1.76±1.11	0.42±0.70	−0.43±0.71	0.372
Z-score (% change/year)	−14.05±10.19	−11.36±3.16	18.92±55.75	0.943
Z-score (final)	−0.20±0.24	−0.72±0.16	0.33±0.21	0.254
Ward's triangle				
BMD (% change/year)	4.35±2.33	0.47±0.80	−1.33±1.03	0.025
Z-score (% change/year)	−20.2±8.42	−11.02±2.99	7.93±37.33	0.991
Z-score (final)	−0.40±0.39	−1.03±0.22	−0.34±0.18	0.065

Well-treated men initially had better bone mass
Untreated men had greater increase with Rx

Objective: Androgen deficiency (AD) leads to bone loss and contributes to osteoporotic fractures in men. Although low bone mineral density (BMD) in AD men is improved by testosterone replacement, the responses vary between individuals but the determinants of this variability are not well defined.

Design and methods: Retrospective review of dual energy X-ray absorptiometry (DEXA) of the lumbar spine and proximal femur in men with established AD requiring regular androgen replacement therapy (ART). After a DEXA scan all men were treated with testosterone implants (800 mg, 6 month intervals). Patients were classified as having a congenital, childhood, or post-pubertal onset, as well as according to the adequacy of treatment prior to their first DEXA scan as untreated, partially treated or well treated.

Results: Men with AD requiring regular ART (n = 169, aged 46.3^1.1 years, range 22–84 years) underwent a DEXA scan prior to being treated with testosterone implants (800 mg, ,6 month intervals). In cross-sectional analysis at the time of the first DEXA scan untreated men (n = 24) had significantly reduced age-adjusted BMD at all four sites (L1–L4, femoral neck, Ward's triangle and trochanter). Well-treated men (n = 77) had significantly better age-adjusted BMD at all four sites compared with those who were partially treated (n = 66) or untreated (n = 24) with their age adjusted BMD being normalized. In a longitudinal assessment of men (n =

60) who had two or more serial DEXA scans, at the second DEXA scan after a median of 3 years, men who were previously partially treated (n = 19) or untreated (n = 11) had proportionately greater improvements in BMD, significantly for Ward's triangle (P = 0.025) and the trochanter (P = 0.044) compared with men (n = 30) previously well treated.

Conclusions: The present study demonstrates a positive relationship between adequacy of testosterone replacement and BMD in men with overt organic AD. Additionally, the BMD of well-treated AD men approximates that of age-matched non-AD controls. The greatest BMD gains are made by those who have been either untreated or partially treated, and optimal treatment over time (median 3 years) normalizes BMD to the level expected for healthy men of the same age.

Male Hypogonadism: Bone Quality

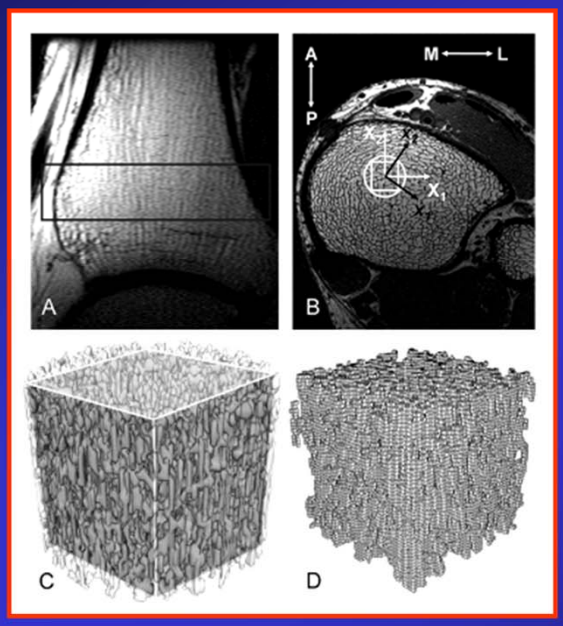


FIG. 1. Anatomic site for MRI-based FE (microfinite element)

(A) Sagittal localizer image of the distal right tibia. The rectangle encompasses the area from which the trans-axial high-resolution image data in B were collected.

(B) The high-resolution cross-sectional image through the tibia, perpendicular to the vertical axis of the image in A, showing the trabecular architecture of the tibial metaphysis. The circle marks the virtual bone biopsy core. The rectangular VOI (volume of interest) indicates the region for which FE analysis was performed. X1, X2, and X3 represent the image coordinate system (with X3 representing the direction perpendicular to the display plane); x1, x2, and x3 represent the new material principal coordinate system calculated from FE analysis.

(C) Cylindrical virtual bone biopsy core with the cubic VOI in the center.

(D) FE mesh for the cubic VOI.

Zhang et al, J Bone Miner Res 23:1426-34, 2008

ABSTRACT: Osteoporosis is a major public health problem in men. Hypogonadal men have decreased BMD and deteriorated trabecular bone architecture compared with eugonadal men. Testosterone treatment improves their BMD and trabecular structure. We tested the hypothesis that testosterone replacement in hypogonadal men would also improve their bone's mechanical properties. Ten untreated severely hypogonadal and 10 eugonadal men were selected. The hypogonadal men were treated with a testosterone gel for 24 mo to maintain their serum testosterone concentrations within the normal range. Each subject was assessed before and after 6, 12, and 24 mo of testosterone treatment by MRI of the distal tibia. A subvolume of each MR image was converted to a microfinite element (FE) model, and six analyses were performed, representing three compression and three shear tests. The anisotropic stiffness tensor was calculated, from which the orthotropic elastic material constants were derived. Changes in microarchitecture were also quantified using newly developed individual trabeculae segmentation (ITS)-based and standard morphological analyses. The accuracy of these techniques was examined with simulated MR images. Significant differences in four estimated anisotropic elastic material constants and most morphological parameters were detected between the eugonadal and hypogonadal men. No significant change in estimated elastic moduli and morphological parameters was detected in the eugonadal group over 24 mo. After 24 mo of treatment, significant increases in estimated elastic moduli E22 (9.0%), E33 (5.1%), G23 (7.2%), and G12 (9.4%) of hypogonadal men were detected. These increases were accompanied by significant increases in trabecular plate thickness. These results suggest that 24 mo

of testosterone treatment of hypogonadal men improves estimated elastic moduli of tibial trabecular bone by increased trabecular plate thickness.

Methods:

VOI images were processed to construct FE models by converting the image voxels representing bone to eight-node brick elements. The bone tissue material properties were chosen as isotropic, linearly elastic with a Young's modulus of 15 GPa, and a Poisson's ratio of 0.3 for all models. Using an element-by-element preconditioned conjugate gradient solver, six analyses were performed for each image, representing three uniaxial compression tests and three uniaxial shear tests.(17,34) The anisotropic stiffness tensor of each VOI was calculated in the original image coordinate system (X1, X2, and X3). Subsequently, the best-fit orthotropic stiffness matrix and the principal directions of the stiffness matrix were calculated by minimizing off diagonal terms, and the compliance matrix was transformed to the new principal coordinate system (x1, x2, and x3; Fig.1,(17) whereas x3 was always in the longitudinal direction of the tibia). Based on the compliance matrix, estimated elastic material constants (three Young's moduli, **E11, E22, E33**, and three shear moduli, **G23, G31, G12**) were calculated. The estimated elastic material constants were sorted such that E11 represented the smallest modulus and E33 the largest(E33 > E22 > E11).

ITS-based morphological analysis was performed.(32) Digital topological analysis (DTA)(35–40) combined with a volumetric reconstruction was used to segment trabecular bone microstructure into individual trabecular plates and rods.(30,32) A series of ITS-based morphological parameters of trabecular bone microstructure were calculated,(32) including

plate bone volume fraction (**pBV/TV**), rod bone volume fraction (**rBV/TV**), trabecular plate and rod number density (**pTb.N** and **rTb.N**, 1/mm), mean trabecular plate thickness (**pTb.Th**, mm), mean trabecular rod thickness (**rTb.Th**, mm), mean trabecular plate surface area (**pTb.S**, mm2), and mean trabecular rod length (**rTb**., mm).

Standard model-independent morphological analyses were also performed using a commercial software package (SCANCO Medical, Bassersdorf, Switzerland). These included

bone volume fraction (**BV/TV**), surface-to-volume ratio (**BS/BV**), mean trabecular number (**Tb.N***, 1/mm), mean trabecular thickness (**Tb.Th***, mm), mean trabecular separation (**Tb.Sp***, mm), and connectivity density (**Conn.D**, 1/mm3). The geometrical degree of anisotropy (**DA**) and structure model index (**SMI**) were also calculated. The SMI is a parameter expressing the plate-likeness of the structure, with 0 for an ideal plate and 3 for an ideal rod structure.(29) DA was defined as the ratio between the maximal and minimal axes of the mean intercept length (MIL) ellipsoid.

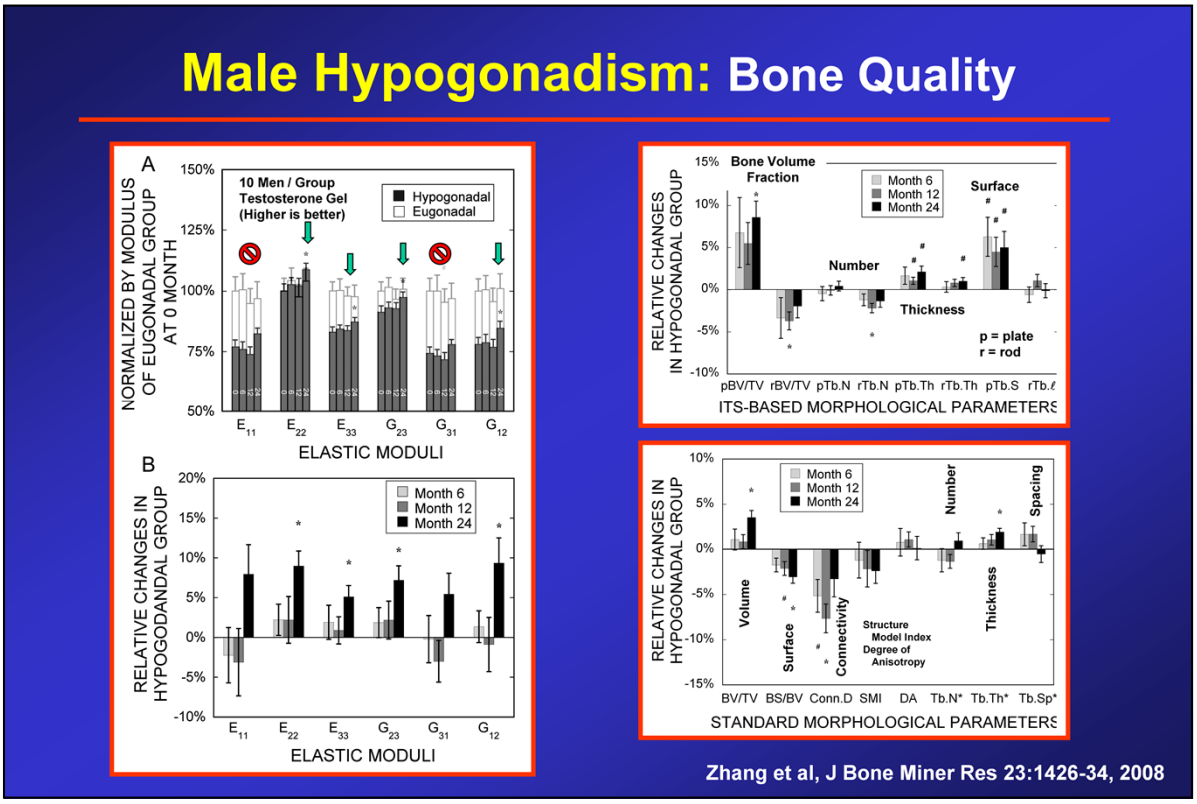


FIG. 2. (A) Normalized elastic moduli of both hypogonadal and eugonadal groups (normalized by the corresponding modulus in the eugonadal group at baseline).

(B) Relative changes in elastic moduli of the hypogonadal group from baseline at 6, 12, and 24 mo of treatment. Values shown are means ± SE. #$p < 0.05$ and *$p < 0.01$ indicate significant difference compared with the baseline.

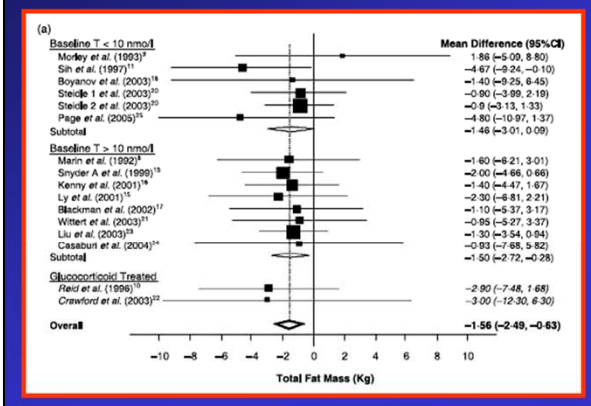
FIG. 3. Changes of ITS-based morphological parameters in the hypogonadal group after 6, 12, and 24 mo of treatment relative to the baseline. Values shown are means ± SE. #$p < 0.05$ and *$p < 0.01$ indicate significant difference compared with the baseline.

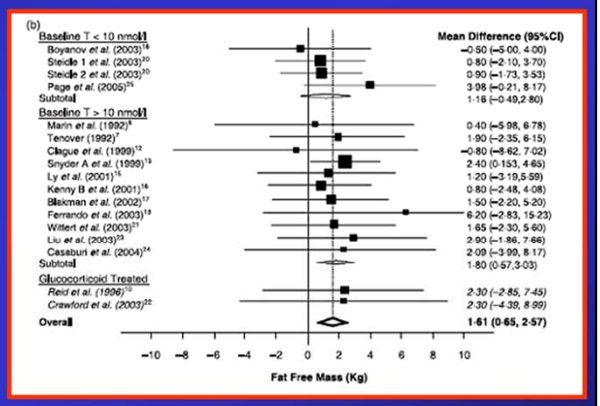
FIG. 4. Changes of standard morphological parameters in the hypogonadal group after 6, 12, and 24 mo of treatment relative to the baseline. Values shown are means ± SE. #$p < 0.05$ and *$p < 0.01$ indicate significant difference compared with the baseline.

Male Hypogonadism

- Sexual Function – Libido, erectile function
- Bone Metabolism
- Muscle Mass & Strength
- Body Composition, Obesity, Insulin Resistance
- Lipoproteins
- Vascular Disease & Atherosclerosis
- Cancer: Prostate, Breast
- Neuro-psychological
- Erythropoiesis
- Skin

Male Hypogonadism: Muscle





Meta-analysis: 1083 men, age 64.5 yrs (50 - 78)
Testo: 314 ng/dl (225 - 547)

Fat Mass reduced (~1.5 kg)
Fat-Free Mass increased (~1.5 kg)

Isidori AM et al. Clinical Endocrinology (2005) 63, 280–293

Objectives Ageing in men is associated with a gradual decline in serum testosterone levels and a concomitant loss of muscle mass, accumulation of central adiposity, impaired mobility and increased risk of bone fractures. Whether androgen treatment might be beneficial in these subjects is still under debate. We have carried out a systematic review of randomized controlled trials (RCTs) evaluating the effects of testosterone (T) administration to middle-aged and ageing men on body composition, muscle strength, bone density, markers of bone metabolism and serum lipid profile.

Data source A comprehensive search of all published randomized clinical trials was performed using the MEDLINE, Cochrane Library, EMBASE and *Current Contents* databases.

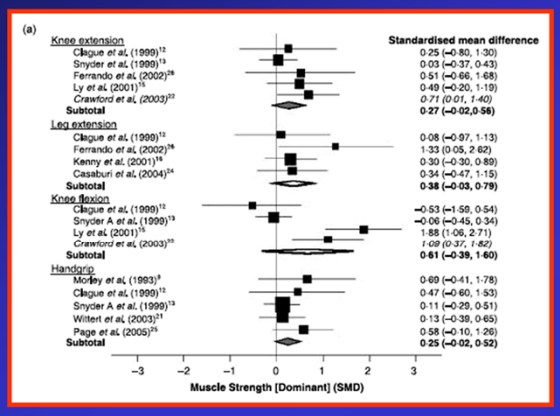
Review methods Guided by prespecified criteria, software-assisted data abstraction and quality assessed by two independent reviewers, 29 RCTs were found to be eligible. For each investigated variable, we reported the results of pooled estimates of testosterone treatment using the random effect model of meta-analysis. Heterogeneity, reproducibility and consistency of the findings across studies were explored using sensitivity and meta-regression analysis.

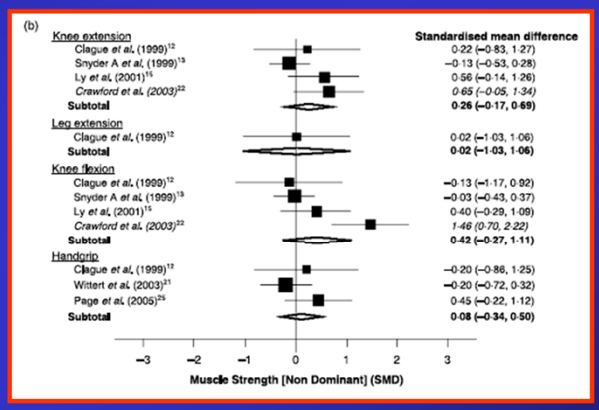
Results Overall, 1083 subjects were evaluated, 625 randomized to T, 427 to

placebo and 31 to observation (control group). Weighted mean age was 64·5 years (range 49·9–77·6) and mean serum testosterone was 10·9 nmol/ l (range 7·8–19). Testosterone treatment produced: (i) a reduction of 1·6 kg (CI: 2·5–0·6) of total body fat, corresponding to −6·2% (CI: 9·2–3·3) variation of initial body fat, (ii) an increase in fat free mass of 1·6 kg (CI: 0·6–2·6), corresponding to +2·7% (CI: 1·1–4·4) increase over baseline and (iii) no change in body weight. The effects of T on muscle strength were heterogeneous, showing a tendency towards improvement only at the leg/knee extension and handgrip of the dominant arm (pooled effect size = 0·3 standard mean difference (SMD), CI:−0·0 to 0·6). Testosterone improved bone mineral density (BMD) at the lumbar spine by +3·7% (CI: 1·0–6·4%) compared to placebo, but not at the femoral neck, and produced a consistent reduction in bone resorption markers (pooled effect size = −0·6 SMD, CI: −1·0 to −0·2). Testosterone also reduced total cholesterol by 0·23 mmol/ l (CI: −0·37 to −0·10), especially in men with lower baseline T concentrations, with no change in low density lipoprotein (LDL)-cholesterol. A significant reduction of high density lipoprotein (HDL)-cholesterol was found only in studies with higher mean T-values at baseline (−0·085 mmol/l, CI: −0·017 to −0·003). Sensitivity and meta-regression analysis revealed that the dose / type of T used, in particular the possibility of aromatization, explained the heterogeneity in findings observed on bone density and HDL-cholesterol among studies.

Conclusion The present analysis provides an estimate of the average treatment effects of testosterone therapy in middle-aged men. Our findings are sufficiently strong to justify further interventional studies focused on alternative targets of androgenic treatment carrying more stringent clinical implications, in particular the cardiovascular, metabolic and neurological systems.

Male Hypogonadism: Muscle





Meta-analysis: 1083 men, age 64.5 yrs (50 - 78)
Testo: 314 ng/dl (225 - 547)

Dominate muscle strength tended to improve
Non-dominate muscle strength was not effected

Young: Improved w/o exercise
Older: Improved only w/ exercise

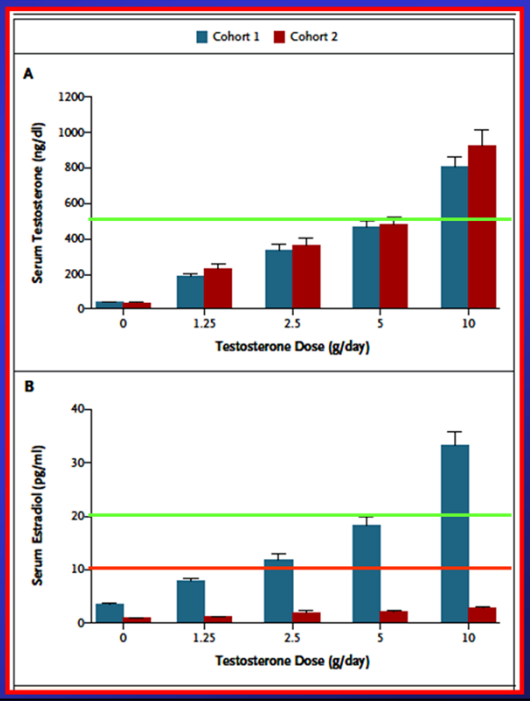
Isidori AM et al. Clinical Endocrinology (2005) 63, 280–293

Male Hypogonadism: Muscle

Gonadal Steroids and Body Composition, Strength, and Sexual Function in Men

Finkelstein et al
NEJM 369(11):1011-22, 2013

400 healthy men – 20 to 50 years → goserelin (suppress endogenous T & E_2)
Replaced: placebo, 1.25 g, 2.5 g, 5 g, or 10 g T gel daily (16 weeks)
Half given aromatase inhibitor (anastrozole)



Background Current approaches to diagnosing testosterone deficiency do not consider the physiological consequences of various testosterone levels or whether deficiencies of testosterone, estradiol, or both account for clinical manifestations.

Methods We provided 198 healthy men 20 to 50 years of age with goserelin acetate (to suppress endogenous testosterone and estradiol) and randomly assigned them to receive a placebo gel or 1.25 g, 2.5 g, 5 g, or 10 g of testosterone gel daily for 16 weeks. Another 202 healthy men received goserelin acetate, placebo gel or testosterone gel, and anastrozole (to suppress the conversion of testosterone to estradiol). Changes in the percentage of body fat and in lean mass were the primary outcomes. Subcutaneous- and intraabdominal-fat areas, thigh-muscle area and strength, and sexual function were also assessed.

Results The percentage of body fat increased in groups receiving placebo or 1.25 g or 2.5 g of testosterone daily without anastrozole (mean testosterone level, 44±13 ng per deciliter, 191±78 ng per deciliter, and 337±173 ng per deciliter, respectively). Lean mass and thigh-muscle area decreased in men receiving placebo and in those receiving 1.25 g of testosterone daily without anastrozole. Leg-press strength fell only with placebo administration. In general, sexual desire declined as the testosterone dose was reduced.

Conclusions The amount of testosterone required to maintain lean mass, fat mass, strength, and sexual function varied widely in men. Androgen deficiency accounted for decreases in lean mass, muscle size, and strength; estrogen deficiency primarily accounted for increases in body fat; and both contributed to the decline in sexual function. Our findings support changes in the approach to evaluation and management of hypogonadism in men.

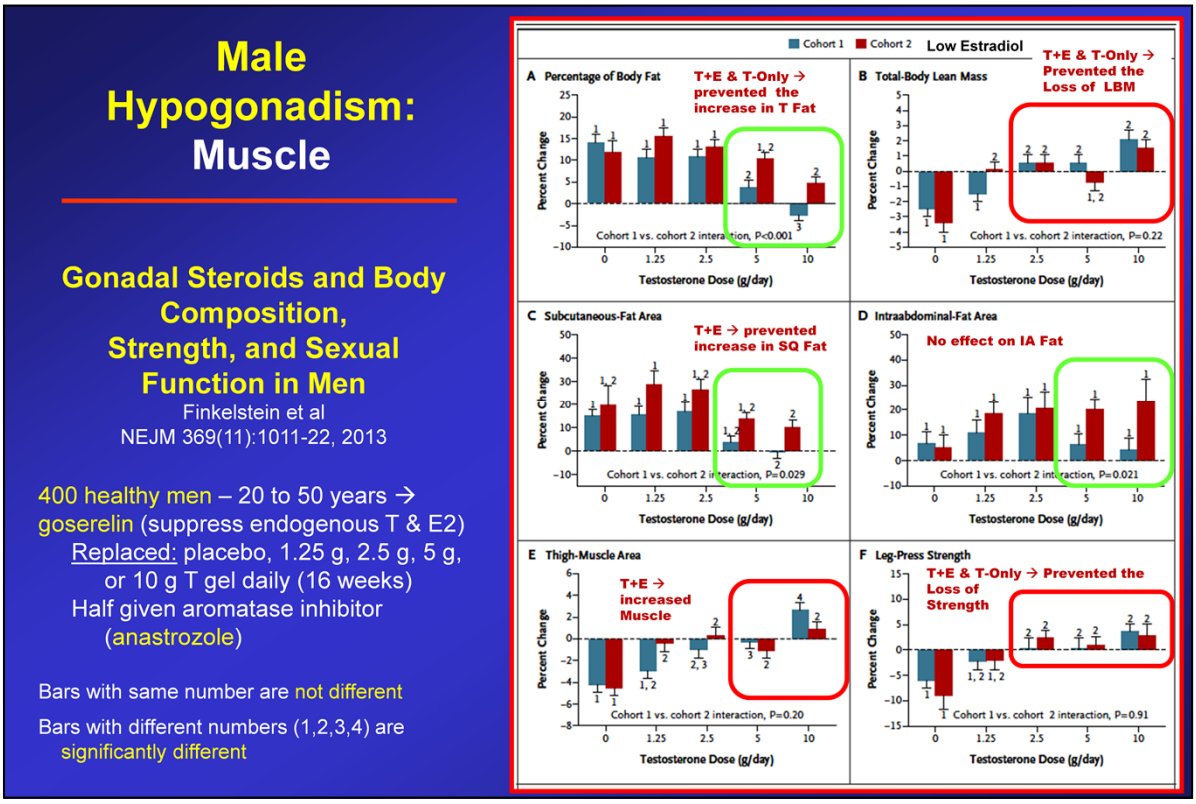


Figure 3. Mean Percent Change from Baseline in Percentage of Body Fat, Lean Body Mass, Subcutaneous- and Intraabdominal-Fat Area, Thigh-Muscle Area, and Leg-Press Strength, According to Testosterone Dose and Cohort.

T bars indicate standard errors. Within each cohort, bars with the same number indicate no significant difference between dose groups. For example, the change in the percentage of body fat (Panel A) did not differ significantly among the groups that received 0 g, 1.25 g, or 2.5 g of testosterone daily in cohort 1 (all labeled “1”). The change in each of those three groups differed significantly from the change in the group that received 5 g per day (labeled “2”) and the change in the group that received 10 g per day (labeled “3”), and the change also differed significantly between these latter two groups. P values are for the cohort–testosterone dose interaction terms in analyses of variance comparing changes in each outcome measure between cohorts 1 and 2.

Male Hypogonadism

- Sexual Function – Libido, erectile function
- Bone Metabolism
- Muscle Mass & Strength
- Body Composition, Obesity, Insulin Resistance
- Lipoproteins
- Vascular Disease & Atherosclerosis
- Cancer: Prostate, Breast
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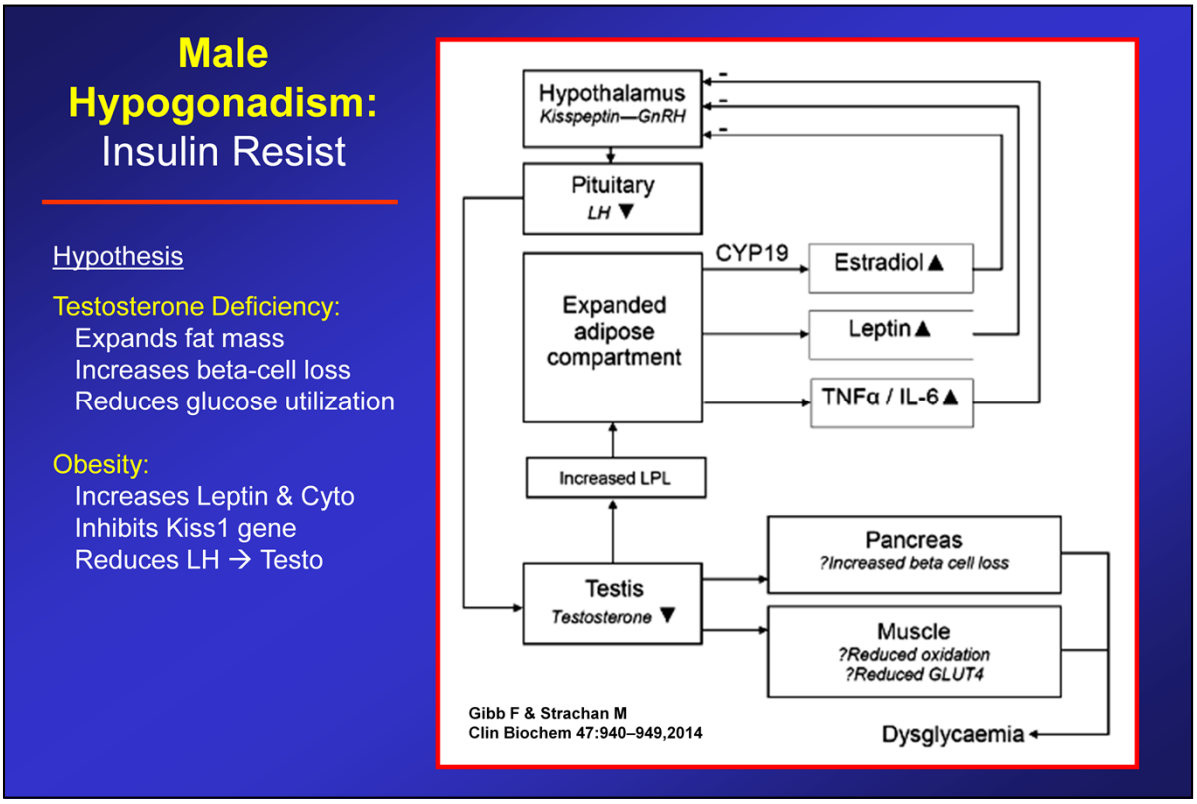


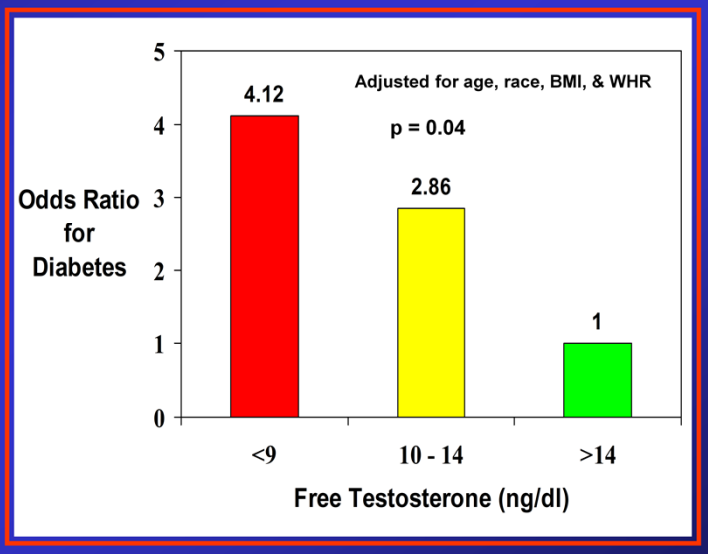
The rising incidence of T2DM is well recognised and associated with trends in obesity and ageing. It is estimated that 2.8% of the world population had a diagnosis of diabetes mellitus in 2000, which is projected to rise to 4.3% by 2030. Diabetes, obesity and ageing are also associated with an increased risk of isolated male hypogonadotropic hypogonadism, often labelled 'late onset hypogonadism' (LOH) to distinguish it from hypogonadism secondary to distinct hypothalamo-pituitary pathology. Whether the incidence of hypogonadism is increasing is open to question; the past decade, however, has witnessed a marked increase in the prescription of testosterone replacement therapy. Testosterone deficiency appears to be particularly common in type 2 diabetes with a prevalence of 33% observed in one cohort of 103 men (mean age 54.7). However, the diagnosis of androgen deficiency states is not necessarily straightforward, depending amongst other factors, upon whether a biochemical threshold or a syndromic approach (mandating the presence of certain key clinical features) is employed. The pathogenic mechanisms underlying obesity and diabetes related hypogonadism remain unclear with several competing theories, most of which are not mutually exclusive. Whilst a large body of epidemiological evidence associates testosterone deficiency with increased risk of cardiovascular disease and mortality, little evidence exists to support a protective effect of testosterone replacement. The benefits of androgen replacement in younger men with pituitary disease are well established, however, the potential benefits and safety of androgen replacement in older men is much less well developed. At present, replacement therapy in older men is advocated principally for the amelioration of sexual symptoms. This review will seek to

explore issues around the pathogenesis, diagnosis, clinical consequences and management of male hypogonadism as it relates to T2DM.

Male Hypogonadism: Insulin Resist

NHANES III:
Men >19 years

	DM	non-DM
Number:	101	1,312
Age:	42	57
BMI:	26.2	29.5



Diabetes Care 30:234–238, 2007

OBJECTIVE— Low levels of androgens in men may play a role in the development of diabetes; however, few studies have examined the association between androgen concentration and diabetes in men in the general population. The objective of this study is to test the hypothesis that low normal levels of total, free, and bioavailable testosterone are associated with prevalent diabetes in men.

RESEARCH DESIGN AND METHODS— The study sample included 1,413 adult men aged 20 years who participated in the morning session of the first phase of the Third National Health and Nutrition Examination Survey, a cross-sectional survey of the civilian, noninstitutionalized population of the U.S. Bioavailable and free testosterone levels were calculated from serum total testosterone, sex hormone–binding globulin, and albumin concentrations.

RESULTS— In multivariable models adjusted for age, race/ethnicity, and adiposity, men in the first tertile (lowest) of free testosterone level were four times more likely to have prevalent diabetes compared with men in the third tertile (odds ratio 4.12 [95% CI 1.25–13.55]). Similarly, men in the first tertile of bioavailable testosterone also were approximately four times as likely to have prevalent diabetes compared wth men in the third tertile (3.93 [1.39 –11.13]). These associations persisted even after excluding men with clinically abnormal testosterone concentrations defined as total testosterone 3.25 ng/ml or free testosterone 0.07 ng/ml. No clear association

was observed for total testosterone after multivariable adjustment (*P* for trend across tertiles 0.27).

CONCLUSIONS— Low free and bioavailable testosterone concentrations in the normal range were associated with diabetes, independent of adiposity. These data suggest that low androgen levels may be a risk factor for diabetes in men.

Male Hypogonadism: Insulin Resist

Table 4—*Adjusted* OR (95% CI) of diabetes by tertiles of sex steroid hormone concentrations after mutually adjusting the hormones, NHANES III*

	Q1 (lowest)	Q2	Q3 (highest)	*P* trend
Total testosterone (ng/ml) (≤4.54, 4.55–6.27, >6.27)	1.99 (0.76–5.19)	0.64 (0.15–2.65)	1.00 (reference)	0.014
Estradiol (E2) (pg/ml) (≤31.90, 31.91–40.26, >40.26)	0.71 (0.24–2.07)	0.99 (0.29–3.33)	1.00 (reference)	0.33
SHBG (nmol/l) (≤28.03, 28.04–43.50, >43.50)	0.48 (0.20–1.18)	0.76 (0.35–1.63)	1.00 (reference)	0.32

*Simultaneously adjusted for age, race/ethnicity, BMI, waist-to-hip ratio, and the other two hormones.

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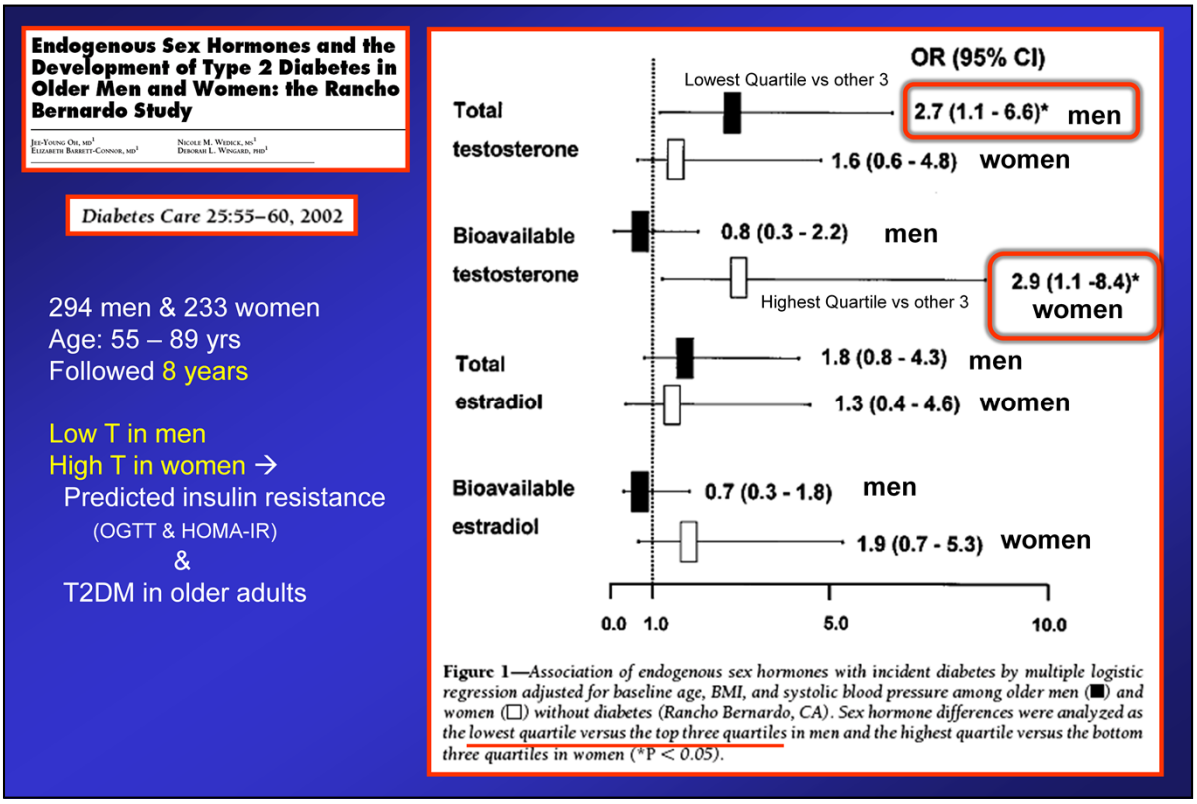
***Diabetes Care* 30:234–238, 2007**



OBJECTIVE— To determine the prospective association between endogenous sex hormones and the development of type 2 diabetes in older men and women.

RESEARCH DESIGN AND METHODS— A standardized medical history was obtained, an oral glucose tolerance test was performed, and plasma samples for sex hormones and covariates were collected from ambulatory, community-dwelling men and women at baseline from 1984 to 1987. Approximately 8 years later (1992–1996), another medical history was obtained, an oral glucose tolerance test was performed, fasting and 2-h insulin levels were measured, and the homeostasis model assessment for insulin resistance (HOMA-IR) was evaluated. This report is based on the 294 men and 233 women, aged 55–89 years, who completed both visits and who did not have diabetes as determined by history or glucose tolerance test at baseline, as well as women who were postmenopausal and not taking replacement estrogen.

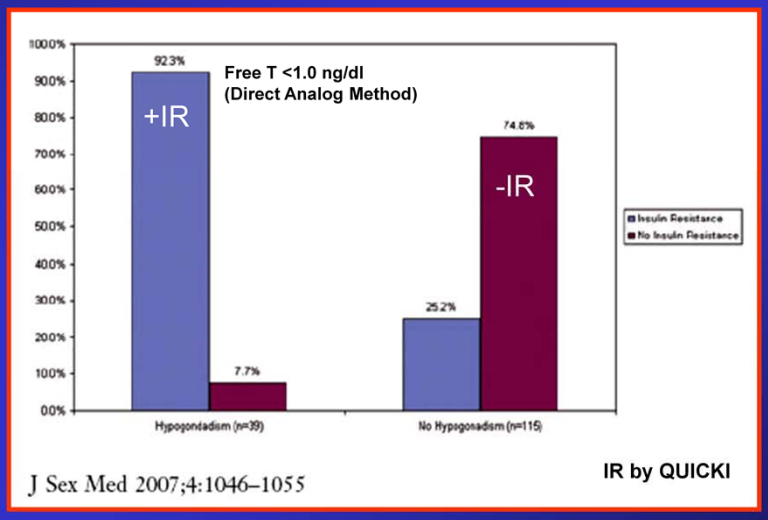
RESULTS— In age-adjusted correlation analyses, total testosterone was inversely and significantly related to subsequent levels of fasting and post-challenge glucose and insulin in men, whereas bioavailable testosterone and bioavailable estradiol were positively and significantly related to fasting and post-challenge glucose and insulin in women (all *P* 0.05). There was similar significant association with insulin resistance (HOMA-IR) in unadjusted and multiply adjusted analyses (*P* 0.05). There

were 26 men and 17 women with new (incident) diabetes. The odds for new diabetes were 2.7 (95% CI 1.1– 6.6) for men in the lowest quartile of total testosterone and 2.9 (1.1– 8.4) for women in the highest quartile of bioavailable testosterone.

CONCLUSIONS— Low testosterone levels in men and high testosterone levels in women predict insulin resistance and incident type 2 diabetes in older adults.

Male Hypogonadism: Insulin Resist

Men referred for ED → Hypogonadal men had much higher risk of IR



Introduction. Erectile dysfunction (ED) in men increases with age, as does cardiovascular disease (CVD). Major risk factors of CVD are similar to ED, including insulin resistance (IR) and metabolic syndrome (MS). Hypogonadism has been associated with MS and IR in general populations.

Aim. To determine the association between hypogonadism and MS and/or IR in men with ED, and to determine if hypogonadism is related to these cardiovascular (CV) risks.

Main Outcome Measures. To compare the mean testosterone levels in men with and without IR and MS, and to show the difference in hypogonadism prevalence in mutually exclusive definitions of MS.

Methods. Mean testosterone for the National Cholesterol Education Program (NCEP) and the World Health Organization (WHO) criteria of MS were calculated using independent *t*-tests. Multiple range *t*-tests were used to compare and contrast four groups: (i) only NCEP-Third Adult Treatment Panel criteria; (ii) only the WHO criteria; (iii) men with no MS; and (iv) men fulfilling both MS definitions. Chi-squared analysis was employed to determine the association of hypogonadism with IR.

Results. The prevalence of IR was 79% and of MS was 35 % by the WHO but 43% by the NCEP. Differences in point prevalences were negligible when mutually exclusive groups of MS were compared. Mean free testosterone was lower for the WHO MS or the WHO and NCEP MS ($P = 0.04$) but not for only the NCEP MS criteria. IR was significantly associated with low free testosterone and hypogonadism ($P = 0.02$ for each). If more than one criteria were present for either the WHO or NCEP MS, free testosterone was lower ($P = 0.02$).

Conclusion. MS and IR are strongly associated with lower testosterone and hypogonadism. The WHO criteria are a more sensitive indicator of MS and may predict ED better. Men with ED should not only have CV risks evaluated, but should also have testosterone levels drawn.

Guay A, and Jacobson J. The relationship between testosterone levels, the metabolic syndrome (by two criteria), and insulin resistance in a population of men with organic erectile dysfunction. J Sex Med 2007;4:1046–1055.

Male Hypogonadism: Insulin Resist

Naharci et al, Endocr Pract 13:629, 2007

Table 1
Pretreatment Anthropometric, Hormonal, and Metabolic Values in 24 Male Patients With Idiopathic Hypogonadotropic Hypogonadism and 20 Male Control Subjects*

Variable	IHH	Control subjects	*P* value
Age (yr)	20.75 ± 0.74	21.05 ± 0.83	NS
Body weight (kg)	62.94 ± 8.81	61.70 ± 5.90	NS
Body mass index (kg/m^2)	20.93 ± 2.12	20.81 ± 2.08	NS
Body fat mass (%)	26.55 ± 6.51	12.75 ± 4.44	<0.0001
Body mass without fat (%)	73.45 ± 6.51	87.25 ± 4.44	<0.0001
Total testosterone (ng/mL)	1.66 ± 0.37	5.07 ± 1.16	<0.0001
Free testosterone (pg/mL)	2.83 ± 1.24	22.42 ± 4.09	<0.0001
Estradiol (pg/mL)	4.52 ± 2.45	30.26 ± 2.55	<0.0001
SHBG (nmol/L)	30.22 ± 6.42	20.53 ± 4.60	<0.0001
Fasting plasma glucose (mg/dL)	85.17 ± 6.91	75.30 ± 4.99	<0.0001
Fasting plasma insulin (µU/mL)	25.61 ± 8.36	13.44 ± 4.27	<0.0001
HOMA-IR (I×G/405)	5.41 ± 1.96	2.54 ± 0.95	<0.0001
QUICKI (1/log I+log G)	0.30 ± 0.01	0.34 ± 0.02	<0.0001

Objective: To assess the presence of insulin resistance (IR) among a homogeneous cohort of male patients with idiopathic hypogonadotropic hypogonadism (IHH) and to investigate the effects of testosterone therapy on IR in this specific group.

Methods: Twenty-four male patients with untreated IHH and 20 age-, sex-, and weight-matched eugonadal healthy control subjects were recruited for the study. Plasma glucose, plasma insulin, total and free testosterone, follicle-stimulating hormone, luteinizing hormone, estradiol, and sex hormone-binding globulin levels were measured in fasting blood samples, and biochemical and hormonal analyses were performed for all study participants. IR was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR) formula and the quantitative insulin sensitivity check index (QUICKI). Body mass index was calculated by weighing and measuring the heights of all study participants at the beginning of the investigation. Body fat mass and body lean mass were calculated as percentages of body weight by bioelectrical impedance analysis of body composition. Sustanon 250 (a combination of 4 testosterones) was administered intramuscularly once every 3 weeks for 6 months to male patients with IHH after a basal anthropometric, biochemical, and hormonal evaluation. The response to therapy was monitored by regular clinical examinations and serum testosterone measurements. After 6 months of testosterone treatment, the entire anthropometric, biochemical, and hormonal evaluation was repeated 14 days after the last injection of testosterone.

Results: Before treatment, male patients with IHH had higher fasting plasma glucose concentrations, higher fasting plasma insulin levels, a higher HOMA-IR score, and a lower QUICKI when compared with the control group. After testosterone treatment in the patient group, the HOMA-IR score decreased dramatically to the level in the control group. The high body fat mass of the male patients with IHH was reduced significantly after testosterone treatment, concomitant with significant increases in body mass index and body lean mass.

Conclusion: Insulin sensitivity improves and body fat mass decreases with long-term testosterone replacement therapy. (**Endocr Pract. 2007;13:629-635)**

Male Hypogonadism: Insulin Resist

Naharci et al, Endocr Pract 13:629, 2007

Table 3
Changes in Anthropometric, Hormonal, and Metabolic Values in 24 Male Patients With Idiopathic Hypogonadotropic Hypogonadism From Baseline to After 6 Months of Testosterone Therapy in Comparison With 20 Control Subjects*

Age ~21 years – Primary Hypogonadism → Induced puberty w/ IM Testo

Variable	IHH (N = 24) Baseline	IHH (N = 24) 6 mo	*P*	Control subjects (N = 20)
Body weight (kg)	62.94 ± 8.81	69.38 ± 8.67	<0.0001	61.70 ± 5.90
Body mass index (kg/m²)	20.93 ± 2.12	22.58 ± 1.95	<0.0001	20.81 ± 2.08
Body fat mass (%) →	26.55 ± 6.51	11.13 ± 4.25	<0.0001	12.75 ± 4.44
Body mass without fat (%) →	73.45 ± 6.51	88.88 ± 4.25	<0.0001	87.25 ± 4.44
Total testosterone (ng/mL) →	1.66 ± 0.37	4.37 ± 0.93	<0.0001	5.07 ± 1.16
Free testosterone (pg/mL)	2.83 ± 1.24	21.57 ± 3.46	<0.0001	22.42 ± 4.09
Estradiol (pg/mL)	4.52 ± 2.45	26.70 ± 4.70	<0.0001	30.26 ± 2.55
SHBG (nmol/L)	30.22 ± 6.42	18.47 ± 4.26	<0.0001	20.53 ± 4.60
Fasting plasma glucose (mg/dL)	85.17 ± 6.91	77.75 ± 7.09	<0.0001	75.30 ± 4.99
Fasting plasma insulin (μU/mL) →	25.61 ± 8.36	11.24 ± 3.98	<0.0001	13.44 ± 4.27
HOMA-IR (I×G/405) →	5.41 ± 1.96	2.21 ± 0.86	<0.0001	2.54 ± 0.95
QUICKI (1/log I+log G)	0.30 ± 0.01	0.34 ± 0.02	<0.0001	0.34 ± 0.02

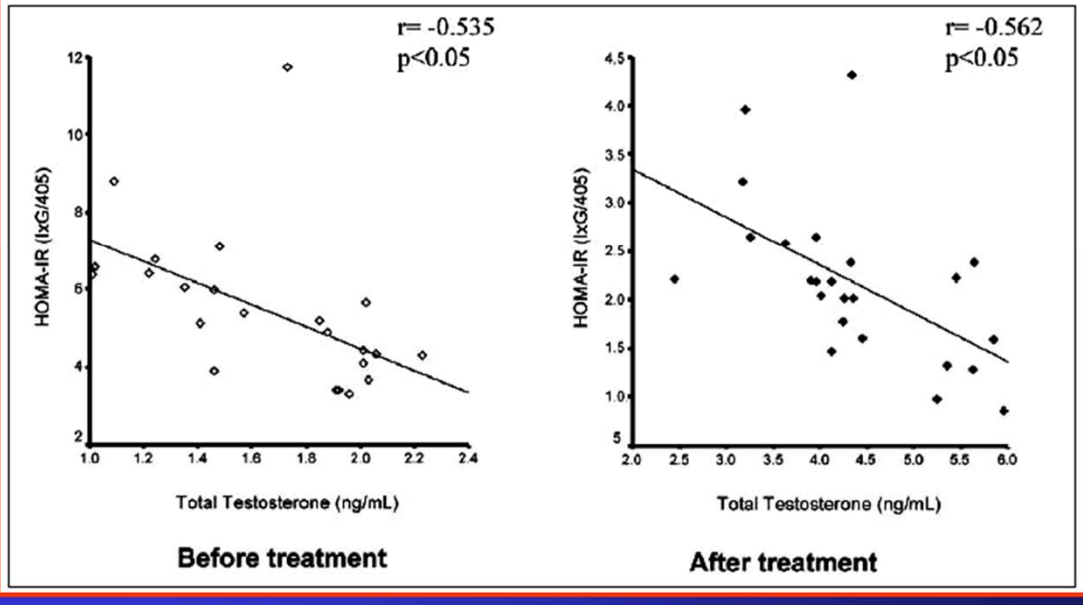
Objective: To assess the presence of insulin resistance (IR) among a homogeneous cohort of male patients with idiopathic hypogonadotropic hypogonadism (IHH) and to investigate the effects of testosterone therapy on IR in this specific group.

Methods: Twenty-four male patients with untreated IHH and 20 age-, sex-, and weight-matched eugonadal healthy control subjects were recruited for the study. Plasma glucose, plasma insulin, total and free testosterone, follicle-stimulating hormone, luteinizing hormone, estradiol, and sex hormone-binding globulin levels were measured in fasting blood samples, and biochemical and hormonal analyses were performed for all study participants. IR was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR) formula and the quantitative insulin sensitivity check index (QUICKI). Body mass index was calculated by weighing and measuring the heights of all study participants at the beginning of the investigation. Body fat mass and body lean mass were calculated as percentages of body weight by bioelectrical impedance analysis of body composition. Sustanon 250 (a combination of 4 testosterones) was administered intramuscularly once every 3 weeks for 6 months to male patients with IHH after a basal anthropometric, biochemical, and hormonal evaluation. The response to therapy was monitored by regular clinical examinations and serum testosterone measurements. After 6 months of testosterone treatment, the entire anthropometric, biochemical, and hormonal evaluation was repeated 14 days after the last injection of testosterone.

Results: Before treatment, male patients with IHH had higher fasting plasma glucose concentrations, higher fasting plasma insulin levels, a higher HOMA-IR score, and a lower QUICKI when compared with the control group. After testosterone treatment in the patient group, the HOMA-IR score decreased dramatically to the level in the control group. The high body fat mass of the male patients with IHH was reduced significantly after testosterone treatment, concomitant with significant increases in body mass index and body lean mass.

Conclusion: Insulin sensitivity improves and body fat mass decreases with long-term testosterone replacement therapy. (**Endocr Pract. 2007;13:629-635)**

Male Hypogonadism: Insulin Resist



Naharci et al, Endocr Pract 13:629, 2007

Effect of 12 mths of Testosterone Therapy on Metabolic Syndrome Components in Hypogonadal Men (Testim Registry in the US)

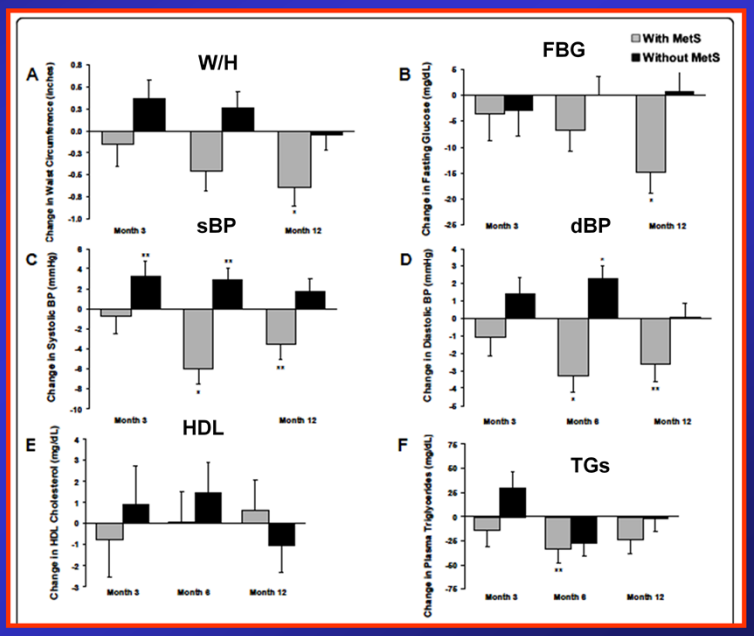
581 Men: +MS v -MS
Mean ~52 yrs (20-85)
FBS: 118 v 97 mg/dl
sBP: 134 v 123
HDL: 38 v 48
TG: 212 v 141

CVD: 27% v 15%
DM: 25% v 5%

Testosterone Gel
~90% Compliant

Initial TT: 260 v 315
12 mth TT: 487 v 512

Bhattacharya et al; BMC Endo Disorders 11:18, 2011



Background: Recent evidence suggests that there may be a bidirectional, physiological link between hypogonadism and metabolic syndrome (MetS), and testosterone replacement therapy (TRT) has been shown to improve some symptoms of MetS in small patient populations. We examined the effect of 12 months of TRT on MetS components in a large cohort of hypogonadal men.

Methods: Data were obtained from TRiUS (Testim® Registry in the United States), a 12-month, multicenter, prospective observational registry (N = 849) of hypogonadal men prescribed Testim 1% testosterone gel (5-10 g/day). Data analyzed included age, total testosterone (TT), free testosterone (FT), sex hormone-binding globulin (SHBG), and MetS components: waist circumference, blood pressure, fasting blood glucose, plasma triglycerides, and HDL cholesterol.

Results: Of evaluable patients (581/849) at baseline, 37% were MetS+ (n = 213) and 63% were MetS- (n = 368). MetS+ patients had significantly lower TT ($p < 0.0001$) and SHBG ($p = 0.01$) levels. Patients with the lowest quartile TT levels (<206 ng/dL [<7.1 nmol/L]) had a significantly increased risk of MetS+ classification vs those with highest quartile TT levels (≥331 ng/dL [≥11.5 nmol/L]) (odds ratio 2.66; 95% CI, 1.60 to 4.43). After 12 months of TRT, TT levels significantly increased in all patients ($p < 0.005$). Despite having similar TT levels after TRT, only MetS+ patients demonstrated significant decreases in waist circumference, fasting blood

glucose levels, and blood pressure; lowest TT quartile patients demonstrated significant decreases in waist circumference and fasting blood glucose. Neither HDL cholesterol nor triglyceride levels changed significantly in either patient population.

Conclusion: Hypogonadal MetS+ patients were more likely than their MetS- counterparts to have lower baseline TT levels and present with more comorbid conditions. MetS+ patients and those in the lowest TT quartile showed improvement in some metabolic syndrome components after 12 months of TRT. While it is currently unclear if further cardiometabolic benefit can be seen with longer TRT use in this population, testing for low testosterone may be warranted in MetS+ men with hypogonadal symptoms.

Male Hypogonadism: Diabetes

24 older, obese men w/ T2DM treated with a variety of DM therapies
- Serum Testosterone < 335 ng/dl
- DBPC cross-over study
- IM Testosterone 200 mg q2 weeks for 3 months

Table 1 Baseline characteristics of whole population. European Journal of Endocrinology (2006) 154 899–906

Parameter		Mean ± S.E.M.	Sample range
Age (years)		64 ± 1.34	52–76
Total testosterone (nmol/l)	(249: 67 – 335 ng/dl)	8.63 ± 0.51	2.34–11.62
SHBG (nmol/l)		27.37 ± 2.59	11.67–63.45
Bioavailable testosterone (nmol/l)		2.73 ± 0.18	0.6–4
FSH (U/l)		12.95 ± 2.6	2.9–58.1
LH (U/l)		7.63 ± 1.1	2.2–24.7
PSA (μg/l)		1.35 ± 0.23	0.09–3.91
BMI		33 ± 0.86	26.4–45
Waist circumference (cm)		115.1 ± 2.4	97.5–141
Waist/hip ratio		1.02 ± 0.01	0.9–1.14
HbA1c (%)		7.28 ± 0.19	5.8–9.4

Objective: Low levels of testosterone in men have been shown to be associated with type 2 diabetes, visceral adiposity, dyslipidaemia and metabolic syndrome. We investigated the effect of testosterone treatment on insulin resistance and glycaemic control in hypogonadal men with type 2 diabetes.

Design: This was a double-blind placebo-controlled crossover study in 24 hypogonadal men (10 treated with insulin) over the age of 30 years with type 2 diabetes.

Methods: Patients were treated with i.m. testosterone 200 mg every 2 weeks or placebo for 3 months in random order, followed by a washout period of 1 month before the alternate treatment phase. The primary outcomes were changes in fasting insulin sensitivity (as measured by homeostatic model index (HOMA) in those not on insulin), fasting blood glucose and glycated haemoglobin. The secondary outcomes were changes in body composition, fasting lipids and blood pressure. Statistical analysis was performed on the delta values, with the treatment effect of placebo compared against the treatment effect of testosterone.

Results: Testosterone therapy reduced the HOMA index (-1.73±0.67, P=0.02, n=14), indicating an improved fasting insulin sensitivity. Glycated haemoglobin was also reduced (-0.37±0.17%, P=0.03), as was the fasting blood glucose (-1.58±0.68

mmol/l, P=0.03). Testosterone treatment resulted in a reduction in visceral adiposity as assessed by waist circumference (-1.63±0.71 cm, P=0.03) and waist/hip ratio (-0.03±0.01, P=0.01). Total cholesterol decreased with testosterone therapy (-0.4±0.17 mmol/l, P=0.03) but no effect on blood pressure was observed.

Conclusions: Testosterone replacement therapy reduces insulin resistance and improves glycaemic control in hypogonadal men with type 2 diabetes. Improvements in glycaemic control, insulin resistance, cholesterol and visceral adiposity together represent an overall reduction in cardiovascular risk.

Male Hypogonadism: Diabetes

Table 3 Comparison of the effects of placebo and testosterone on insulin sensitivity, glycaemic control, lipid profile, body composition and blood pressure in type 2 diabetic men.

European Journal of Endocrinology (2006) **154** 899–906

	Placebo		Testosterone		Analysis of the difference: testosterone vs placebo (delta)		
Parameter	Baseline	Post-treatment	Baseline	(nadir) Post-treatment	Mean effect	*P*	95% confidence intervals
Total testosterone (nmol/l)	8.14±0.59	8.38±0.58	8.83±0.55	12.79±0.79 (368 ng/dl)	3.7±0.93	**0.001**	1.8 to 5.6
Bioavailable testosterone (nmol/l)	2.59±0.18	2.65±0.17	2.75±0.17	3.8±0.23	1.09±0.28	**0.001**	0.51 to 1.67
Fasting insulin (mIU/l)*	12.37±1.87	12.36±2.13	13.68±1.95	11.76±1.76	−1.9±1.1	0.1	0.49 to −4.3
Fasting glucose (mmol/l)	7.6±0.43	8.73±0.61	7.83±0.49	7.38±0.37	−1.58±0.68	**0.03**	−0.17 to −2.99
Total cholesterol (mmol/l)	4.95±0.15	5.07±0.17	5.11±0.17	4.83±0.2	−0.4±0.17	**0.03**	−0.04 to −0.75
HDL cholesterol (mmol/l)	1.04±0.04	1.02±0.04	1.02±0.04	0.97±0.04	−0.03±0.04	0.3	−0.11 to 0.04
LDL cholesterol (mmol/l)†	2.64±0.16	2.81±0.17	2.79±0.15	2.74±0.18	−0.23±0.15	0.2	−0.55 to 0.1
Triglyceride (mmol/l)	2.7±0.2	2.76±0.26	2.9±0.25	2.56±0.26	−0.4±0.3	0.2	−1.03 to 0.23
% Body fat	33.73±1.04	33.14±1.09	33.79±1.13	32.77±1.1	−0.85±0.55	0.1	−1.99 to 0.29
BMI	32.85±0.88	32.97±0.95	33.28±0.92	33.62±0.91	0.23±0.21	0.3	−0.2 to 0.66
Fat free mass	66.99±2.17	67.66±2.24	67.08±2.17	68.31±2.14	0.56±0.76	0.4	−1.01 to 2.13
Systolic blood pressure (mm Hg)‡	131±3.1	127.5±2.9		127.6±2.8	0.43±2.7	0.8	−5.18 to 6.05
Diastolic blood pressure (mm Hg)§	74±1.4	72.7±1.7		72.6±1.5	0.26±1.5	0.8	−2.7 to 3.2

Male Hypogonadism: Diabetes

European Journal of Endocrinology (2006) 154 899–906

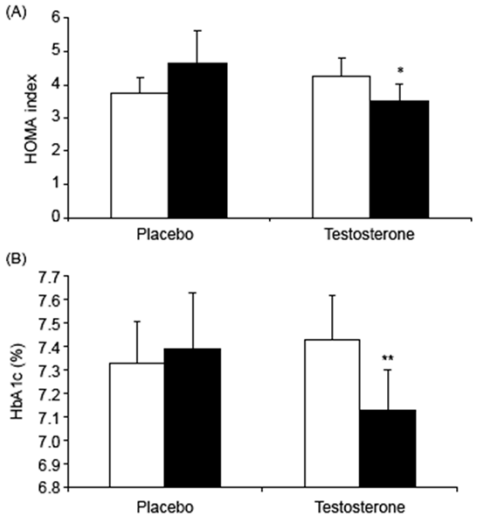


Figure 1 Effect of testosterone replacement compared to placebo on (A) HOMA index and (B) HbA1c. White, baseline; black, after 3 months of treatment (mean±S.E.M.) *P=0.02, **P=0.03.

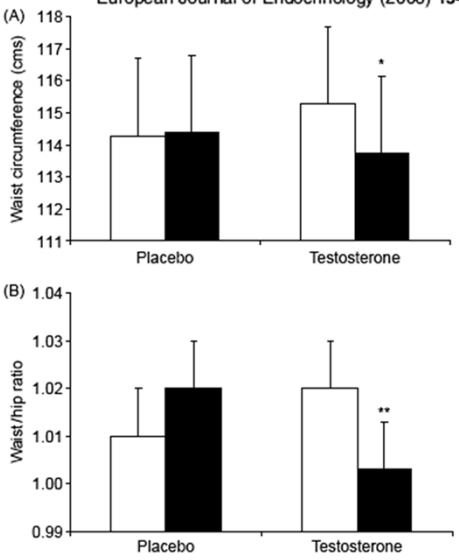


Figure 2 Effect of testosterone replacement compared to placebo on (A) waist circumference and (B) waist/hip ratio (mean±S.E.M.) *P=0.03, **P=0.01 vs placebo.

Testosterone Replacement in Hypogonadal Men with Type 2 Diabetes and/or Metabolic Syndrome (TIMES2 Study)

220 Men (Europe) – 118 Completed
Multi-Center, Randomized, D-B, Plac-Cont
Mean ~60 yrs (37-88)

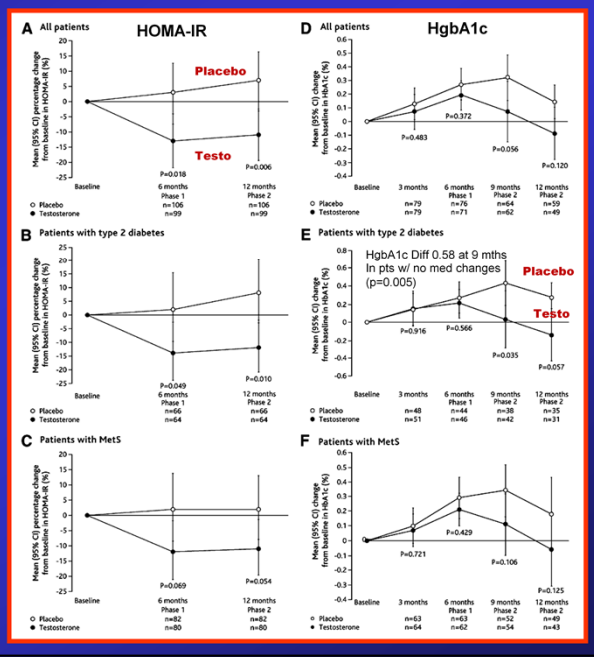
Testosterone Patch:
Phase 1 – no med changes
Phase 2 – DM meds adjusted

Initial TT: 271 (63 – 593) ng/dl
FT: 5.7 (1.0 – 10.4) ng/dl
TT Increased by 547 ng/dl at 6 mths

Waist Circum improved in DM
FBG, Insulin, HOMA-B, BP: no change
MetS: LDL (-9%), Lp(a) (-16%), & HDL (-6%)

Sexual Function Improved
CV Events: P 10.7% v T 4.6%
MI: one in Placebo group

PSA & Hct: no difference
Hgb: +1.42 v +0.06 g/dl



Jones et al; Diabetes Care 34:828–837, 2011

OBJECTIVE—This study evaluated the effects of testosterone replacement therapy (TRT) on insulin resistance, cardiovascular risk factors, and symptoms in hypogonadal men with type 2 diabetes and/or metabolic syndrome (MetS).

RESEARCH DESIGN ANDMETHODS—The efficacy, safety, and tolerability of a novel transdermal 2% testosterone gel was evaluated over 12 months in 220 hypogonadal men with type 2 diabetes and/or MetS in a multicenter, prospective, randomized, double-blind, placebo controlled study. The primary outcome was mean change from baseline in homeostasis model assessment of insulin resistance (HOMA-IR). Secondary outcomes were measures of body composition, glycemic control, lipids, and sexual function. Efficacy results focused primarily on months 026 (phase 1; no changes in medication allowed). Medication changes were allowed in phase 2 (months 6212).

RESULTS—TRT reduced HOMA-IR in the overall population by 15.2% at 6 months (P = 0.018) and 16.4% at 12 months (P = 0.006). In type 2 diabetic patients, glycemic control was significantly better in the TRT group than the placebo group at month 9 (HbA1c: treatment difference, 20.446%; P = 0.035). Improvements in total and LDL cholesterol, lipoprotein a (Lp(a)), body composition, libido, and sexual function occurred in selected patient groups. There were no significant differences between groups in the frequencies of adverse events (AEs) or serious AEs. The

majority of AEs (.95%) were mild or moderate.

CONCLUSIONS—Over a 6-month period, transdermal TRT was associated with beneficial effects on insulin resistance, total and LDL-cholesterol, Lpa, and sexual health in hypogonadal men with type 2 diabetes and/or MetS.

Male Hypogonadism: Cytokines

European Journal of Endocrinology (2007) **156** 595–602

20 Diabetic Men
Double-blind, cross-over 3 months
Testo: 200 mg IM every 2wks

Testo increases IGF-1 (JCEM 77:776, 1993)

Table 1 Baseline characteristics of the population.

Parameter	Mean ± S.E.M.	Sample range
Age (years)	63.15 ± 1.5	52–76
Total testosterone (nmol/l)	7.54 ± 0.55	2.78–10.7
Sex hormone-binding globulin (nmol/l)	27.01 ± 2.89	11.67–63.45
Bioavailable testosterone (nmol/l)	2.48 ± 0.19	0.84–3.87
Leptin (pg/ml)	17 774.27 ± 1971	5366–36 357
Adiponectin (ng/ml)	8468.63 ± 1392	1163–23 209
Resistin (ng/ml)	20.59 ± 1.66	8.75–35.66
TNF-α (pg/ml)	2.1 ± 0.15	1.09–3.52
IL-6 (pg/ml)	1.88 ± 0.29	0.77–5.17
CRP (mg/ml)	4.93 ± 0.76	0.44–8.7
BMI	33.28 ± 1.02	26.4–45
Waist circumference (cm)	115.95 ± 2.72	98–141
Percentage body fat	33.97 ± 1.2	24.3–45.2
HbA1c (%)	7.28 ± 0.19	5.8–9.4

Table 2 Comparison of the effects of placebo and testosterone on adipocytokines, CRP and body composition in type 2 diabetic men.

	Placebo		Testosterone		Analysis of the difference testosterone versus placebo (δ)		
Parameter	Baseline	Post-treatment	Baseline	Post-treatment	Mean effect	*P*	95% confidence intervals
Total testosterone (nmol/l)[a]	7.53 ± 0.56	7.86 ± 0.61	8.36 ± 0.6	12.63 ± 0.9	3.98 ± 1.03	0.001	1.83 to 6.1
Bioavailable testosterone (nmol/l)[a]	2.44 ± 0.18	2.52 ± 0.19	2.61 ± 0.18	3.79 ± 0.27	1.16 ± 0.31	0.001	0.51 to 1.81
Leptin (pg/ml)	16 370.24 ± 2017.4	17 231.67 ± 2034.4	19 611.28 ± 2291.8	13 330.8 ± 1793	−7141.9 ± 1461.8	0.0001	−4082.4 to −10 201
Adiponectin (ng/ml)	7869.46 ± 1089.1	8182.87 ± 1332.1	8569.11 ± 1461	6806.69 ± 1108.3	−2075.8 ± 852.28	0.02	−292.03 to −3859.6
Resistin (ng/ml)	21.29 ± 1.75	19.68 ± 1.63	22.59 ± 1.63	24.03 ± 2.02	3.05 ± 2.7	0.28	−2.67 to 8.76
TNF-α (pg/ml)[b]	2.43 ± 0.15	2.72 ± 0.25	2.18 ± 0.16	2.68 ± 0.25	0.21 ± 0.37	0.58	−0.59 to 1.0
IL-6 (pg/ml)[b]	1.97 ± 0.26	3.63 ± 1.96	1.46 ± 0.18	1.79 ± 0.26	−1.32 ± 1.8	0.28	−5.24 to 2.59
CRP (mg/ml)[b]	4.89 ± 0.64	4.06 ± 0.74	4.54 ± 0.72	4.25 ± 0.83	0.55 ± 0.57	0.35	−0.66 to 1.76
Waist circumference (cm)	115.1 ± 2.8	115.2 ± 2.86	116.2 ± 2.86	114.2 ± 2.82	−2.1 ± 0.81	0.02	−3.79 to −0.41
Percentage body fat %	33.36 ± 1.2	32.86 ± 1.3	33.55 ± 1.3	32.32 ± 1.3	−1.23 ± 0.62	0.06	−2.52 to 0.06
BMI	33.09 ± 1.04	33.22 ± 1.1	33.59 ± 1.09	33.86 ± 1.08	0.15 ± 0.24	0.5	−0.36 to 0.66

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-a (TNF-a), 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

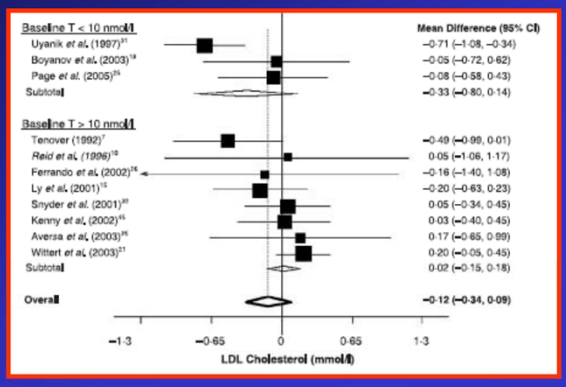
(r=-0.59; P=0.01). Testosterone treatment reduced leptin (-7141.9±1461.8 pg/ml; P=0.0001) and adiponectin levels (-2075.8±852.3 ng/ml; P=0.02). There was a significant reduction in waist circumference. No significant effects of testosterone therapy on resistin, TNF-a, IL-6 or CRP levels were observed.

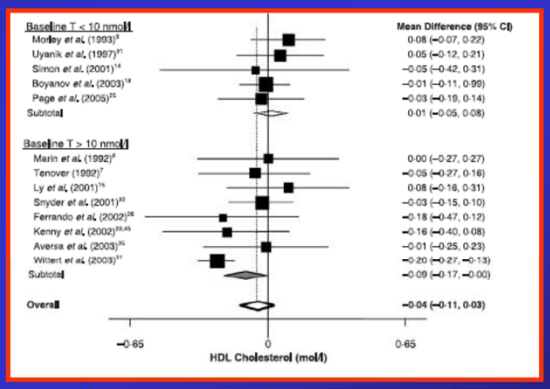
Conclusion: Testosterone replacement treatment decreases leptin and adiponectin levels in type 2 diabetic men. Moreover, low levels of testosterone in men are associated with pro-inflammatory profile, though testosterone treatment over 3 months had no effect on inflammatory markers.

Male Hypogonadism

- Sexual Function – Libido, erectile function
- Bone Metabolism
- Muscle Mass & Strength
- Body Composition, Obesity, Insulin Resistance
- Lipoproteins
- Vascular Disease & Atherosclerosis
- Cancer: Prostate, Breast
- Neuro-psychological
- Erythropoiesis
- Skin

Male Hypogonadism: Lipids





Meta-analysis: 1083 men, age 64.5 yrs (50-78)
- Testo: 314 ng/dl (225-547)
- Small reduction in LDL-C (4.7 mg/dl)
- Small reduction in HDL-C (1.6 mg/dl)
- Neither significant

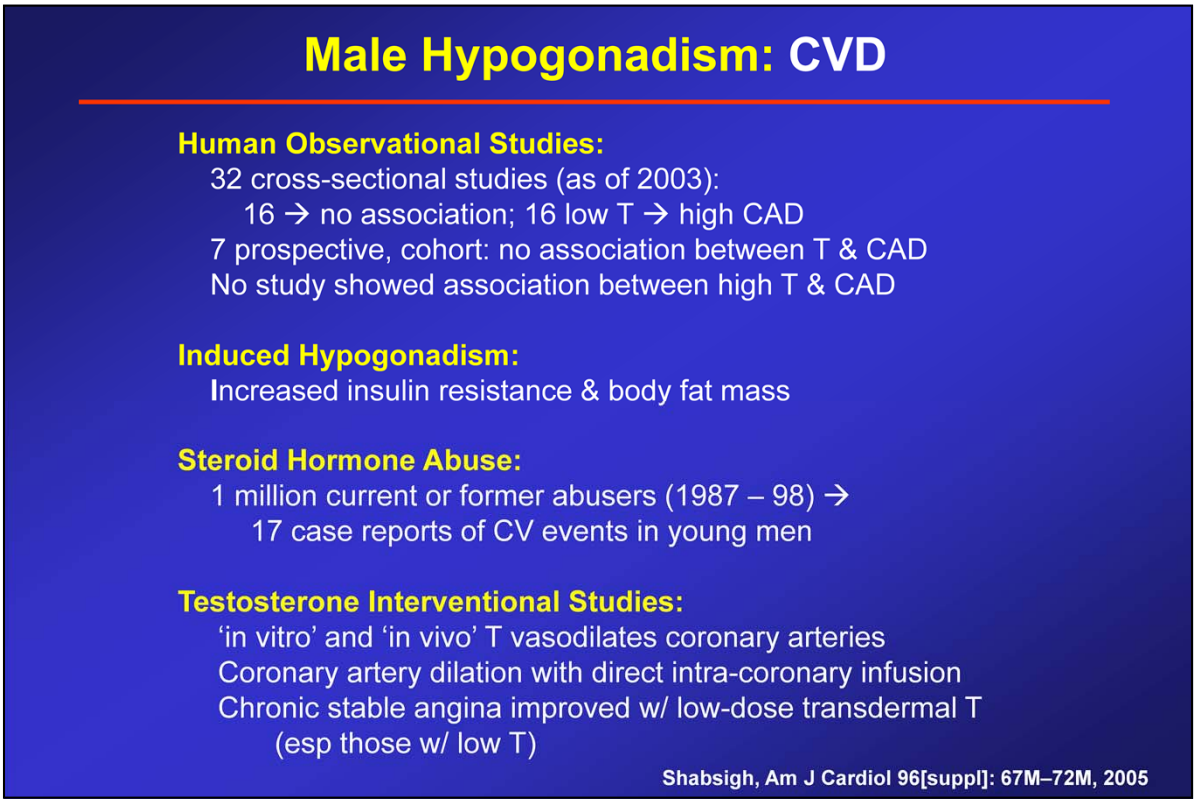
Apolipoproteins or particles (5 studies):
- HDL_2 increased in 3, fell in 1
- LpA-I increased in 2, no change in 1
- LpA-I:A-II fell in one, no change in 2
- apoA-I fell in one, no change in 3
- apoB increased in 1, no change in 3

VLDL apoB metabolism not affected in 1 study
GH & IGF Res 16:308, 2006

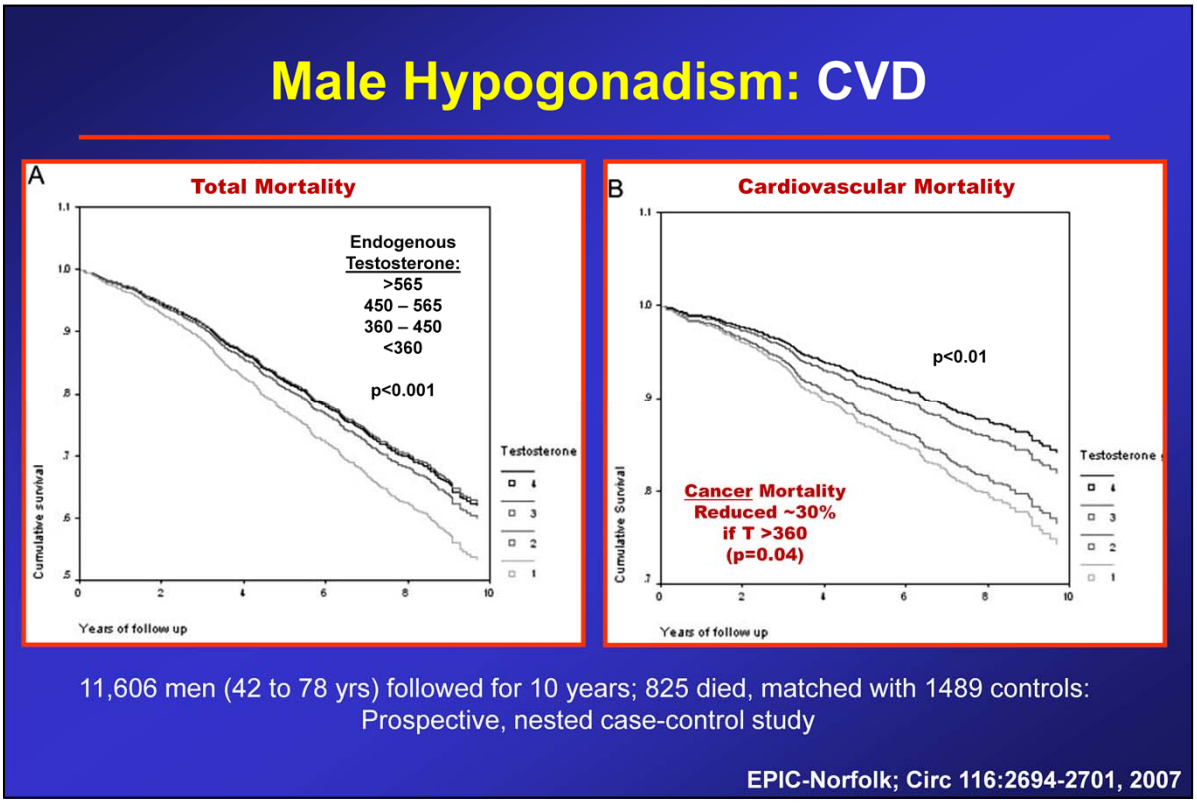
Isidori AM et al. Clinical Endocrinology (2005) 63, 280–293

Male Hypogonadism

- Sexual Function – Libido, erectile function
- Bone Metabolism
- Muscle Mass & Strength
- Body Composition, Obesity, Insulin Resistance
- Lipoproteins
- Vascular Disease & Atherosclerosis
- Cancer: Prostate, Breast
- Neuro-psychological
- Erythropoiesis
- Skin



A systematic literature search was conducted to investigate the cardiovascular issues related to hypogonadism and testosterone therapy. Vascular cells contain sex steroid hormone receptors. Testosterone can exert effects on the vascular wall, either by itself or through aromatization as estrogen. Hypogonadism is associated with central obesity; insulin resistance; low levels of high-density lipoprotein (HDL); high cholesterol levels; and high levels of low-density lipoprotein (LDL), triglycerides, fibrinogen, and plasminogen activator–1. Some observational studies show a correlation between low testosterone and cardiovascular disease (CVD), and others show no correlation. Interventional studies do not reveal a direct long-term relation between testosterone therapy and CVD. Short-term data suggest cardiovascular benefits of testosterone. Testosterone therapy has beneficial and deleterious effects on cardiovascular risk factors. It improves insulin sensitivity, central obesity, and lowers total cholesterol and LDL. In some studies, testosterone therapy has an HDL-lowering effect, and in other studies this effect is insignificant. This should not be assumed to be atherogenic because it might be related to reverse cholesterol transport and effects on the HDL_3 subfraction. The cardiovascular effects of testosterone therapy may be neutral to beneficial. There is no contraindication for testosterone therapy in men with CVD and diagnosed hypogonadism with or without erectile dysfunction. Caution should be exercised regarding occasional increases in hematocrit levels, especially in patients with congestive heart failure. Conversely, evidence does not support testosterone therapy in aging men for the purpose of cardiovascular benefit, despite claims to this effect.

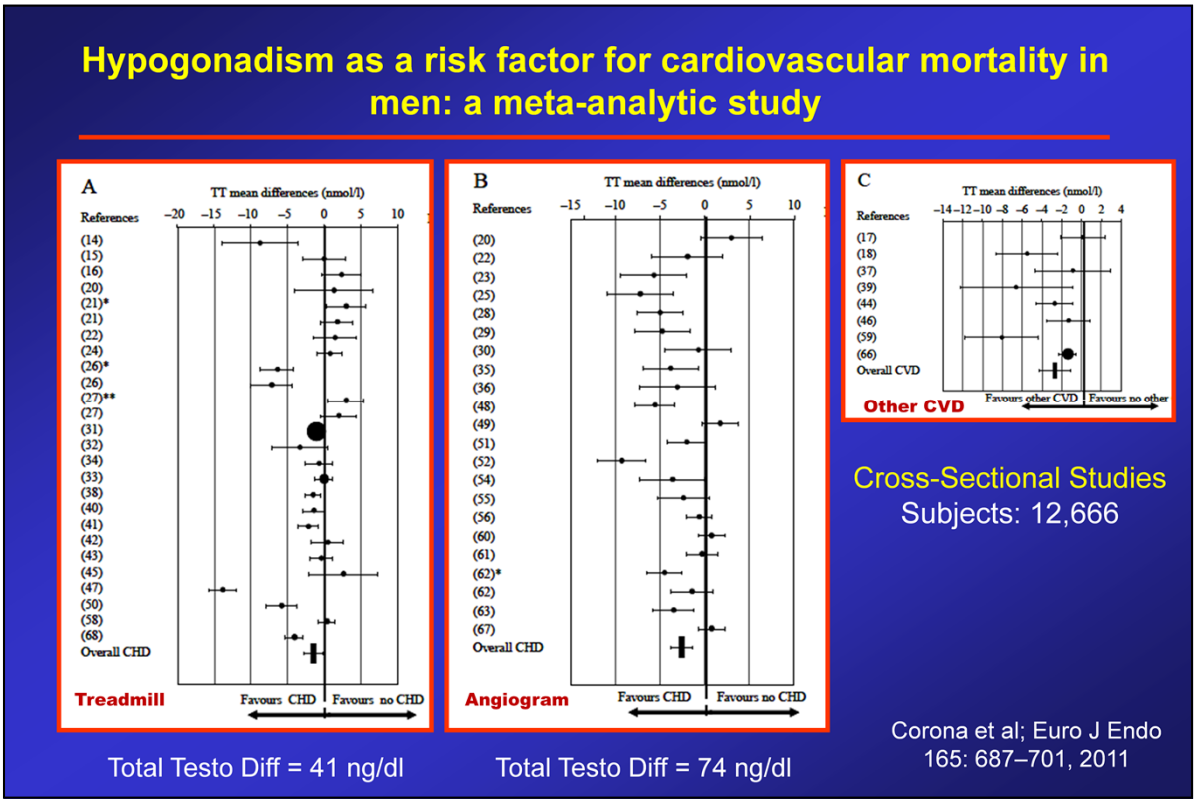


BACKGROUND: The relation between endogenous testosterone concentrations and health in men is controversial.

METHODS AND RESULTS: We examined the prospective relationship between endogenous testosterone concentrations and mortality due to all causes, cardiovascular disease, and cancer in a nested case-control study based on 11,606 men aged 40 to 79 years surveyed in 1993 to 1997 and followed up to 2003. Among those without prevalent cancer or cardiovascular disease, 825 men who subsequently died were compared with a control group of 1489 men still alive, matched for age and date of baseline visit.
Endogenous testosterone concentrations at baseline were inversely related to mortality due to all causes (825 deaths), cardiovascular disease (369 deaths), and cancer (304 deaths). Odds ratios (95% confidence intervals) for mortality for increasing quartiles of endogenous testosterone compared with the lowest quartile were 0.75 (0.55 to 1.00), 0.62 (0.45 to 0.84), and 0.59 (0.42 to 0.85), respectively ($P<0.001$ for trend after adjustment for age, date of visit, body mass index, systolic blood pressure, blood cholesterol, cigarette smoking, diabetes mellitus, alcohol intake, physical activity, social class, education, dehydroepiandrosterone sulfate, androstanediol glucuronide, and sex hormone binding globulin). An increase of 6 nmol/L serum testosterone (approximately 1 SD) was associated with a 0.81 (95% confidence interval 0.71 to 0.92, $P<0.01$) multivariable-adjusted odds ratio for mortality. Inverse relationships were also observed for deaths due to cardiovascular

causes and cancer and after the exclusion of deaths that occurred in the first 2 years.

CONCLUSIONS: In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes.
Low testosterone may be a predictive marker for those at high risk of cardiovascular disease.



Objective: To verify whether hypogonadism represents a risk factor for cardiovascular (CV) morbidity and mortality and to verify whether testosterone replacement therapy (TRT) improves CV parameters in subjects with known CV diseases (CVDs).

Design: Meta-analysis.

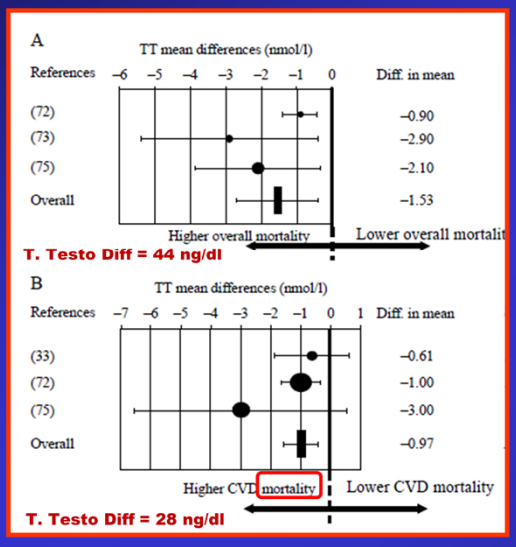
Methods: An extensive Medline search was performed using the following words 'testosterone, CVD, and males'. The search was restricted to data from January 1, 1969, up to January 1, 2011.

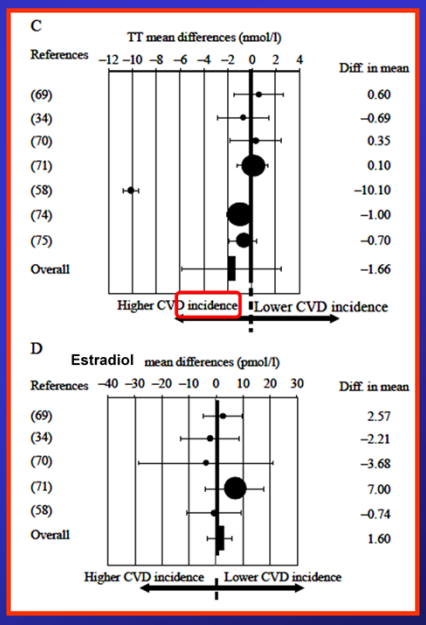
Results: Of the 1178 retrieved articles, 70 were included in the study. Among cross-sectional studies, patients with CVD have significantly lower testosterone and higher 17-b estradiol (E2) levels. Conversely, no difference was observed for DHEAS. The association between low testosterone and high E2 levels with CVD was confirmed in a logistic regression model, after adjusting for age and body mass index (hazard ratio (HR)=0.763 (0.744–0.783) and HR=1.015 (1.014–1.017), respectively, for each increment of total testosterone and E2 levels; both P<0.0001). Longitudinal studies showed that baseline testosterone level was significantly lower among patients with incident overall- and CV-related mortality, in comparison with controls. Conversely, we did not observe any difference in the baseline

testosterone and E2 levels between case and controls for incident CVD. Finally, TRT was positively associated with a significant increase in treadmill test duration and time to 1 mm ST segment depression.

Conclusions: Lower testosterone and higher E2 levels correlate with increased risk of CVD and CV mortality. TRT in hypogonadism moderates metabolic components associated with CV risk. Whether low testosterone is just an association with CV risk, or an actual cause–effect relationship, awaits further studies.

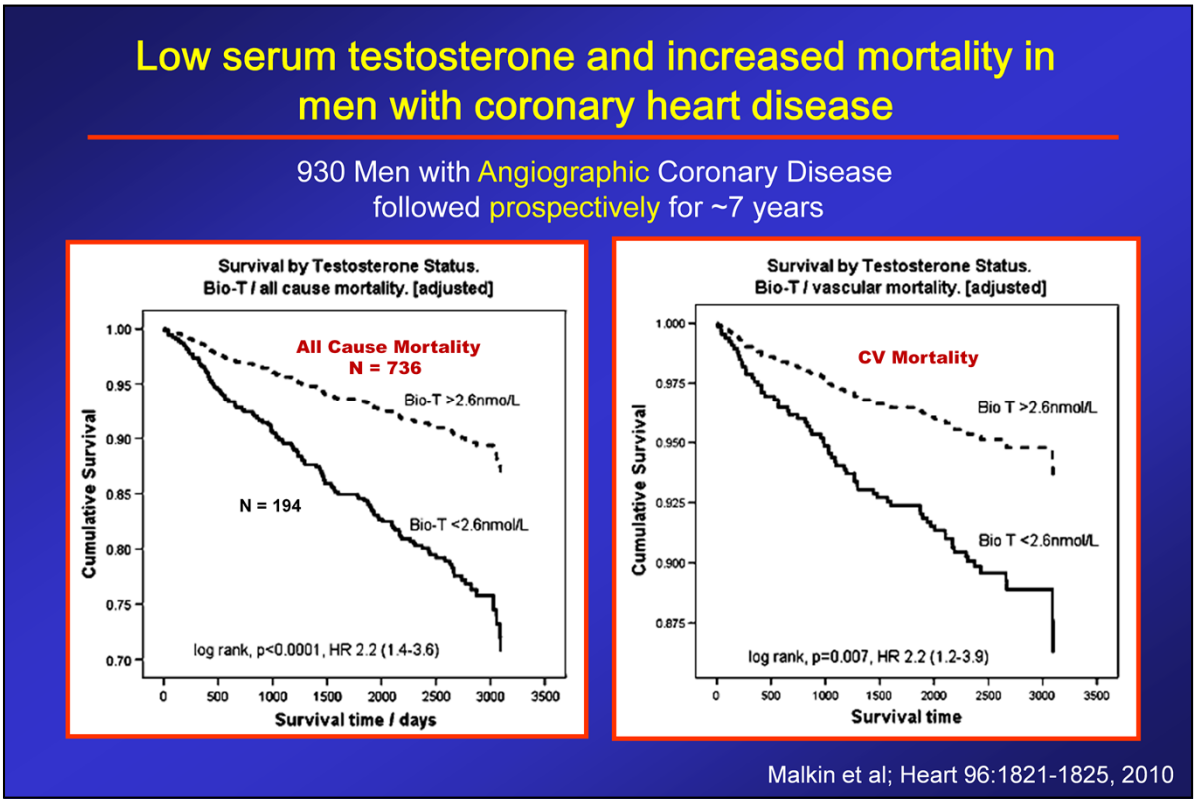
Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study





Corona et al; Euro J Endo
165: 687–701, 2011

Longitudinal Studies
Subjects: 12,375



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.

Male Hypogonadism: CVD

Table 3 Effects of androgens on cytokines

Reference	Androgen	Model	Effect
Chao *et al.* (1995)	T	Rat macrophage	Trend to ↓ TNF production
D'Agostino *et al.* (1999)	T	Mouse marophage	↓ LPS-induced TNF ↑ LPS-induced IL-10
Kanda *et al.* (1996)	T	Human monocytes	↓ IL-6 production
Kanda *et al.* (1997)	T	Human monocytes (patients with systemic lupus erythematosus)	↓ IL-6 production
Li *et al.* (1993)	T	Human monocytes (patients with rheumatoid arthritis and healthy subjects)	↓ IL-1 production
Gornstein *et al.* (1999)	T	Human gingival fibroblasts	↓ IL-6 production
Hofbauer *et al.* (1999)	T	Human osteoblasts	↓ IL-6 production
Hatakeyama *et al.* (2002)	T	Human aortic endothelium	↓ TNF induced VCAM-1 and NFκβ
Araneo *et al.* (1991)	DHT	Mouse cells	↓ γ-interferon, IL-4
Dalal *et al.* (1997)	DHT	Mice with auto-immune disease*	↓ γ-interferon, ↑ IL-10
Kimura *et al.* (1998)	DHEA	Obese rats*	↓ TNF
Ben-Nathan *et al.* (1999)	DHEA	Mice*	↓ IL-1, ↓ LPS-induced TNF
Padgett & Loria (1998)	DHEA	Mouse macrophages	↓ LPS-induced TNF, IL-1, IL-6
Straub *et al.* (1998)	DHEA	Human monocytes	↓ IL-6 production
Spinedi *et al.* (1992)	Castration	Mice*	↑ LPS-induced TNF

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. *Journal of Endocrinology* (2003) **178,** 373–380

Male Hypogonadism: CVD

Proposed Mechanisms for Adverse Effects of Testosterone Therapy:

- Increased Blood Pressure
- Polycythemia
- Elevated LDL-C & Reduced HDL-C
- Hyperviscosity of the blood
- Increased Platelet Aggregation & Thromboxane A_2
- Increased SMC proliferation & ICAM
- Worsening Sleep Apnea
- Elevated Estradiol →
  - Decreased Coagulation Inhibitors
  - Protein C resistance

- Important to consider these parameters during treatment

Male Hypogonadism: Cytokines

Non-Diabetic Men
Single-blind, cross-over
4 weeks
Testo: 100 mg IM q2wks

Concomitant disease (n)	
Chronic heart failure	2
Coronary heart disease	20
Previous myocardial infarction	9
Hypertension	10
Diabetes mellitus	9
Current smoker	4
Drugs (n)	
Aspirin/clopidogrel	19/1
HMG-CoA inhibitor	20
Oral nitrate	13
β-Blocker	12
Calcium antagonist	16
ACE/ARB	10/1
Diuretic	4

Clinical characteristic/normal range	Patients (n = 27)	Range
Age (yr)	61.6 ± 9.3	36–78
BMI (kg/m^2) (20–25)	30.9 ± 6.9	21.5–57
Total testosterone (nmol/liter) (>12 nmol/liter)	4.39 ± 1.24	0.9–17
Bioavailable testosterone (nmol/liter) (>2.5 nmol/liter)	2.42 ± 1.07	0.2–6.4
FSH (IU/liter)	12.4 ± 10.5	1.9–46.8
LH (IU/liter)	8.6 ± 12.2	1.2–59.5
SHBG (nmol/liter)	16.9 ± 7.1	8.7–32.7

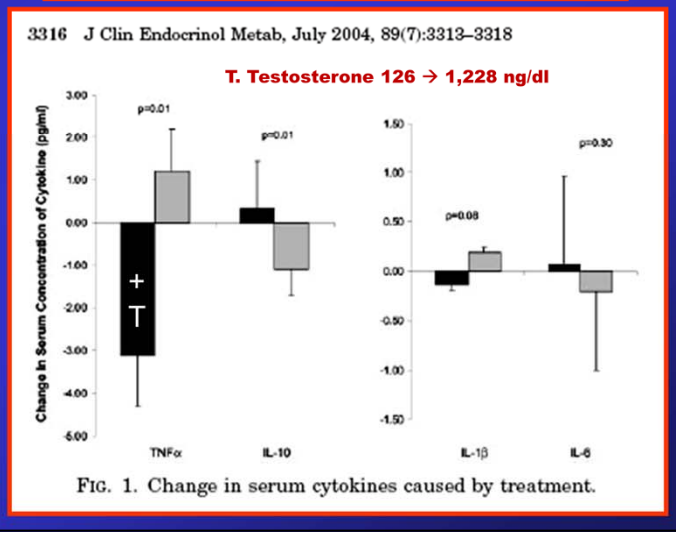


FIG. 1. Change in serum cytokines caused by treatment.

Testosterone has immune-modulating properties, and current *in vitro* evidence suggests that testosterone may suppress the expression of the proinflammatory cytokines TNF, IL-1, and IL-6 and potentiate the expression of the anti-inflammatory 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±nmol/liter). Compared with placebo, testosterone induced reductions in TNF (3.1±8.3 *vs.* 1.3±5.2 pg/ml;*P*=0.01) and IL-1 (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 TNF and IL-1 were positively correlated (rS=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 pro-inflammatory cytokines mediate the development and complications associated with atheromatous plaque, these properties may have particular relevance in men with overt vascular disease. (*J Clin Endocrinol Metab* 89: 3313–3318, 2004)

Male Hypogonadism: CVD

Placebo-Controlled Trials of Testosterone Therapy

TABLE 2. Randomized placebo-controlled studies of testosterone treatment in men with coronary artery disease

Study	Ref.	Design	n	Duration	Drug	Treatment	Dosage	Pain	Stress test
Chronic effects									
Jaffe (1977)	271	PG	50	2 months	im TC	200 mg/wk	High	↔	↑[c]
Wu and Weng (1993)	272	XO	62	1 month	Oral TU	40–120 mg/d	Standard	↓	↑[c]
English *et al.* (2000)	274	PG	46	3 months	T patch	5 mg/d	Standard	↓	↑[c]
Acute effects									
Webb *et al.* (1999)	275	XO	14	10 min	iv T	2.3 mg	Very high	↔	↑[c]
Rosano *et al.* (1999)	276	XO	14	5 min	iv T	2.5 mg	Very high	↔	↑[c]
Thompson *et al.* (2002)	277	XO	32	20 min	iv T	Titrated	Physiological	↔	↔[a,b]

PG, Parallel group study; XO, cross-over study; T, testosterone; TC, testosterone cypionate; TU, testosterone undecanoate.
[a] Exercise stress electrocardiogram.
[b] Adenosine sestamibi SPECT scan.

Short-term Administration – improved exercise and chest pain

Acute Administration of Testosterone (IV) – improved exercise

Globally, cardiovascular disease will continue causing most human deaths for the foreseeable future. The consistent gender gap in life span of approximately 5.6 yr in all advanced economies must derive from gender differences in age specific cardiovascular death rates, which rise steeply in parallel for both genders but 5–10 yr earlier in men. The lack of inflection point at modal age of menopause, contrasting with unequivocally estrogen-dependent biological markers like breast cancer or bone density, makes estrogen protection of premenopausal women an unlikely explanation. Limited human data suggest that testosterone exposure does not shorten life span in either gender, and oral estrogen treatment increases risk of cardiovascular death in men as it does in women. Alternatively, androgen exposure in early life (perinatal androgen imprinting) may predispose males to earlier onset of atherosclerosis. Following the recent reevaluation of the estrogen-protection orthodoxy, empirical research has flourished into the role of androgens in the progression of cardiovascular disease, highlighting the need to better understand androgen receptor (AR) coregulators, nongenomic androgen effects, tissue-specific metabolic activation of androgens, and androgen sensitivity. Novel therapeutic targets may arise from understanding how androgens enhance early plaque formation and cause vasodilatation via nongenomic androgen effects on vascular smooth muscle, and how tissue specific variations in androgen effects are modulated by AR coregulators as well as metabolic activation of testosterone to amplify (via 5-reductase to form dihydrotestosterone acting on AR) or diversify (via aromatization to estradiol acting upon estrogen receptor /) the biological effects of testosterone on the vasculature. Observational studies show that blood

testosterone concentrations are consistently lower among men with cardiovascular disease, suggesting a possible preventive role for testosterone therapy, which requires critical evaluation by further prospective studies. Short-term interventional studies show that testosterone produces a modest but consistent improvement in cardiac ischemia over placebo, comparable to the effects of existing antianginal drugs. By contrast, testosterone therapy has no beneficial effects in peripheral arterial disease but has not been evaluated in cerebrovascular disease. Erectile dysfunction is most frequently caused by pelvic arterial insufficiency due to atherosclerosis, and its sentinel relationship to generalized atherosclerosis is insufficiently appreciated. The commonality of risk factor patterns and mechanisms (including endothelial dysfunction) suggests that the efficacy of anti-atherogenic therapy is an important challenge with the potential to enhance men's motivation for prevention and treatment of cardiovascular diseases. (*Endocrine Reviews* 24: 313–340, 2003)

Male Hypogonadism: CVD

Testosterone Replacement - Angina Threshold and Atheroma

Testo (7) vs Placebo (6): Age ~65 w/ Stable Angina → Testo Injections

Table 3 Treatment effect.

Parameter	Treatment effect visit 4 (week 14) Placebo	Testosterone	P	Treatment effect visit 6 (week 28) Placebo	Testosterone	P	Treatment effect visit 8 (week 52) Placebo	Testosterone	P	ANOVA treatment effect
Exercise time (s)	−27.8±56.2	54.3±41.1	0.01	13.5±32.0	55.2±49.6	0.1	30.1±46.0	64.5±13.3	0.1	0.07
Time ST depression (s)	0.33±24.3	75.4±36.5	0.001	0.5±17.7	109.9±62.6	0.002	11.5±17.6	129.3±48.0	0.0001	0.02
Peak METS	−0.57±0.86	1.0±0.72	0.004	0.18±0.66	1.2±1.0	0.06	0.32±0.64	1.4±0.53	0.007	0.02
Prostate specific antigen (μg/l)	−0.017±0.41	−0.01±0.48	0.98	0.00001±0.2	0.33±0.6	0.2	0.1±0.15	0.2±0.61	0.6	0.26
C-reactive protein (μg/ml)	0.2±2.8	0.6±2.1	0.76	−0.46±1.97	0.06±0.9	0.54	1.1±2.2	0.17±0.86	0.38	0.9
Haemoglobin (g/dl)	−0.8±0.6	0.8±0.7	0.05	−0.1±0.7	0.8±0.48	0.02	−0.03±0.5	0.38±0.62	0.2	0.04
Haematocrit (%)	−0.003±0.018	0.03±0.03	0.034	−0.003±0.2	0.03±0.03	0.05	−0.003±0.02	0.01±0.03	0.23	0.03
Mass (kg)	2.75±1.25	1.0±0.64	0.008	3.2±1.8	0.29±1.5	0.009	3.5±2.3	−0.93±3.6	0.02	0.06
Body mass index (mass/kg^2)	1.0±0.69	0.34±0.3	0.04	1.3±0.75	0.23±0.46	0.009	1.3±1.0	−0.29±1.3	0.03	0.04
Waist-to-hip ratio	0.01±0.05	−0.01±0.035	0.3	0.02±0.05	−0.01±0.03	0.15	−0.005±0.04	−0.01±0.04	0.7	0.09
Total testosterone (nmol/l)	−1.0±1.04	6.2±6.7	0.02	−0.03±4.3	9.2±8.5	0.35	−2.0±1.5	6.2±8.3	0.04	0.01
FSH (nmol/l)	0.27±1.6	−3.2±2.2	0.008	0.6±2.0	−2.9±2.2	0.01	0.3±2.3	−1.4±2.8	0.24	0.03
LH (nmol/l	1.3±2.1	−2.1±1.5	0.005	0.13±1.3	−1.96±1.68	0.03	−0.07±1.7	−1.3±1.2	0.25	0.06
Total cholesterol (mmol/l)	−0.25±0.54	−0.16±0.43	0.74	0.07±1.1	−0.17±0.48	0.6	0.18±1.1	−0.29±0.58	0.37	0.3
HDL (mmol/±l)	−0.82±0.17	0.22±0.53	0.2	0.02±0.24	−0.11±0.15	0.23	0.08±0.22	−0.06±0.28	0.34	0.85
Triglycerides (mmol/l)	0.21±0.59	−0.06±0.35	0.32	0.2±1.2	−0.1±0.57	0.56	0.27±1.2	−0.36±0.4	0.27	0.05
CIMT average				−0.068±0.05	−0.32±0.13	0.12	−0.043±0.034	−0.48±0.1	0.002	0.16
CIMT max				−0.11±0.65	−0.37±0.16	0.18	−0.09±0.06	−0.58±0.11	0.004	0.18
Glucose (mmol/l)	0.07±3	0.9±1.7	0.5	0.65±1.9	0.6±1.2	0.9	0.8±2.8	−0.2±2.8	0.5	0.9
Insulin (mIU/l)	51.9±67.5	224±379	0.3	106±132	114±133	0.9	366±563	108±132	0.3	0.5

HDL, high-density lipoprotein; CIMT, carotid intima-media thickness.

Mathur: Euro J Endo 161: 443–449, 2009

Introduction: In short-term studies, testosterone replacement therapy has been shown to protect male subjects from exercise-induced ischaemia and modify cardiovascular risk factors such as insulin resistance, fat mass and lipid profiles.

Methods: This randomised parallel group controlled trial was designed to assess the treatment effect of testosterone therapy (Nebido) compared with placebo in terms of exercise-induced ischaemia, lipid profiles, carotid intima-media thickness (CIMT) and body composition during 12 months treatment in men with low testosterone levels and angina.

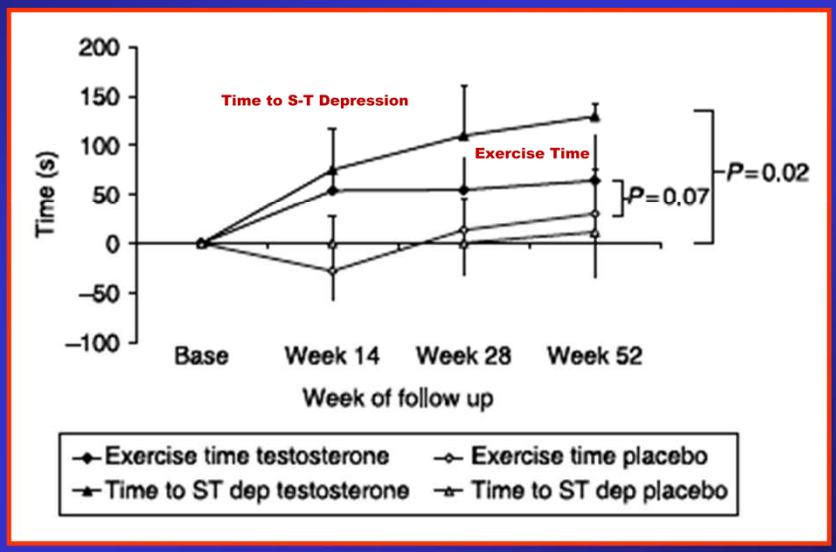
Results: A total of 15 men were recruited but 13 (n=13) reached adequate duration of follow-up; seven were treated with testosterone and six with placebo. Testosterone increased time to ischaemia (129±48 s versus 12±18, P=0.02) and haemoglobin (0.4±0.6 g/dl versus -0.03±0.5, P=0.04), and reduced body mass index (-0.3 kg/m^2 versus 1.3±1, P=0.04) and triglycerides (-0.36±0.4 mmol/l versus 0.3±1.2, P=0.05). The CIMT decreased in the testosterone group more than placebo, but full between group analyses suggested this was only a statistical trend (-0.5±0.1 vs -0.09±0.06, P=0.16). There were no significant effects on serum prostate specific antigen, total or high-density lipoprotein cholesterol; or on mood and symptom scores as assessed by Seattle Angina Score and EuroQol.

Conclusion: The protective effect of testosterone on myocardial ischaemia is maintained throughout treatment without decrement. Previously noted potentially beneficial effects of testosterone on body composition were confirmed and there were no adverse effects. European Journal of Endocrinology 161 443–449

Male Hypogonadism: CVD

Testosterone Replacement - Angina Threshold and Atheroma

Testo (7) vs Placebo (6): Age ~65 w/ Stable Angina → Testo Injections



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Male Hypogonadism: CVD

Testosterone Supplementation in Heart Failure: A Meta-Analysis
Toma et al: *Circ Heart Fail* 5:315-321, 2012

Four trials: n = 198
Mean Age - 67 years
EF: 28%
47%, 51%, and 2% →
Class II, III, and IV symptoms
Baseline Testosterone: 168 ng/dl
IM & Transdermal supplements
12 weeks to 12 months

No change in EF or BNP
Improve Functional Class ≥1 step
35% of Testo vs 10% of Controls
No change in PSA

1 sudden death in Control Group
CV Events: 7% v 6% (T v C) NS

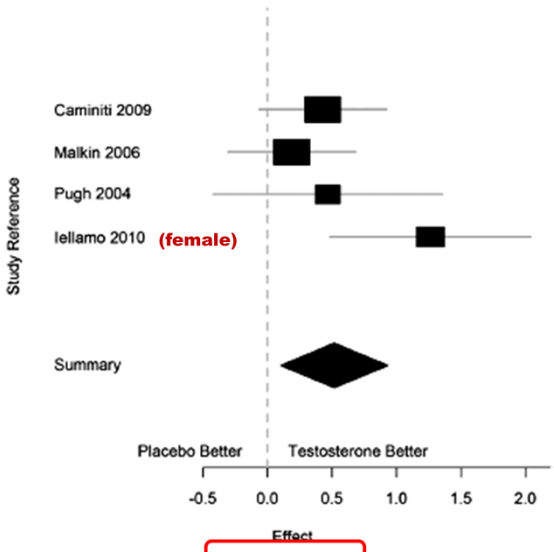


Figure 2. Forest plot of exercise capacity in all studies, normalized using SD. This forest plot shows that testosterone therapy resulted in a net pooled improvement in exercise capacity of 0.52 SD (95% CI, 0.10–0.94 SD).

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 whether testosterone therapy improves exercise capacity in patients with stable chronic HF.

Methods and Results—We searched Medline, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (1980 –2010). Eligible studies included randomized controlled trials (RCTs) reporting the effects of testosterone on exercise capacity in patients with HF. Reviewers determined the methodological quality of studies and collected descriptive, quality, and outcome data. Four trials (n198; men, 84%; mean age, 67 years) were identified that reported the 6-minute walk test (2 RCTs), incremental shuttle walk test (2 RCTs), or peak oxygen consumption (2 RCTs) to assess exercise capacity after up to 52 weeks of treatment. Testosterone therapy was associated with a significant improvement in exercise capacity compared with placebo. The mean increase in the 6-minute walk test, incremental shuttle walk test, and peak oxygen consumption between the testosterone and placebo groups was 54.0 m (95% CI, 43.0–65.0 m), 46.7 m (95% CI, 12.6–80.9 m), and 2.70 mL/kg per min (95% CI, 2.68 –2.72 mL/kg per min), respectively. Testosterone therapy was associated with a significant increase in exercise capacity as measured by units of pooled SDs (net effect, 0.52 SD; 95% CI, 0.10–0.94 SD). 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 patients with HF. Adequately powered RCTs are required to assess the benefits of testosterone in this high-risk population with regard to quality of life, clinical events, and safety. **(*Circ Heart Fail*. 2012;5:315-321.)**

Male Hypogonadism: CVD

Adverse Events Associated with Testosterone Administration

Baseline: Age ~74; Very Limited Mobility; 50% +CVD; TT ~250 ng/dl (→ 574); FT ~ 4.6

Testo vs Plac: Black 14 vs 4% Anti-HT Rx 85 vs 73% (p=0.04)
HLP 63 vs 50% (p=0.05) Statins 62 vs 47% (p=0.03)

Table 5. Changes in Measures of Muscle Performance and Physical Function from Baseline to the End-of-Study Assessment, among Men Receiving Testosterone Therapy.*

Strength and Performance Measures	Testosterone		Placebo		Difference between Treatments			
					Unadjusted		Adjusted for Baseline Mobility	
	#106 no. of men	mean (95% CI)	#103 no. of men	mean (95% CI)	mean (95% CI)	P value†	mean (95% CI)	P value‡
Leg-press strength (newtons)	49	156.9 (89.2 to 224.6)	54	27.1 (−28.3 to 82.6)	129.8 (43.9 to 215.6)	0.003	129.4 (43.5 to 215.4)	0.004
Chest-press strength (newtons)	38	34.7 (18.7 to 51.4)	44	0.28 (−13.8 to 14.3)	34.5 (13.2 to 55.8)	0.002	34.5 (13.1 to 56.2)	0.002
Grip strength in dominant hand (kg)	63	1.0 (−0.1 to 2.0)	70	0.7 (−0.3 to 1.7)	0.27 (−1.1 to 1.7)	0.69	0.26 (−1.1 to 1.7)	0.71
50-m walking speed (m/sec)	Baseline 0.94 m/sec							
Without a load	39	0.074 (−0.004 to 0.153)	43	0.024 (−0.018 to 0.066)	0.050 (−0.035 to 0.135)	0.26	0.048 (−0.037 to 0.133)	0.27
With a load	26	0.139 (0.023 to 0.256)	29	0.065 (0.013 to 0.116)	0.074 (−0.05 to 0.19)	0.24	0.090 (−0.030 to 0.209)	0.14
Stair-climbing power (W)								
Without a load	49	19.5 (7.4 to 31.5)	52	10.7 (−2.9 to 24.3)	8.7 (−9.2 to 26.7)	0.34	8.1 (−9.9 to 26.2)	0.37
With a load	46	39.2 (14.4 to 64.0)	50	9.0 (−8.4 to 26.4)	30.2 (0.3 to 60.1)	0.05	29.7 (0.2 to 59.3)	0.05
Lift-and-lower test§	36	4.4 (2.5 to 6.4)	45	2.6 (0.8 to 4.3)	1.9 (−0.8 to 4.5)	0.16	1.9 (−0.7 to 4.4)	0.15

* The end-of-study assessment was performed either at the end of the 6-month intervention period or at the last visit, if possible, in cases in which the study medication was discontinued before 6 months. Results are reported only for men who were able to perform the relevant tests at baseline. CI denotes confidence interval.
† We calculated the P values in the unadjusted analysis using two-sample Student's t-tests of equal change in the trial groups, allowing unequal variance and using Satterthwaite's approximation to degrees of freedom.
‡ We calculated the P values in the adjusted analysis using multiple linear regression, with adjustment for baseline total score on the Short Physical Performance Battery and self-report of limitations in mobility.
§ The scores on the lift-and-lower test refer to the number of shelves a subject was able to touch with a weighted basket in 1 minute. Higher scores indicate better performance.

Only 11 men in each group completed the 24-week study

Basaria, NEJM 363:109-122, 2010

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

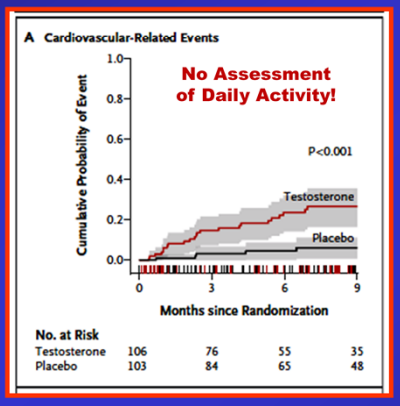
remained constant throughout the 6-month treatment period. As compared with the placebo group, the testosterone group had significantly greater improvements in leg-press and chest-press strength and in stair climbing while carrying a load.

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.)

Male Hypogonadism: CVD

Adverse Events Associated with Testosterone Administration

Testo vs Plac: 50% +CVD
Black 14 vs 4%
Anti-HT Rx 85 vs 73% (p=0.04)
HLP 63 vs 50% (p=0.05)
Statins 62 vs 47% (p=0.03)
Lower LDL (-4.2) & HDL (-1.1 mg/dl)



Basaria, NEJM 363:109-122, 2010

Table 3. Subjects with One or More Cardiovascular-Related Adverse Events.*

Subject No.	Adverse Event	MedDRA-Classified Cardiac Event	Cardiovascular-Related Event	Atherosclerosis-Related Event	Method of Confirmation†
			no. of events		
Testosterone group					
1	Acute coronary syndrome and chest pain	1	2	1	Review of medical records
2	Chest pain		1	1	Examination by study physician
3	Syncope		1		Self-report
4	Syncope		1		Self-report
5	Myocardial infarction treated with angioplasty and placement of pacemaker	1	1	1	Review of medical records
6	Myocardial infarction	1	1	1	Review of medical records
7	Angioplasty and coronary-artery bypass grafting		1	1	Review of medical records
8	Peripheral edema		1		Examination by study physician
9	Peripheral edema		1		Examination by study physician
10	Ectopy on ECG (premature ventricular contractions, couplets)	1	1		ECG evaluation by study physician
11	Left ventricular strain pattern during exercise testing	1	1		ECG evaluation by study physician
12	ST-segment depression during exercise testing		1	1	ECG evaluation by study physician
13	Elevated blood pressure		1		Examination by study physician
14	Atrial fibrillation with rapid ventricular rate and shortness of breath and exacerbation of congestive heart failure, which necessitated hospitalization	2	2		Examination by study physician (atrial fibrillation) and report of primary care physician (exacerbation of congestive heart failure)
15	Stroke		1		Review of medical records
16	Elevated blood pressure and atrial fibrillation	1	1		Review of medical records
17	Peripheral edema		1		Examination by study physician
18	Peripheral edema		1		Examination by study physician
19	Elevated blood pressure		1		Examination by study physician
20	Tachycardia with fatigue	1	1		Self-report
21	Death, suspected myocardial infarction	1	1	1	Notification by physician
22‡	Peripheral edema		1		Examination by study physician
23	Congestive heart failure exacerbation	1	1		Review of medical records

Associated with increased activity?

Male Hypogonadism: CVD

Adverse Events Associated with Testosterone Administration

Baseline: **Age ~74; Very Limited Mobility; 50% +CVD; TT ~250 ng/dl (→ 574); FT ~ 4.6**

Testo vs Plac: Black 14 vs 4% Anti-HT Rx 85 vs 73% (p=0.04)

HLP 63 vs 50% (p=0.05) Statins 62 vs 47% (p=0.03)

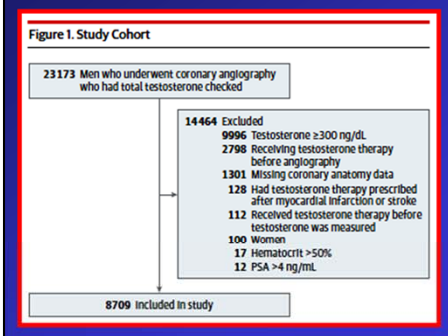
Table 3. (Continued.)

Subject No.	Adverse Event	MedDRA-Classified Cardiac Event	Cardiovascular-Related Event	Atherosclerosis-Related Event	Method of Confirmation†
			no. of events		
Placebo group					
1	Syncope resulting in hospitalization		1		Self-report
2	Tachycardia		1		Examination by study physician
3	Elevated blood pressure		1		Examination by study physician
4	Arrhythmia–ectopy noted on ECG before exercise testing	1	1		Examination by study physician
5	Carotid bruit and carotid-artery plaque identified on ultrasonography		1	1	Examination by study physician and review of medical records

Basaria, NEJM 363:109-122, 2010

Male Hypogonadism: CVD

Association of Testosterone Therapy With Mortality, MI, & Stroke



Retrospective Cohort Study
Men with **Coronary Angiogram**
Testosterone <300 ng/dl

Filled **1 script** for T (most patches)
Started ~531 days post-cath
17.6% filled only 1 script
Mean: last script 376 days

Table 1. Characteristics of Patients at Study Entry Who Did and Did Not Receive Testosterone Therapy

	Unweighted Covariates at Study Entry, No. (%) of Patients		
	No Testosterone Therapy (n = 7486)	Testosterone Therapy (n = 1223)	*P* Value
Age, mean (SD), y	63.8 (9.0)	60.6 (7.6)	<.001
Total testosterone, mean (SD), ng/dL	206.5 (73.8)	175.5 (62.3)	<.001
Coronary arteries			
Normal	900 (12.3)	197 (16.1)	<.001
Nonobstructed	2089 (27.9)	356 (29.1)	.64
Obstructed	4497 (60.1)	670 (54.8)	.001
Hypertension	6952 (92.9)	1101 (90.0)	.001
Hyperlipidemia	6611 (88.3)	1051 (85.9)	.02
Diabetes	4171 (55.7)	650 (53.2)	.09
Obesity	4033 (53.9)	703 (57.5)	.02
Depression	2641 (35.3)	448 (36.6)	.37
Prior PCI	2181 (29.1)	335 (27.4)	.22
Obstructive sleep apnea	1980 (26.4)	341 (27.9)	.30
Congestive heart failure	1826 (24.4)	222 (18.2)	<.001
Prior myocardial infarction	1816 (24.3)	248 (20.3)	.002
Chronic obstructive pulmonary disease	1622 (21.7)	228 (18.6)	.02
Peripheral vascular disease	1463 (19.5)	201 (16.4)	.01
Cerebrovascular disease	1222 (16.3)	136 (11.1)	<.001

Vigen et al: JAMA 310(17):1829-36, 2013

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.

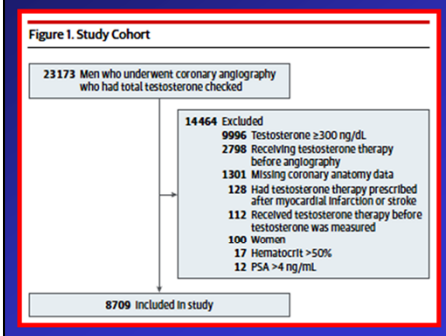
RESULTS Of the 8709 men with a total testosterone level lower than 300 ng/dL, 1223 patients started testosterone therapy after a median of 531 days following

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. At 3 years after coronary angiography, the Kaplan-Meier estimated cumulative percentages with 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%). 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.

Male Hypogonadism: CVD

Association of Testosterone Therapy With Mortality, MI, & Stroke



Retrospective Cohort Study
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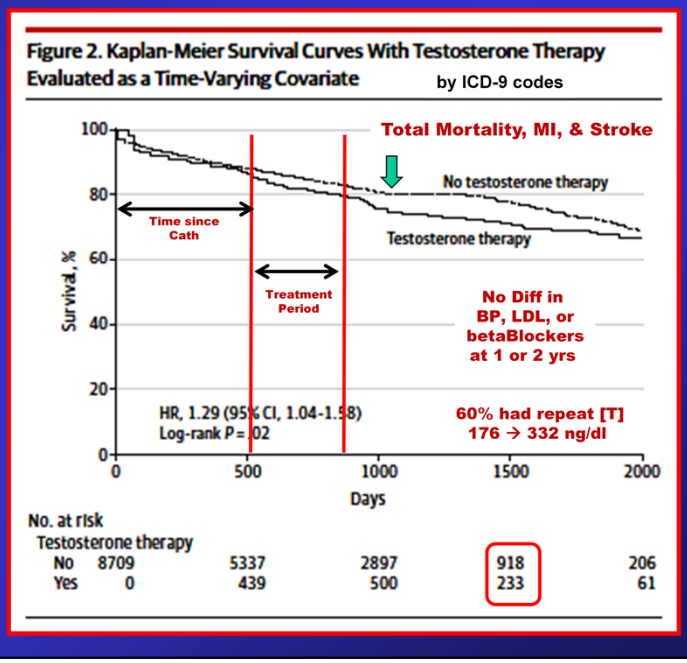

Male Hypogonadism: CVD

Increased Risk of *Non-Fatal MI* Following Testosterone Therapy

Truven Health MarketScan Commercial Claims and Encounters Database

Data from 2006 to 2010; no data on compliance, lab, or lifestyle

Study Periods: Pre-Rx (12 mths) → Rx (3 & 25 mths) → Post-Rx (3 & 6 mths)

Table 1. Rates of myocardial infarction per 1,000 persons per year (PY) in men under age 65 years and those age 65 years and older, in pre- and post-prescription intervals for an initial prescription for testosterone therapy rate ratios (RR) and 95% confidence intervals (CI). by ICD-9 codes

	All Ages	Age <65 Years	Age ≥65 Years
Patients (N)	55,593	48,539	7,054
Pre-prescription			
Cases	193	156	37
Rate per 1,000 PY (95%CI)	3.48 (3.02, 4.01)	3.22 (2.75, 3.77)	5.27 (3.81, 7.27)
Post-prescription			
Cases	65	45	20
Rate per 1,000 PY (95%CI)	4.75 (3.72, 6.05)	3.76 (2.81, 5.04)	11.52 (7.43, 17.86)
Rate Ratio (post/pre) (95%CI)	1.36 (1.03, 1.81)	1.17 (0.84, 1.63)	2.19 (1.27, 3.77)

Finkle et al: PLOSone 9(1):1-7, 2014

Absolute Rates: 1.27 / 0.54 / 6.25 extra MI's per 1000 patient years

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.

Male Hypogonadism: CVD

Increased Risk of Non-Fatal MI Following Testosterone Therapy

Table 2. Distribution of baseline covariates for all Medicare and commercial insurance enrollees in the TT prescription and PDE5I cohorts before and after weighting.

by ICD-9 codes

Variable	TT Prescription	PDE5I Before Weighting	PDE5I After Weighting
N	55,593	167,279	141,031
Age, years	54.4	56.0	54.3
Medicare, %	12.3	14.5	12.0
Prior Diagnoses (ICD-9), %			
Hyperlipidemia (272)	26.5	23.5	26.3
Hypertension (401–405)	26.8	24.7	26.5
Heart Disease (404,414,420–429)	10.4	9.2	10.2
Osteoarthritis (715,720–721)	8.5	6.0	8.3
Asthma (493,495)	2.3	1.6	2.2
Prior Prescriptions, %			
Anticoagulant	2.8	2.4	2.7
Antiplatelets	3.4	2.8	3.3
Ace Inhibitors	18.1	18.8	18.3
Beta Blockers	15.5	15.2	15.6
Calcium Channel Blockers	11.7	11.4	11.8
Hypolipidemics	37.0	33.7	36.7
Anti-hypertensives NOS	3.2	3.1	3.2
Vasodialators	2.0	1.3	1.9
Other cardiac drugs	13.8	11.5	13.6
NSAIDs	16.3	13.5	16.1
SSRIs	20.7	11.8	20.4
Corticosteroids	12.7	9.2	12.6
Insulin	3.9	2.9	3.9
Diuretics	10.4	9.9	10.4
Anti-diabetes drugs	15.2	12.7	15.0

Finkle et al: PLOSone 9(1):1-7, 2014

Male Hypogonadism: CVD

Finkle et al: PLOSone 9(1):1-7, 2014

Table 4. Rates of myocardial infarction in men under and 65 and those 65 and older per 1,000 per year (PY) in pre- and post-prescription intervals for an initial prescription for TT or PDE5 inhibitors, with adjusted* rate ratios (RR), ratio of rate ratios (RRR) and 95% confidence limits (CL) by history of heart disease.

No data on control of Lipids, BP, or Diabetes

	Heart Disease History		No Heart Disease History	
	TT Prescription	PDE5I	TT Prescription	PDE5I
Age <65 Years				
Patients (N)	4,006	10,681†	44,533	130,831†
Pre-prescription				
Cases	21	65	135	491
Rate per 1,000 PY (95%CI)	5.26 (3.43, 8.06)	5.26 (3.43, 8.06)	3.04 (2.57, 3.60)	3.04 (2.57, 3.60)
Post-prescription				
Cases	15	20	30	99
Rate per 1,000 PY (95%CI)	15.22 (9.18, 25.25)	7.34 (6.89, 7.82)	2.73 (1.91, 3.91)	3.01 (2.95, 3.08)
Rate Ratio (post/pre) (95%CI)	2.9 (1.49, 5.62)	1.4 (0.91, 2.14)	0.90 (0.61, 1.34)	0.99 (0.84, 1.17)
RRR‡ (95%CI)	2.07 (1.05, 4.11)	10.0 / 1,000 PY	0.91 (0.60, 1.37)	-0.3 / 1,000 PY
Age ≥65 Years				
Patients (N)	2,047	5,492†	5,057	20,275†
Pre-prescription				
Cases	15	35	22	104
Rate per 1,000 PY (95%CI)	7.36 (4.44, 12.22)	7.36 (4.44, 12.22)	4.41 (2.90, 6.7)	4.41 (2.90, 6.7)
Post-prescription				
Cases	8	13	12	20
Rate per 1,000 PY (95%CI)	15.91 (7.96, 31.81)	8.35 (7.36, 9.48)	9.74 (5.53, 17.14)	4.04 (3.69, 4.42)
Rate Ratio (post/pre) (95%CI)	2.16 (0.92, 5.10)	1.13 (0.68, 1.88)	2.21 (1.09, 4.46)	0.92 (0.60, 1.39)
RRR‡ (95%CI)	1.90 (0.66, 5.50)	8.6 / 1,000 PY	2.41 (1.12, 5.17)	5.3 / 1,000 PY

Male Hypogonadism → TRT

• Sexual Function – Libido, ED	improves (young)
• Bone Metabolism	improves (severe)
• Muscle Mass & Strength	modest increase
• Body Compos, Obesity, Insulin Res	improves
• Lipoproteins	minor decreases
• CVD	suggestive benefit
• Cancer: Prostate, Breast	
• Neuro-psychological	
• Erythropoiesis	
• Skin	