

Androgen Deficiency Syndromes in Men: An Evidence-Based, Best Practices Approach

Shalender Bhasin, MD

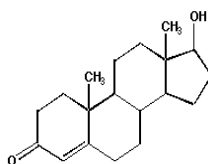
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Independence Center for Function Promoting Therapies

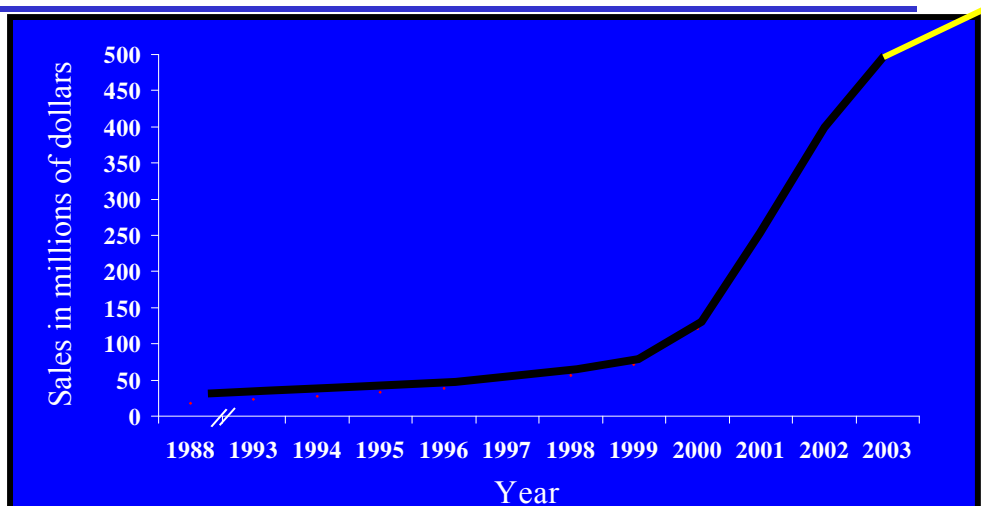
Boston Medical Center



Presenter Disclosure Information Shalendar Bhasin, M.D.

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Other Financial or Material Interest	No relevant conflicts of interest to declare

Testosterone Prescription Sales



Source: IMS Sales Data, BMC Corp.

Courtesy: Reed Selby, ALZA Corporation; Michael Bailey, SmithKline Beecham; Kevin Rose, Solvay-Unimed

Definition

“Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis”

— The Endocrine Society
Clinical Practice Guidelines

Bhasin S et al. *J Clin Endocrinol Metab.* 2006;91:1995-2010.

The Endocrine Society Guidelines: Diagnosis

- ◆ We recommend making a diagnosis of androgen deficiency only **in men with consistent symptoms and signs** and low serum testosterone levels. 1|⊕○○○
- ◆ We suggest the measurement of morning total T level by a **reliable assay** as the initial diagnostic test. 2|⊕○○○
- ◆ We recommend confirmation of the diagnosis by repeating measurement of total T and in some patients by measurement of free or bioavailable T level, using an appropriate assay. 1|⊕○○○

Expert Panel

S Bhasin (Chair)
GR Cunningham
F Hayes
A Matsumoto
PJ Snyder
RS Swerdloff
V Montori
(Methodologist)

Bhasin et al, JCEM 2006

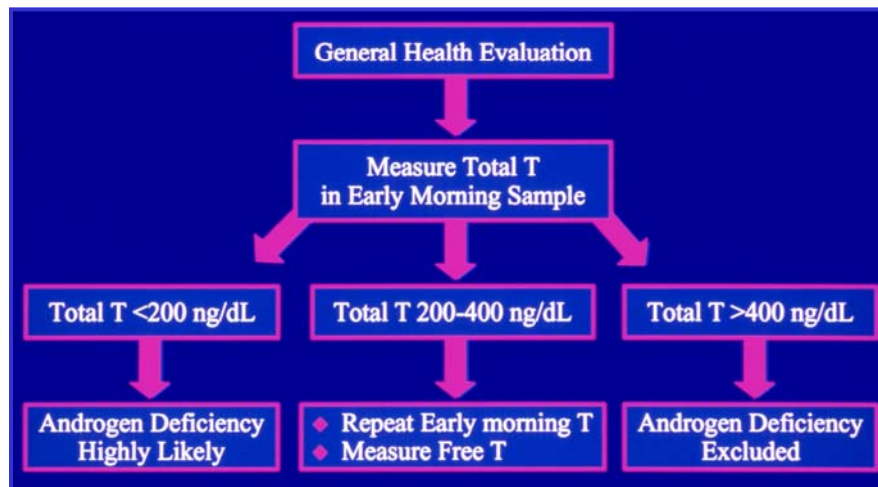
Which of these men has hypogonadism?

1. 24-year old man is evaluated for failure to develop secondary sex characteristics. PE reveals eunuchoidal proportions, few facial hair, female pattern escutcheon, phallus 3 cm, and testes 4 mL bilaterally. Serum total T level is 70 ng/dL, free T 10 pg/mL, LH 1 U/L, FSH 0.5 U/L.
2. 35-yr old HIV+ man on multiple anti-retroviral drugs is evaluated for 20 lb weight loss over 6-months, without a discernible cause. Normal facial and pubic hair; phallus 9 cm; testes 15 mL b/L. Serum T 220 ng/dL, LH 4 U/L, FSH 4 U/L, prolactin 15 ng/mL. Pituitary MRI normal.

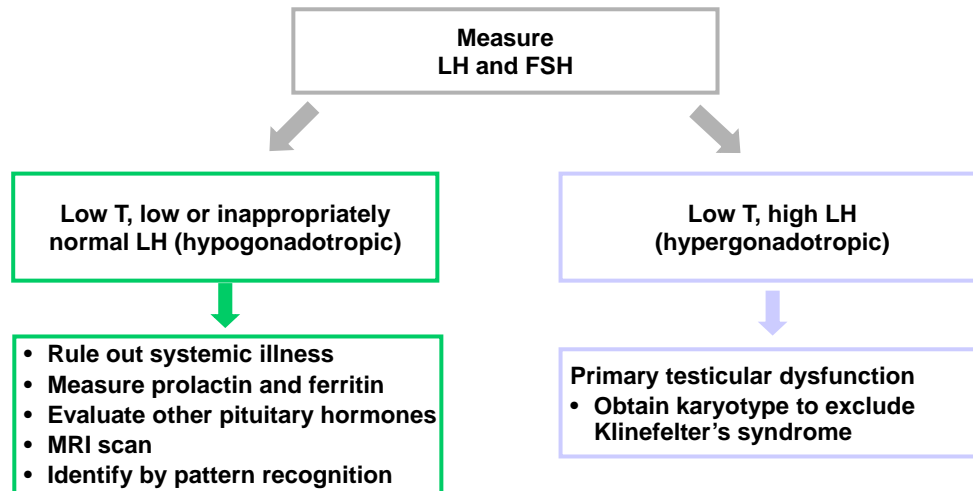
Which of these men has hypogonadism?

3. 55-year old man is evaluated for difficulty in achieving erections. He is being treated for hypertension with benazepril. PE reveals normal hair growth, phallus 9 cm, testes 20 mL b/L. Serum total T is 305 ng/dL, LH 5 U/L, FSH 4 U/L, prolactin 15 ng/ml. MRI of sella is normal.
4. 75-year old man complaints of fatigue, and difficulty with erections and memory. T 250 ng/dL, LH 10.5 U/L. FSH 12 U/L

Diagnostic Work Up of Androgen Deficiency



Further Workup of Patients With Androgen Deficiency



Adapted from Bhasin et al, JCEM 2006

Challenges in Making the Diagnosis of Androgen Deficiency

- ◆ Signs and symptoms are nonspecific and depend on:
 - age of onset
 - Severity and duration
 - Co-morbid illnesses
 - Variations in androgen sensitivity
 - Previous T therapy
- ◆ Threshold T level unknown
- ◆ T levels vary
 - Circadian, circannual rhythms, & episodic secretion
 - Assay variations
 - Variations in SHBG concentrations

Variability in T Levels Across Visits: BACH Study

Two testosterone values obtained 1-3 days apart

VISIT 1		VISIT 2		TOTAL
ng/dL	≤ 300 ng/dL	$> (300$ ng/dL)		
≤ 300	16	5		21
> 300	7	93		100
TOTAL	23	98		121

Diagnosis of androgen deficiency should not be made on a single low value.
The lower the first T level, the lower the risk of misclassification.

* 300 ng/dL = 10.4 nmol/L ; Brombilla et al, Clin Endocrinol 2007

Inter-Laboratory and Inter-Assay Variability in Testosterone RIAs

Instrument/Assay	Laboratories (n)	Mean	SD	CV	Median	Range	
						Low	High
Abbot Architect	11	243.5	13.8	5.7	243	219	262
Bayer ACS:180	83	317.6	39	12.3	314	227	410
Bayer Centaur	231	324.0	41.5	12.8	319	234	454
Bayer Immuno-1	43	300.6	16.7	5.6	300	254	335
Beckman Access/2	98	297.8	15.3	5.1	298	239	330
Diagnostic Systems solid	10	352.7	80.1	22.7	375	177	440
DPC Coat-a-Count	76	277.8	34.2	12.3	281	196	363
DPC Immulite	86	232.0	32.9	14.2	228	160	330
DPC Immulite 2000	83	210.8	33.5	15.9	215	130	299
Roche Elecsys/E170	87	349.9	23.0	6.6	348	299	408
Ortho Vitros ECI	54	282.3	15.8	5.6	280	254	324
All Instruments	891	293.6	56.2	19.1	297	130	508

Wang C et al. *J Clin Endocrinol Metab.* 2004;89:534-543.

Need for Rigorous Reference Ranges

- ◆ Reference range refers to the statistical distribution of hormone concentrations in general population
- ◆ Rigorously determined reference ranges are crucial for clinical decision making because:
 - Essential for identifying individuals as “healthy” and “diseased”
 - Determine effectiveness of therapy and follow-up of patients
- ◆ Problems:
 - Vary widely across laboratories
 - Population-based reference ranges not available
 - Lower limits as low as 120 ng/dL and upper limits as high as 1,800 ng/dL have been reported

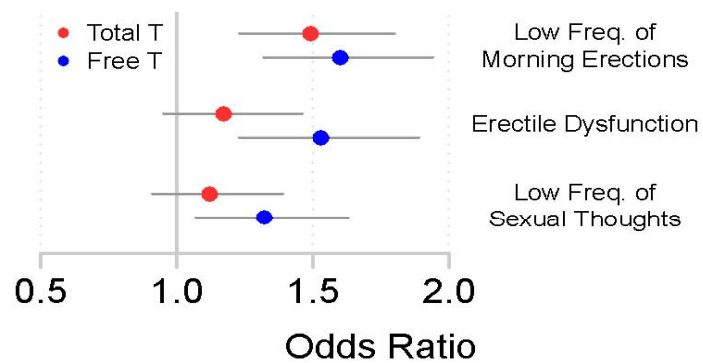
Distribution of Total and Free T in the FHS Reference Sample

	Total T (ng/dL)	Free T (pg/mL)
Mean	724	142
SD	221	45
Median	699	134
Quartile Range (Q3-Q1)	297	60
99 th percentile	1322	266
97.5 th percentile	1197	230
95 th percentile	1124	222
5 th percentile	406	77
2.5 th percentile	348	70
1 st percentile	282	55

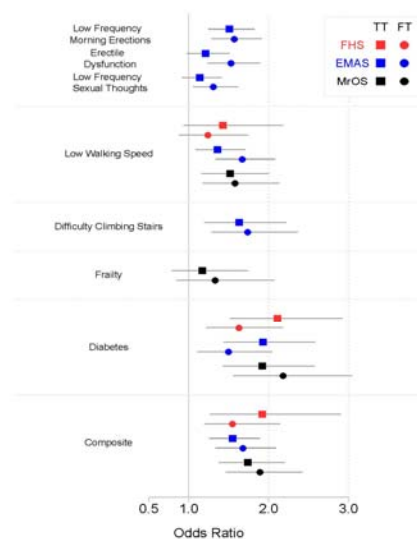
Reference Sample:

- 19-40 years
- Healthy
- Normal chol
- Normal FBG
- No comorbid condition

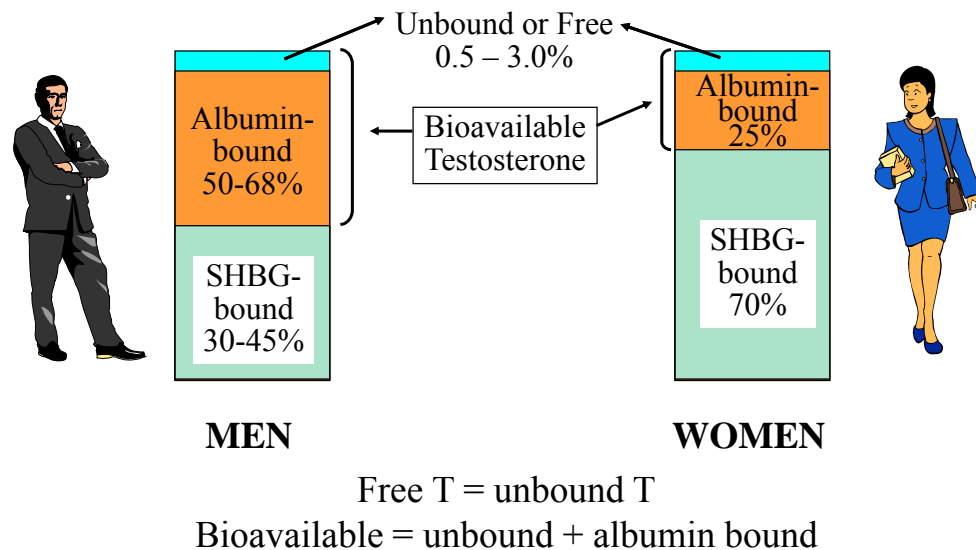
Low T and Sexual Function Measures in EMAS



Low Testosterone and Outcomes



Plasma Binding Proteins and Concept of Free and Bioavailable Testosterone

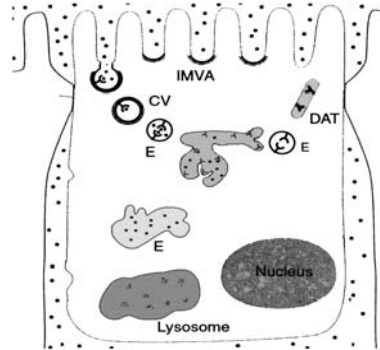


Methods for Free T Measurement

- ◆ Methods with reasonable clinical correlation:
 - Equilibrium dialysis methods
 - Estimates of free T from total T and SHBG concentrations
 - Bioavailable T by ammonium sulfate precipitation
- ◆ Tracer analog methods should Not be used

How Valid Is the Free Hormone Hypothesis?

- ◆ Albumin-bound T dissociates in tissue capillaries of brain and liver¹
- ◆ Excellent correlation between non-SHBG T and
 - Mean clearance rate²
 - Clinical outcomes³
- ◆ SHBG-bound T can be internalized by megalin-mediated process⁴



1. Pardridge WM. *Endo Rev.* 1981;2:103-123. 2. Vermeulen A et al. *Z Klin Chem Klin Biochem.* 1969;7:111. 3. Manni A et al. *J Clin Endocrinol Metab.* 1985;61:705-710. 4. Hammes A et al. *Cell.* 2005;122:751-762.

Five Golden Rules for Making the Diagnosis of Androgen Deficiency in Men

- ◆ Measure T levels only in men with signs and symptoms.
- ◆ Rather than using unvalidated questionnaire, evaluate clinical features with the understanding that sexual and physical symptoms are more informative than behavioral and psychological symptoms.
- ◆ Measurement total T levels by a reliable assay, such as LC-MS/MS, preferably in the morning.
- ◆ Use the normative ranges specific to that assay.
- ◆ Confirm low T level by repeating T measurement.

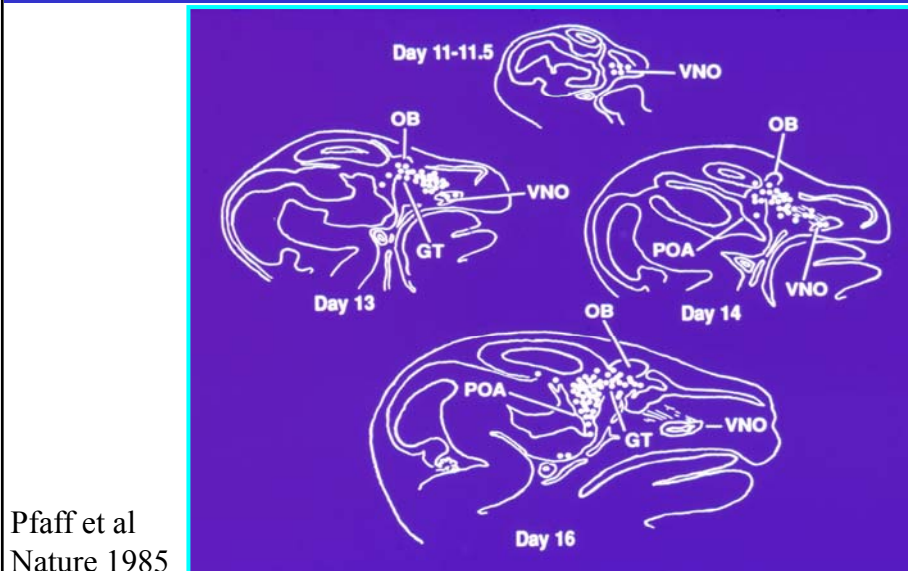
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Genes Associated with Hypogonadotropic Hypogonadism

Inheritance	Gene	Loss of function phenotype
X-linked	Kal1 DAX1	HH+anosmia HH+adrenal insufficiency
Autosomal dominant	FGFR1	Aut dominant form of HH
Autosomal recessive	GnRHR GPR54 SF1 NELF Prok2, Prok2R Tac3, Tac3R Leptin Leptin R GnRH	HH, poor response to GnRH Impaired GnRH secretion Sex reversal + adrenal insufficiency HH+ anosmia HH + anosmia HH Obesity+HH Obesity+HH Hpg mouse, IHH, one case of human mutation

Migration of GnRH Neurons to the Hypothalamus in the Mouse Embryo



Pfaff et al
Nature 1985

***GPR54* Gene as a Regulator of Puberty**

- ◆ A G-protein coupled receptor for kisspeptin family of proteins that regulates reactivation of GnRH neurons at puberty, LH and FSH response to GnRH, and sensitivity to sex steroid feedback
- ◆ Mutations in GPR54 reported in 5% of patients with autosomal recessive IHH
- ◆ Null mutations in GPR54 in mice associated with isolated hypogonadotropic hypogonadism, normal GnRH levels

Seminara et al, NEJM 2003;349:1614

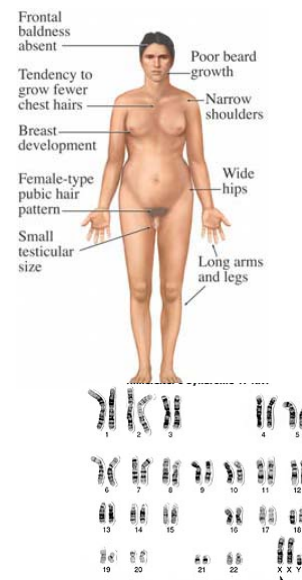
Mutations of Homeodomain Transcription Factors are Associated with heritable Disorders of Pituitary Development

Gene Mutation	PIT1	PROP1	HESX1
GH	Absent	Low	Low
Prl	Absent	Low	?
TSH	Low	Low	?
LH, FSH	Normal	Absent	?
ACTH	Normal	Low in 1/3	?
ADH	Normal	Normal	Normal/Low
Pituitary Size	Small/Medium	S/M/L/XL/XXL	Small
Complex Phenotype	No	No	Septo-optic dysplasia

From: Parks JS. J Clin Endocrinol Metab 1999 Dec. 84(12): 4362-70

Klinefelter's Syndrome

- ◆ 47, XXY karyotype: nondysjunction during meiosis
- ◆ Approx. 1 in 500 males
- ◆ Mosaicism (46, XY/47,XXY) is more common
- ◆ Childhood: behavioral and learning problems
- ◆ Normal pubertal development
- ◆ Present with infertility or androgen deficiency
- ◆ Characteristic phenotype: very small testes, eunuchoidal proportions, gynecomastia
- ◆ Normal performance IQ, but low verbal IQ



Excess Morbidity and Mortality in Klinefelter's Syndrome

- ◆ KS patients are at increased risk for:
 - raised overall mortality
 - Breast cancer
 - Certain types of non-Hodgkin's lymphomas
 - Lung cancer
- ◆ Lower risk for prostate cancer

Men with KS should undergo periodic screening for breast cancer.

Swerdlow et al JNCI 2005 Aug 17;97(16):1204-10; Swerdlow et al JCEM 2005; 2005 Dec;90(12):6516-22

Case 3: 55-Year Old Man with Erectile Dysfunction and Low T Levels

Penile Erections Can Occur in the Absence of Testosterone



“But when the night was half-spent, he bethought him that he had forgotten in his palace somewhat which he should have brought with him, so he returned privily and entered his apartments, where he found the Queen, his wife, asleep on his own carpet bed embracing with both arms a eunuch of loathsome aspect and foul with grease and grime...So he drew his scimitar, and cutting the two in four pieces with a single blow, left them on the carpet....”

Sir Richard Burton, The Arabian Nights, 1850

Role of Testosterone in Spontaneous vs Induced Sexual Response

- ◆ Compared to eugonadal men, hypogonadal men had:
 - Lower self-reported sexual activity, feelings and thoughts
 - Lesser number of spontaneous erections
 - Similar erectile response to visual erotic stimulus
- ◆ Testosterone replacement for hypogonadal men:
 - Increased sexual feelings and thoughts, and sexual activity
 - Increased number of spontaneous erections
 - But did not change erectile response to visual erotic stimulus

**Spontaneous, but not stimulus-induced, erections
are testosterone dependent**
Testosterone stimulates sexual thoughts and feelings

Kwan et al, J Clin Endocrinol Metab 1983;57:557-62

T Improves Many Domains of Sexual Function in Androgen-Deficient Men

- ◆ Spontaneous sexual thoughts and fantasies
(*Kwan 1983, Bancroft 1985*)
- ◆ Frequency of spontaneous erections
(*Kwan 1983, Cunningham 1990*)
- ◆ Sexual arousal and enjoyment in response to erotic auditory stimulus
(*Alexander 1997*)
- ◆ Frequency and duration of nocturnal erections
(*Cunningham 1990, Carami 1990*)
- ◆ Overall sexual activity
(*Wang 1996, 2004, Snyder 2000, Arver 1997*)

Androgen Deficiency and ED are Two Independently Distributed Disorders

- ◆ Frequency of low bioavailable testosterone levels is similar in middle-aged and older men with ED and without ED (*Korenman et al, JCEM 1990;71:963-70*).
- ◆ Six to 10% of men with ED have low testosterone levels (*Buvat and Lemaire J Urol 1997;158:1764-9*)

Meta-analyses of T Effects on Men with Sexual Dysfunction

- ◆ Moderate treatment effect on libido (0.4, 95% CI 0.05, 0.8)
- ◆ Inconsistent effects on erectile function; moderate effect in men with T (<300 ng/dL)
- ◆ No effect on orgasmic and ejaculatory function
- ◆ Inconsistent effects on response to PDE5 inhibitors (Shabsigh 2004; Aversa 2003)

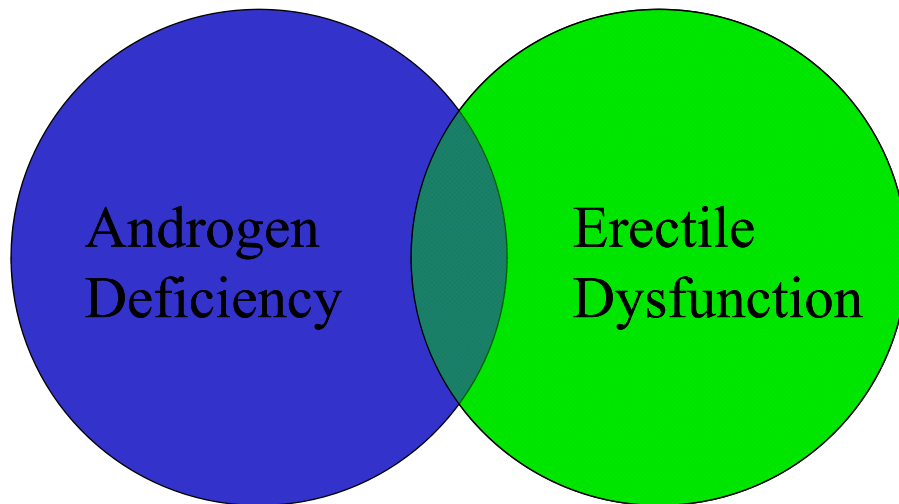
Caveats: imprecise estimates due to subject heterogeneity, variation in treatment regimens; incomplete reporting

Jain et al, 2001; Montori et al 2005

Testosterone Might be Necessary for Achieving Optimal Penile Rigidity

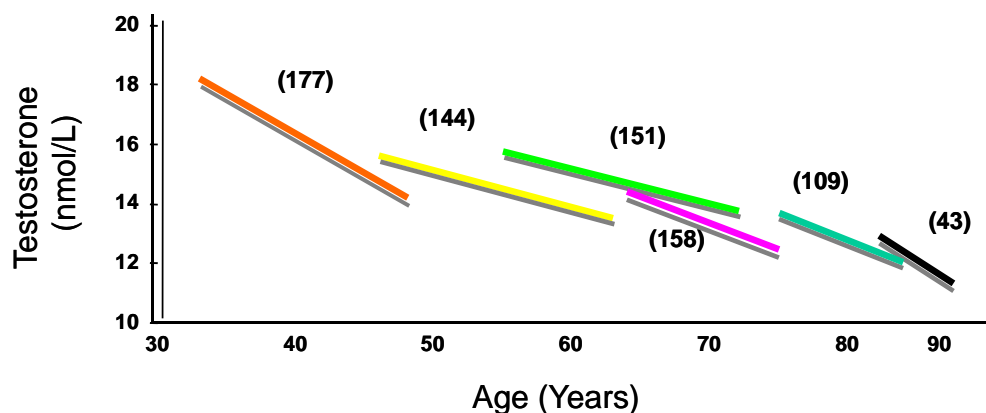
- ◆ T restores penile NOS activity in castrated rats, and regulates PDE5 and Rho kinase activity.
(*Seo 1999; Baba 2000, Penson 1996; Lugg 1996; Traish et al, 2005*).
- ◆ T enhances penile blood flow; essential for venous occlusion
(*Mills et al, 1997, 1998*).
- ◆ T has trophic effects on cavernosal smooth muscle and bulbospongiosus and ischiocavernosus muscles.
(*Shabsigh 2000*)
- ◆ T required for effective veno-occlusion (*Mills et al, 1997, 1998, 2000*)

Androgen Deficiency and Erectile Dysfunction
are Two Independently -Distributed Conditions



-
- ◆ 65-Year Old, Man with Fatigue, Sexual Dysfunction, and Low Testosterone Level:
Clinical Significance of Age-Associated Decline in Serum Testosterone Levels

Longitudinal Changes in Serum T Levels: Baltimore Longitudinal Study of Aging



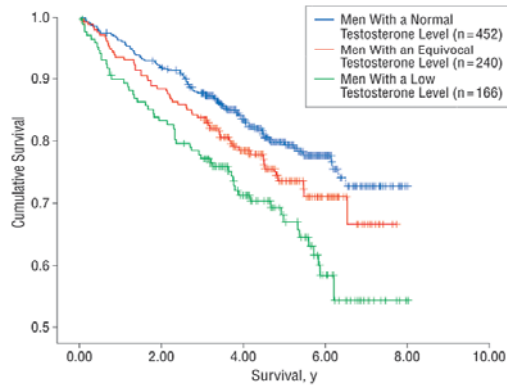
Harman SM, et al. *J Clin Endocrinol Metab.* 2001;86:724-731.

Epidemiological Data: Weak Association of Low T and Outcomes

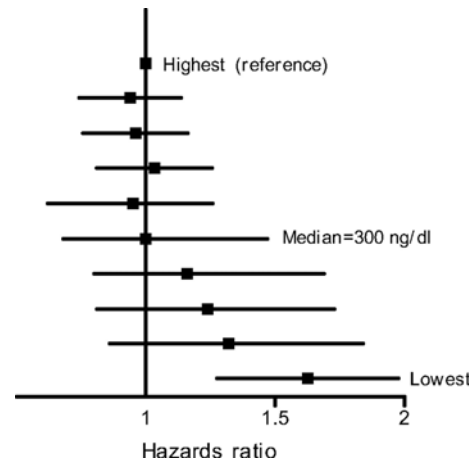
- ◆ Directly weakly associated with:
 - Muscle mass (Baumgartner 1998; Melton 2000), strength (Morley 2000), and physical function (MMAS 2005)
 - Sexual desire (Beutel 2005; Travison 2005)
 - BMD, vBMD and bone geometry (Khosla 2005)
- ◆ Inversely associated with:
 - CAD (Wu 2003; von Eckardstein 2003)
 - Visceral fat (Seidell et al)
 - Mortality (Shore et al 2006)
 - Diabetes mellitus (Haffner 1996; Stellato)
 - Falls and fractures (Orwoll 2007)
- ◆ Not associated with:
 - Aging-related symptoms (T'Sjoen 2004)
 - Prostate volume or LUTS (Schatzl 2000)
 - Erectile Dysfunction (Korenman, 1996 ; Morley 1997)
 - Depression indices (Seidman 2001; Barrett-Connor 2001; Schatzl 2000)

Low Testosterone Levels are Associated with Increased Risk of Death

The VA Study



Rancho Bernardo Study

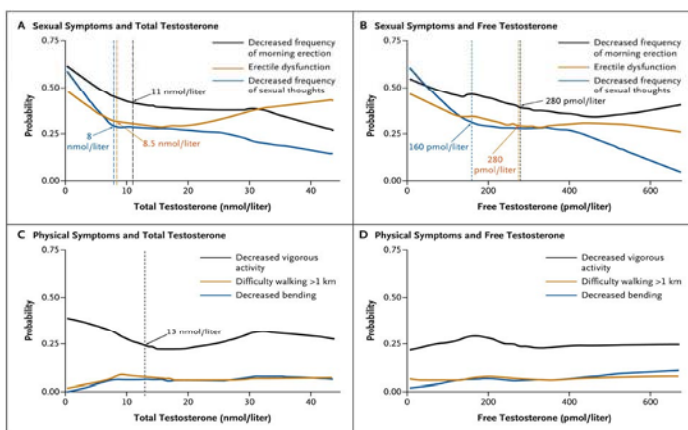


Shores, M. M. et al. Arch Intern Med 2006;166:1660-1665.

Shores et al, Arch Int Med 2006 Laughlin JCEM 2008;93:68-75.

Copyright restrictions may apply.

Identification of Late-Onset Hypogonadism: Probability of Symptoms on the Basis of Total and Free T Levels

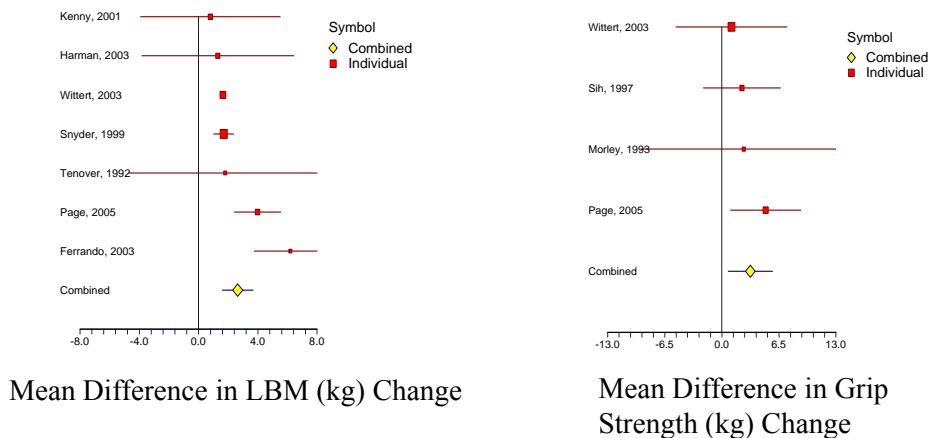


Late-onset hypogonadism can be defined by:

- At least three sexual symptoms, and
- Total T < 320 ng/dL
- Free T < 64 pg/mL

Wu FCW et al. N Engl J Med 2010;363

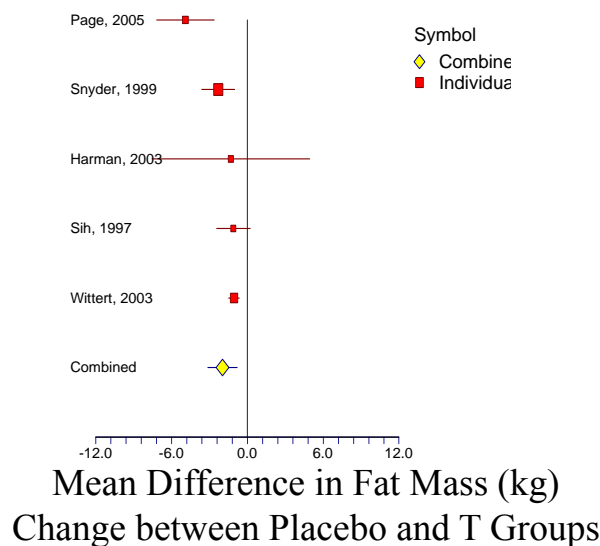
Meta-analysis Plots of Lean Body Mass and Grip Strength Change in Older Men



T increases muscle mass and grip strength

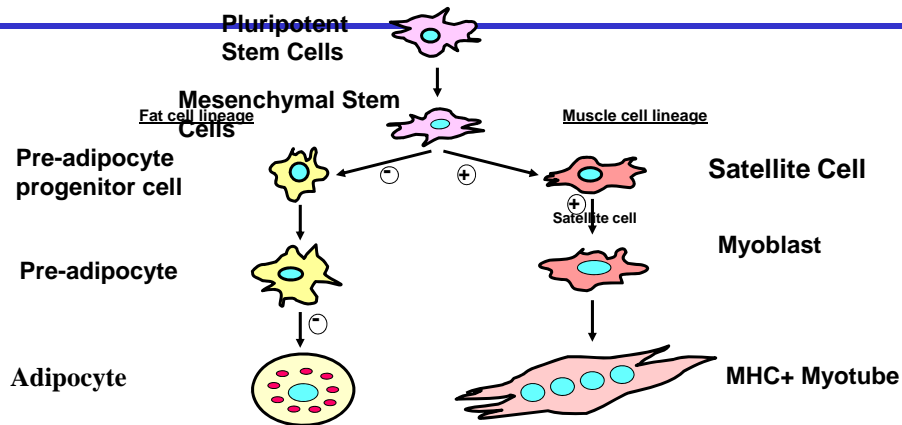
Bhasin Nature CPEM 2005

Meta-analysis Plot of Fat Mass Change in Older Men



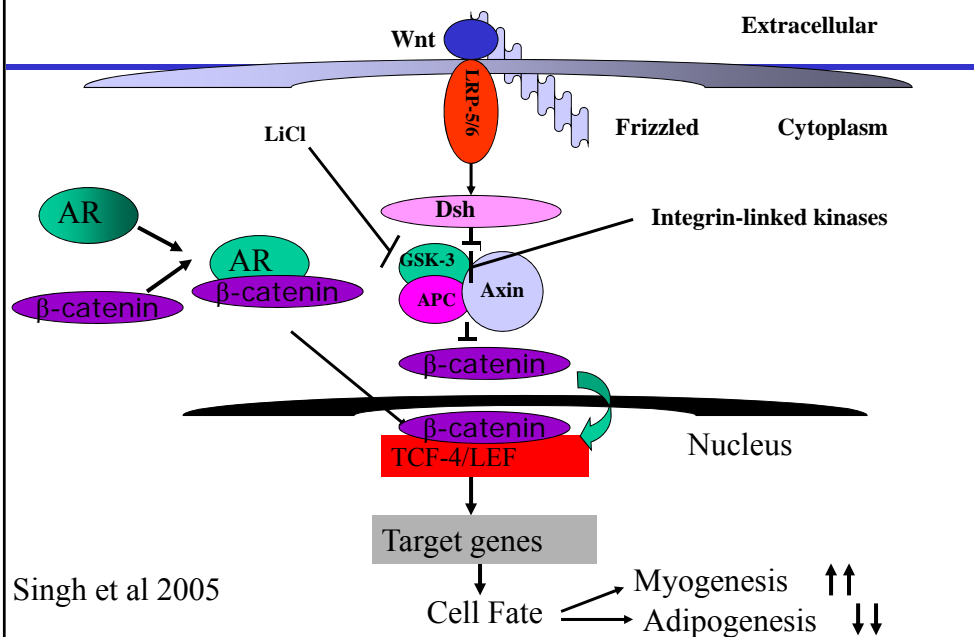
Bhasin et al Nature CPEM 2005

Mechanisms of Androgen Action on the Muscle



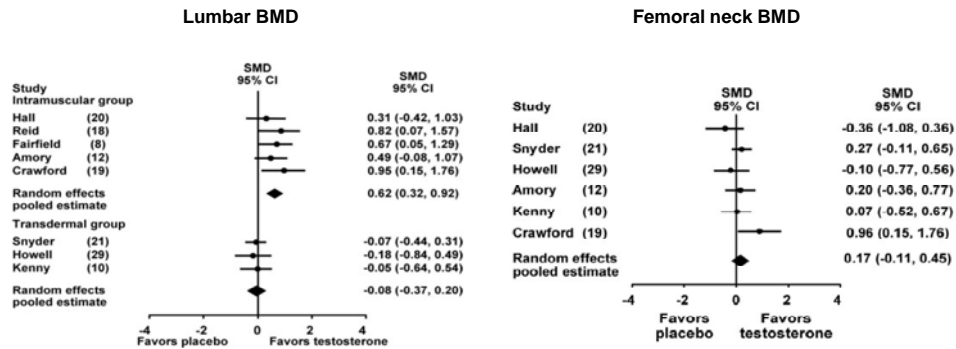
Bhasin et al, *J Gerontol Med Sci* 2003; Singh et al, *Endocrinology* 2003, 2005

Wnt Signalling Pathway



Singh et al 2005

Meta-analysis of the Effects of T Therapy on BMD



Improvements in vertebral but not hip BMD

Tracz et al. JCEM 2006; 91(6):2011–2016

Mood, Cognition, and HRQOL

- ◆ No overall effect on:
 - Cognition
 - HRQOL
- ◆ Improvements in physical function domain of HRQOL (0.5, CI 0.03, 0.9)
- ◆ Anecdotal evidence and evidence from open-label trials of improvement in mood and sense of well being in hypogonadal men (Wang 1996)

Montori 2005

Conditions in which T Therapy is Associated with High Risk of Adverse Outcomes and Should NOT be Administered

Very high risk of adverse outcomes

- ◆ Metastatic prostate cancer
- ◆ Breast cancer

Moderate to high risk of adverse outcomes

- ◆ Undiagnosed prostate nodule or induration
- ◆ Unexplained PSA elevation (>3 ng/mL)
- ◆ Severe lower urinary tract symptoms, as indicated by AUA score > 19
- ◆ Erythrocytosis (Hct > 50%)
- ◆ Untreated obstructive sleep apnea
- ◆ Unstable CHF (Class III or IV)

Testosterone Supplementation: Long-term Monitoring Concerns

- ◆ Erythrocytosis
- ◆ Increasing the risk of detection of prostate events
- ◆ Increasing the growth of metastatic prostate cancer
- ◆ Cardiovascular disease
- ◆ Fluid retention
- ◆ Gynecomastia
- ◆ Sleep apnea
- ◆ Exacerbation of LUTS

Bhasin S, JCEM 2006; Bhasin et al, J Androl 2001;22:718-31; Bhasin et al J Androl 2003; Calof J Gerontol 2005

Meta-Analysis of Adverse Events in Testosterone Replacement Trials in Older Men

Event	Rate for testo-sterone	Rate for placebo	Odds Ratio	95% CI
Prostate cancer	5/643	2/427	1.11	0.48, 2.58
PSA>4	27/643	14/427	1.20	0.68, 2.12
Biopsies	21/643	1/427	1.93	0.86, 4.37
Total prostate events (cancer, biopsies, PSA>4, increased IPSS score)	56/643	18/427	1.80	<u>1.08, 3.00</u>
Hct>50%	36/643	1/427	3.69	<u>1.18, 5.28</u>
All cardiac events (A fib, MI, chest pain, CABG, CVA)	15/643	14/427	1.10	0.55, 2.21
Death	0/643	2/427	0.79	0.31, 1.98

*Clopper-Pearson method ; random effects model; Calof et al, J Gerontol 2006

Testosterone Supplementation and Risk of Prostate Cancer: Issues

- ◆ Many older men have microscopic foci of prostate cancer; T might make these subclinical foci grow.
- ◆ Older men with low T levels may have prostate cancer (Morgentaler et al, 1996)
- ◆ PSA levels increase after T administration (Meikle et al, 1997; Behre et al, 1994; Cooper et al, 1994).
- ◆ Inherent bias towards detection of greater number of prostate events in T-treated men (Calof 2005)

Adapted from Bhasin S, J Androl.2001;22:718-31. Bhasin et al, J Androl 2003; Bhasin et al, JCEM 2006

PSA Monitoring

52-year old man is started on testosterone therapy for androgen deficiency. 3-months after initiating therapy, his PSA rises from 2.4 to 3.2 ng/mL. His DRE reveals slightly enlarged prostate. You should now do the following:

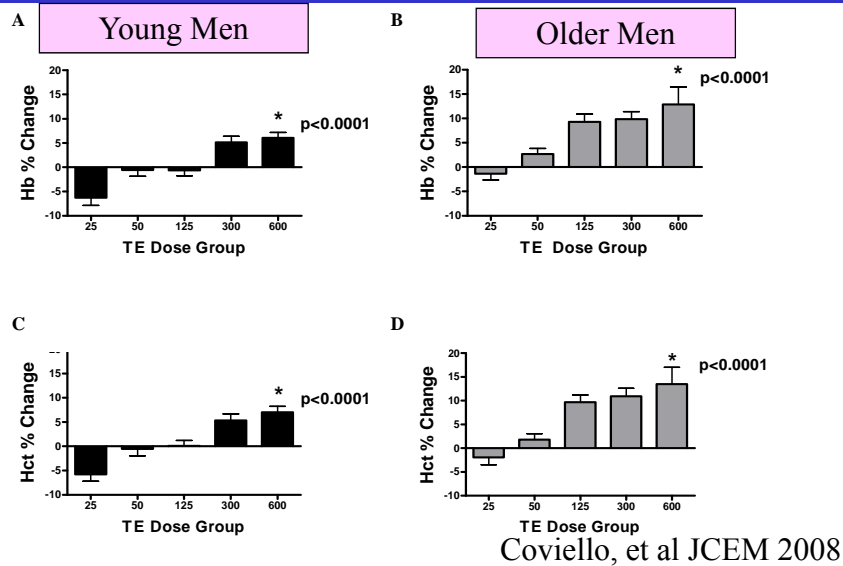
1. Follow-up in one year
2. Repeat PSA
3. Urological consultation
4. Refer for prostate biopsy

Hematocrit Monitoring

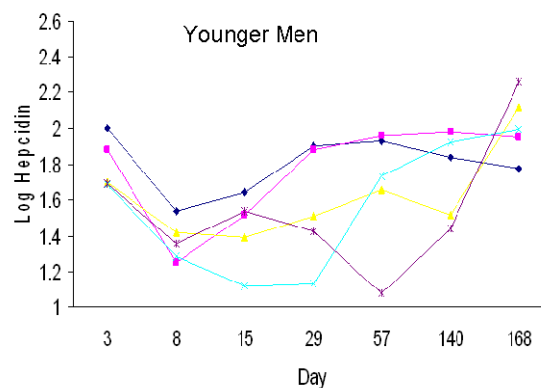
52-year old man is started on testosterone enanthate 100 mg weekly for androgen deficiency. 3-months after initiating therapy, his hematocrit rises from 46% to 55%. He feels well and reports improvements in sexual desire, activity, energy, and mood. You should now do the following:

- ◆ Discontinue testosterone therapy
- ◆ Reduce the dose
- ◆ Switch to a transdermal gel
- ◆ Follow-up in 4-6 weeks
- ◆ Follow-up in 6 months

Older Men Experience Greater Increase in Hb/Hct After T Therapy Than Younger Men



T Suppresses Hepcidin Dose-Dependently



Bachman et al 2009

Endocrine Society Expert Panel's Guidelines for Monitoring During Androgen Therapy

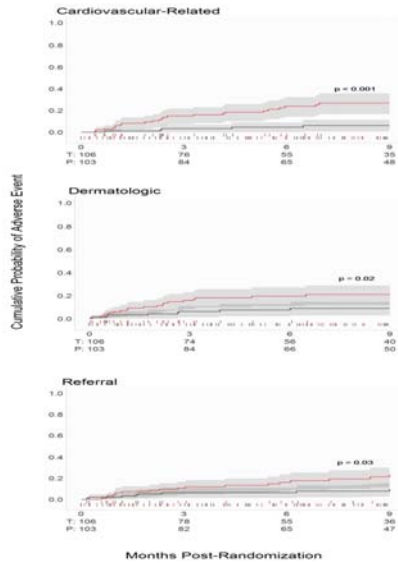
- ◆ At baseline, at 3, 6, 12 months after starting T therapy, monitor hemoglobin, PSA, DRE, AUA symptom score, sleep apnea scores
- ◆ Obtain Urological consultation if:
 - Change in PSA of >1.4 ng/ml in any one year period (*Finasteride Study group, Gormley, 1992*)
 - PSA velocity of >0.40 ng/ml/year (*Carter et al, 1995*).

Bhasin et al, J Androl 2001;22:718-31; Bhasin et al, J Androl 2003; Bhasin et al JCEM 2006

Testosterone and Cardiovascular Risk

- ◆ Testosterone levels are lower in men with CAD than in healthy controls (*Alexanderson 1996*)
- ◆ Physiologic T replacement has little or no effect on plasma HDLC in older men (*Snyder et al, 1999; Tenover 2000; Sih et al, 1997*)
- ◆ Testosterone
 - improves coronary blood flow (*Ong et al, 2000; English et al, 2000*)
 - Reduces visceral fat and improves insulin sensitivity in middle aged men (*Marin et al 1992*)
 - Retards atherosclerosis progression in LDL-receptor deficient mice (*Nathan et al, 2001*)
- ◆ T supplementation induces increase in LV mass (Casaburi unpublished)

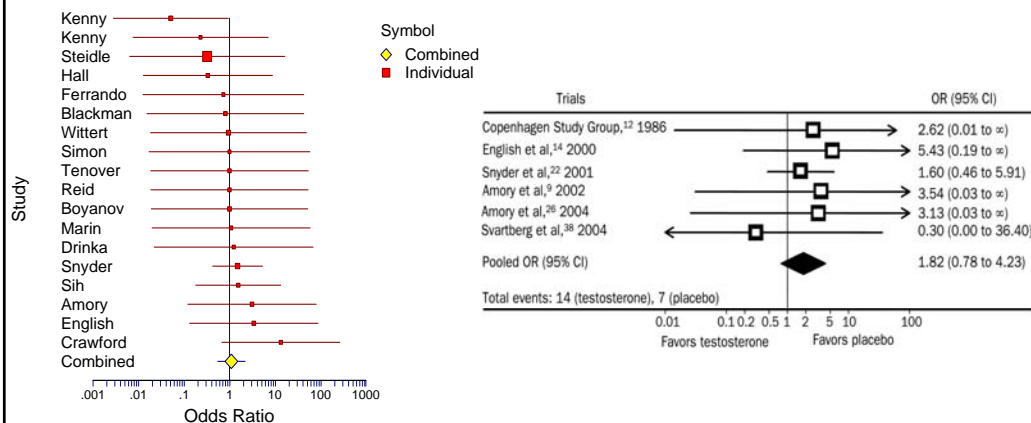
Increased Frequency of CV and Dermatologic Events, and Referrals for Adverse Events in Men Assigned to Testosterone Arm



The Trial's DSMB recommended cessation of enrollment and treatment discontinuation due to increased frequency of CV adverse events.

Basaria S, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363:109-22.

Meta-analyses Cardiovascular Events in Testosterone Trials



Calof et al, *J Gerontol* 2006

Haddad R M et al. *Mayo Clin Proc.* 2007;82:29-39

Summary

- ◆ There is insufficient evidence of either efficacy or safety of T therapy in older men with specific clinical conditions.
- ◆ In older men with mobility limitation and high burden of chronic conditions, T therapy may be associated with increased risk of CV events.
- ◆ If T therapy is instituted on an individualized basis, it should be guided by careful exclusion of CV and prostate risk factors, and a standardized monitoring of PSA, hematocrit, and CV events.

What is Male Hypogonadism?

Patient Category	Does patient have hypogonadism?	Benefits of TRT Demonstrated?	Risks of TRT
Case 1: 24-Year old man with IHH	Yes	Benefits in intermediate outcomes in open-label trials of 3-month to 3 yrs	Low in trials of up to 3-years duration
Case 2: Low T in Illness-Related Sarcopenia	No: Illness-related decline in serum T	T increases body wt, FFM, strength, wellbeing. Effects on health-outcomes unknown.	Short term use relatively low risk; long term risks unknown
Case 3: Low T with ED	AD and ED separate conditions	Possible, but not demonstrated in RCTs	Unknown
Case 4: Age-Associated Decline in T	Significance unknown	Not demonstrated in adequately powered, RCTs	Unknown

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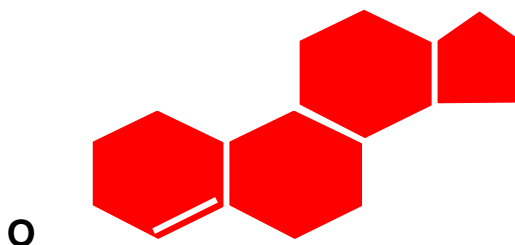
Mechanisms

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King Testosterone



OH



The NIA's T Trials: IOM Report on Future of Testosterone Research

Neither the clinical benefits nor the long term safety of testosterone therapy in older men has been established...

- ◆ Short-term RCTs of no longer than 1-year duration
- ◆ Older men with specific syndromes, attributable to androgen deficiency, and low T levels
- ◆ Replacement doses of testosterone
- ◆ Adequately powered to determine efficacy using clinically relevant outcomes, rather than surrogate endpoints
- ◆ Conduct larger trials to determine safety only if efficacy has been demonstrated

Blazer et al, 2003; Snyder 2004; Barrett-Connor and Bhasin 2004

Inherent Bias Towards Detection of Greater Number of Prostate Events in T-treated Men

- ◆ Prostate biopsies usually triggered by PSA increments in clinical trials
- ◆ PSA increments more likely in T-treated men than in placebo-treated men leading to greater number of biopsies and detection of subclinical prostate events.

Calof *et al* J Gerontol 2006; Bhasin *et al* Nature CPEM 2006

T Therapy in Men with Prostate Cancer Who have been Disease-free

- ◆ **Lack of RCT data precludes general recommendation**
- ◆ Some have suggested that men with low T who have been disease-free for >2 years after radical prostatectomy may be considered for T therapy on an individualized basis (*Kaufman et al. 2004; Agarwal et al, 2005*).

Testosterone and Cardiovascular Risk

- ◆ Testosterone levels are lower in men with CAD than in healthy controls (*Alexanderson 1996*)
- ◆ Physiologic T replacement has little or no effect on plasma HDLC in older men (*Snyder et al, 1999; Tenover 2000; Sih et al, 1997*)
- ◆ Testosterone
 - improves coronary blood flow (*Ong et al, 2000; English et al, 2000*)
 - Reduces visceral fat and improves insulin sensitivity in middle aged men (*Marin et al 1992*)
 - Retards atherosclerosis progression in LDL-receptor deficient mice (*Nathan et al, 2001*)
- ◆ T supplementation induces increase in LV mass (Casaburi unpublished)

Testosterone Effects on HRQOL and Cognition

- ◆ No significant effect on overall SF-36 HRQOL score; significantly greater improvement in physical function domain than placebo (0.5, 95%CI 0.3, 0.9)
- ◆ No significant effect on cognition
- ◆ No significant improvement in depression indices (-5, 95%CI -1.0, +0.1)

Caveats: Limited data, Imprecise results, suboptimal power

Montori et al, unpublished

A Systematic Review of T Effects in Healthy, Hypogonadal Men

- ◆ In men, lowering of T associated with:
 - Loss of muscle mass and strength, and BMD
 - Increase in fat mass
 - Decreased sexual activity and hot flushes (Riggs 2002; Mauras 1998)
- ◆ In young, hypogonadal men, T replacement:
 - Increases FFM (1.7 kg, 95%CI 1.52, 1.96), body mass (1.1 kg, 95%CI 0.4, 2.6)
 - Decreases fat mass (0.7 kg, 95%CI 1.0, -0.5)
 - Increases maximal voluntary strength
 - Overall sexual activity, sexual desire
 - Mood

(Bhasin Nature CPEM 2006; Brodsky 1997; Katznelson 1997; Bhasin 1998; Wang 2000, 2004; Snyder 2000)

T Effects on Bone Outcomes

- ◆ No data on bone fractures
- ◆ Two trials of 3-years duration showed a moderate effect on lumbar bone density (0.4, CI 0.1,0.7) (Snyder 1999; Amory 2004)
- ◆ Ruled out a moderate treatment effect on femoral neck bone density (0.0, CI -0.3, 0.3)

Montori 2005

Indications for Urologic Consultation

We recommend that clinicians obtain urological consultation if there is: 1|⊕○○○

- ◆ Verified serum or plasma PSA concentration >4.0 ng/mL
- ◆ Increase in PSA of >1.4 ng/mL in any 12-month period
- ◆ PSA velocity >0.4 ng/mL/year using the PSA level after 6 months of T therapy as the reference.
 - PSA velocity should be used only if there are longitudinal PSA data for more than 2 years.
- ◆ Detection of a prostatic abnormality on DRE
- ◆ An IPSS/AUA prostate symptom score of >19

Monitoring strategies and schedule

- ◆ We recommend evaluating the patient at 3 months and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering any adverse effects. (1|⊕○○○)
- ◆ We suggest monitoring T levels at 3 months. (2|⊕○○○)
 - Therapy should restore serum testosterone levels to the mid-normal range.
- ◆ We recommend determining hematocrit at baseline, 3 months, and then annually. (1|⊕○○○)
 - If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level, evaluate the patient for hypoxia and sleep apnea, and reinstitute therapy at a reduced dose.
- ◆ We suggest repeating BMD of the lumbar spine, femoral neck, and hip after 1 to 2 years of T therapy in men with osteoporosis/low trauma fracture. (2|⊕○○○)
- ◆ We recommend DRE and PSA measurement before treatment, at 3 months, and then in accordance with guidelines for prostate cancer screening, depending on the age and race of the patient. (1|⊕○○○)

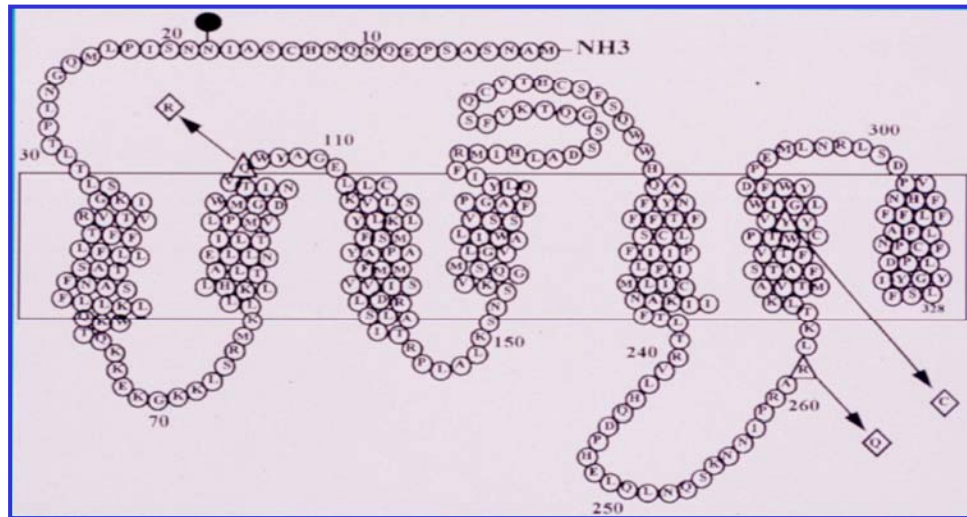
Meta-analyses of T Effects on Men with Sexual Dysfunction

- ◆ Moderate treatment effect on libido (0.4, 95% CI 0.05, 0.8)
- ◆ Inconsistent effects on erectile function; moderate effect in men with T (<300 ng/dL)
- ◆ No effect on orgasmic and ejaculatory function
- ◆ Inconsistent effects on response to PDE5 inhibitors (Shabsigh 2004; Aversa 2003)

Caveats: imprecise estimates due to subject heterogeneity, variation in treatment regimens; incomplete reporting

Jain et al, 2001; Montori et al 2005

Mutations of the GnRH Receptor Gene in Autosomal Recessive Form of IHH

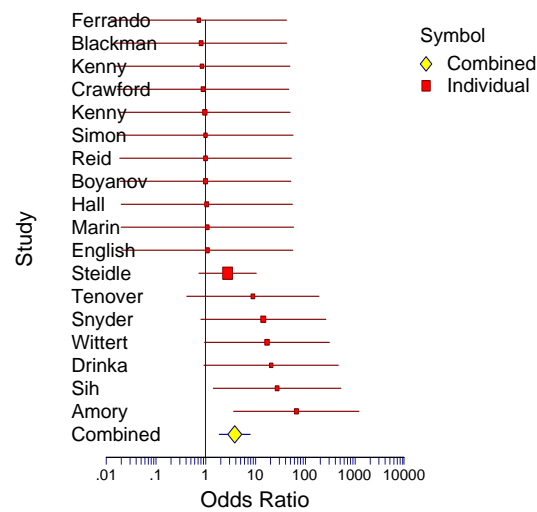


From: Layman: *Fertil Steril*, Volume 71(2), February 1991, 201-218

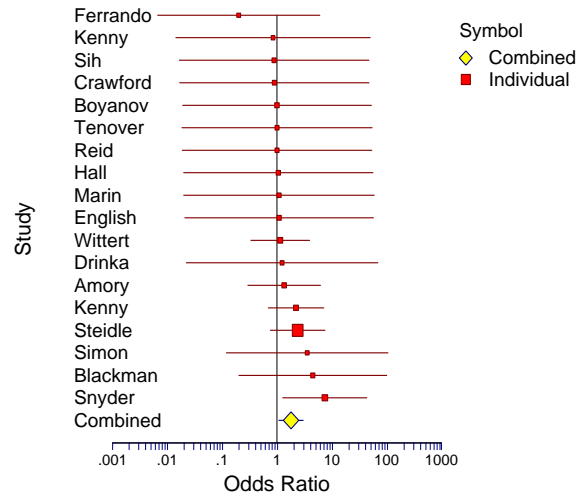
Testosterone, Mood, and Depression

- ◆ Testosterone replacement improves positive aspects of mood and decreases negative aspects of mood in healthy, hypogonadal men (Wang *et al*, 1996; Alexander *et al*, 1998) and HIV-infected men (Grinspoon *et al*, 2000; Rabkin *et al*, 2000).
- ◆ Higher prevalence of low T levels in men with clinical depression (Levitt *et al*, 1988; Seidman *et al*, 2002).
- ◆ Subjects with refractory depression receiving T had greater improvements in Hamilton Depression score than those on placebo (Pope 2003).

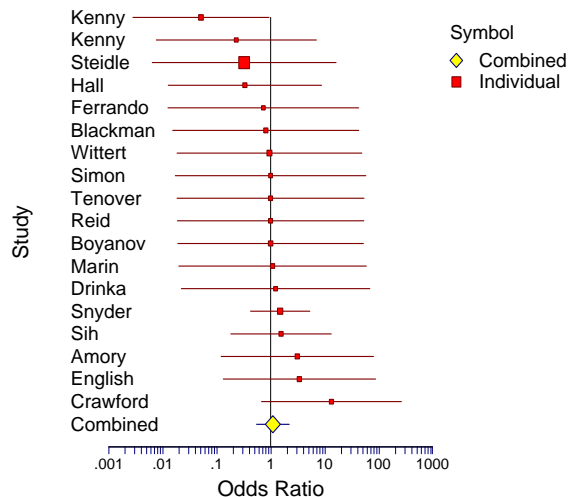
Hematocrit Greater than 50%



Prostate Events



Cardiovascular Events



Summary and Conclusions

- ◆ Hypogonadism in men should be defined as a syndrome of signs and symptoms in association with unequivocally low T levels. The benefits of T replacement in this syndrome have been demonstrated in short term open-label trials.
- ◆ Testosterone isn't just for sex; it has important role in maintenance of many physiologic systems.
- ◆ Measurement of total T is the best screening test.
- ◆ Androgen deficiency can be treated effectively by one of many available formulation with attention to its PK, cost, and patient preference.
- ◆ T replacement should be accompanied by a standardized monitoring plan.

Testosterone Supplementation and Risk of Prostate Cancer: Issues

- ◆ Many older men have microscopic foci of prostate cancer; testosterone might make these subclinical foci grow.
- ◆ Older men with low testosterone levels may have prostate cancer (Morgentaler et al, 1996)
- ◆ PSA levels and prostate volumes increase after T administration (Meikle et al, 1997; Behre et al, 1994; Cooper et al, 1994).
- ◆ More intensive PSA screening might lead to greater number of biopsies and diagnoses of subclinical cancers.

Adapted from Tremblay J, Morales A. *Aging Male*. 1998;1:213-218; Bhasin S, J Androl. 2001;22:718-31. Andropause Consensus Panel 2001.

Evidence for Testosterone Role in Regulating Sexual Function

- ◆ Androgen-deficient men have decreased sexual desire, fantasies, and spontaneous erections than eugonadal men (*Kwan et al, 1983; Cunningham et al, 1990*).
- ◆ Men whose T levels are lowered for sexual offenses or treatment of prostate cancer experience decreased sexual desire and activity (*Bradford, 1997*)
- ◆ T treatment of androgen-deficient men increases sexual activity, desire, and fantasies (*Arver 1996; Wang 2000; Carami 1990; Bagatell 1994*).
- ◆ T replacement in hypogonadal men increases the frequency, size, and duration of nocturnal penile tumescence (*Cunningham 1990*).

Androgen Therapy: Contraindications

- ◆ Prostate cancer
- ◆ Breast cancer
- ◆ BPH with severe symptom score or bladder outlet obstruction
- ◆ Erythrocytosis with hematocrit >52%
- ◆ Severe sleep apnea
- ◆ Severe (class IV) congestive heart failure

Adapted from Bhasin, S, J Androl 2001;22:718-31; Andropause Consensus Panel, 2001
Tremblay J, Morales A. *Aging Male*. 1998;1:213-218.

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Penile Erections Can Occur in the Absence of Testosterone

“But when the night was half-spent, he bethought him that he had forgotten in his palace somewhat which he should have brought with him, so he returned privily and entered his apartments, where he found the Queen, his wife, asleep on his own carpet bed embracing with both arms a eunuch of loathsome aspect and foul with grease and grime...So he drew his scimitar, and cutting the two in four pieces with a single blow, left them on the carpet....”

Sir Richard Burton, The Arabian Nights, 1850

Cost Effectiveness of the Pituitary Work-Up in Men with Secondary Hypogonadism

- ◆ Cost effectiveness unknown
- ◆ Low prevalence of radiological hypothalamic-pituitary abnormalities (*Citron et al, 1996; Buvat et al, 1997*)
- ◆ Diagnostic yield can be improved by limiting imaging studies to men with:
 - Total T < 150 ng/dL
 - Panhypopituitarism
 - Persistent hyperprolactinemia
 - Tumor mass effect

Percent of Community-Dwelling Older Men with Unequivocally Low Testosterone Level

Study	Principal Investigator	# Men > 65 yrs	% Men with T <250 ng/dL
Norwegian	Svartberg	1432	17.1%
MrOs	Orwoll	2623	10%
European Male Aging	Wu	1080	7.3%
Cardiovascular Health Study	Hirsch	639	14.3%

Koch's Postulates Applied to Men with IHH (Case 1) or Panhypopituitarism

- ◆ Men with IHH have:
 - low total and free T levels
 - Loss of sec. sex characteristics
 - Decreased sexual desire and activity
 - Decreased bone mass
 - Changes in body composition

(Crowley et al, 1985, 1988; Finkelstein 1990; Katznelson et al, 1996; Bhasin 2004).
- ◆ Lowering T by GnRH agonist reproduces many of these features:
 - (Mauras 1998; Bhasin and Swerdloff 1985)
- ◆ T replacement of GnRH agonist-treated men corrects abnormalities

(Mauras 1998)