

Increasing Awareness, Diagnosis, and Treatment of Hypogonadism

~ Jacob Rajfer, MD

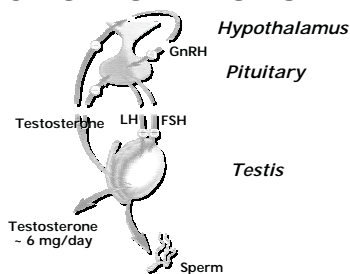
HYPOGONADISM

DEFINITION: PRODUCTION OF SEX HORMONES AND GERM CELLS IS INADEQUATE (ENDOCRINE SOCIETY)

DEFECT OF THE REPRODUCTIVE SYSTEM THAT RESULTS IN LACK OF FUNCTION OF THE GONADS (Wikipedia)

REDUCTION IN TESTICULAR FUNCTION
(www.nature.com/nrg/journal/v2/n4/glossary/nrg0401_245a_glossary.html)

FUNCTION OF TESTIS

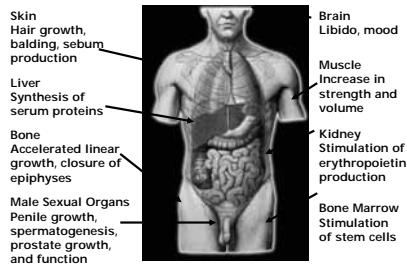


Adapted from Bagatell CJ, Bremner WJ. *N Engl J Med*. 1996;334:707-714.

FUNCTION OF TESTIS

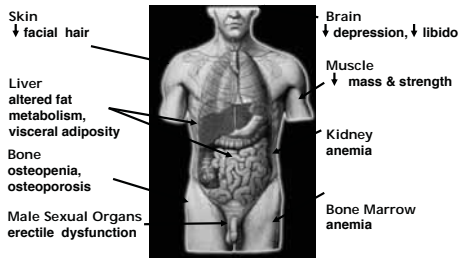
1. SPERMATOGENESIS
 - A. BEGINS AT PUBERTY
 - B. CONTRIBUTES TO ABOUT 80% OF TESTIS VOLUME
 - C. DECREASES WITH AGING (FSH may increase)
2. TESTOSTERONE PRODUCTION
 - A. BEGINS TO INCREASE AT PUBERTY
 - B. PRODUCES ABOUT 6 mg of T per day adult
 - B. DECREASES WITH AGING (LH may increase)

THE IMPACT OF TESTOSTERONE



Ref: AACE Hypogonadism Task Force.
Endocrinol Pract. 2002;8:439-456
Morley JE, et al. *Metabolism.* 2000;49:1239-1242.

THE IMPACT OF ↓ TESTOSTERONE



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What Is a “Low” Level of Testosterone?

- Definition of “low T” varies widely
- Most labs define “low T” based on lowest 2.5% of values
- Yet prevalence is >2.5%
- Most clinical trials use threshold values ranging from 325-400 ng/dL
- Each person may have his own individual threshold value

Diagnosis of Androgen Deficiency/Hypogonadism

- Signs/symptoms of hypogonadism and
- Confirmatory blood test (sT, f T, bT)

(SALIVARY T MEASUREMENT OK BUT NOT STANDARDIZED)

Prevalence of Study-Defined Testosterone Deficiency in Older Men

Study	Ages	N	Serum total testosterone (mg/dL)	Prevalence
Lungimayr	50-87	817	<300	11.4%
Tenover	20-100	300	<317	22% (80-100y) 36% (80-100y)
Tenover (unpublished)	60-83	379	<350 <300 <250	36% 19% 8%
Morley (unpublished)	75-101	77	<245	33%

What is the most common cause of hypogonadism in men > 50 y age

- HIV
- Obesity
- Aging
- Hyperprolactinemia
- Medications

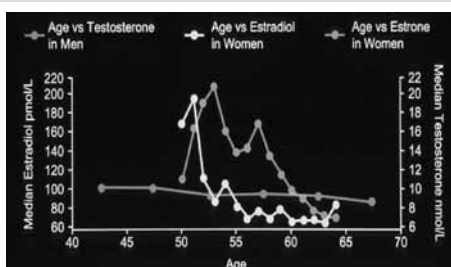
CAUSES OF HYPOGONADISM

- > PRIMARY TESTICULAR FAILURE
- > HYPOGONADOTROPIC HYPOGONADISM (KALLMANN'S SYNDROME, PITUITARY ADENOMA)
- > TRAUMA
- > IDIOPATHIC
- > OBESITY
- > SEVERE SYSTEMIC ILLNESS (INCLUDING HIV)
- > MEDICATIONS
- > CHANGES IN GnRH, PROLACTIN, CORTISOL, AND THYROID HORMONES
- > NORMAL AGING

GnRH=gonadotropin-releasing hormone

Winters S.J. *Arch Fam Med.* 1999;8:257-263.
Tenover J.L. *Endocrinol Metab Clin North Am.* 1998;27:969-987.

T in Men and E2 in Women During the Middle Years



Massachusetts Women's Health Study (1981-1996) and Massachusetts Male Aging Study (1986-1989)

**THE AGING MALE : ANDROPAUSE
CLINICAL SYMPTOMS**

1. LOSS OF LIBIDO, ED - 1st RECOGNITION
2. TIREDNESS, LETHARGY
3. DECREASED COGNITION
4. RESTLESSNESS, DEPRESSION
5. LOSS OF STRENGTH

ANDROPAUSE CAN BE DEFINED AS A SYMPTOM COMPLEX
IN THE PRESENCE OF LOW LEVELS OF TESTOSTERONE

**THE AGING MALE : ANDROPAUSE
CLINICAL SIGNS**

- OSTEOPENIA / OSTEOPOROSIS
- LOSS OF MUSCLE MASS
- INCREASED VISCERAL ADIPOSITY
- TESTICULAR ATROPHY
- GYNecomastia

REF: JCEM 71: 963-69, 1990; JCEM 85: 3276-82, 2000; Am J PSYCH 155: 1310-8, 1998;
BEHAV NEUROSCI 108: 325-32, 1994; J Bone Miner Res 12:1883-43, 1997
Aging Male 2:8-15, 1999; Clin Endocrinol 47: 379, 403, 1997

The ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any 3 other questions.

Morley JE. J Genit Specif Med. 2001;4:49-53.

TRT - WHEN?

- **HYPOGONADISM
OVERT LOW T LEVEL
AT ANY AGE**
- **ANDROPAUSE¹
CLINICAL AGING SYNDROME**

¹F & S: 81:1437-40, 2004

DIAGNOSTIC TESTOSTERONE TESTING

(IF T LEVEL IS OR SUSPECTED TO BE LOW)

Additional Tests:

- **LH and FSH**
– To ascertain whether cause is primary or secondary
- **Serum prolactin**
– High prolactin levels may suggest presence of pituitary tumor

**BENEFITS OF T – TX OF
HYPOGONADISM (LOW T)**

- Preserve or improve bone mass
- Increase muscle mass, rearrange fat
- Increase strength, stamina and physical function
- Improve libido and mood, HRQoL
- **Possibly** decrease cardiovascular risk

(MOST DATA ARE IN YOUNG MEN)

REF: Snyder et al, 1999, 2001; Sih et al, 1997; Kenny et al., 2001, 2002

ANDROGEN R_x OLDER MEN

1. BMD -spine  8% over 3 yrs
-hip  3% over 3 yrs

2. Lean Body Mass  8% over 3 yrs

3. Body Fat  15% over 3 yrs

REF: Adapted from Tenover. *Int J Androl.* 1999;22:300.

**How long after starting TRT will a
hypogonadal symptom start to
improve**

- 3 months
- 6 months
- 9 months
- 12 months.

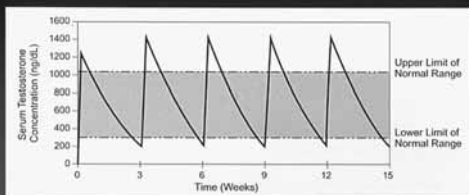
CONTRAINDICATIONS OF TESTOSTERONE REPLACEMENT THERAPY IN MEN

- KNOWN OR SUSPECTED PROSTATE CANCER
- MALE BREAST CANCER
- KNOWN OR SUSPECTED SENSITIVITY TO INGREDIENTS USED IN TESTOSTERONE THERAPY SYSTEMS
- ELEVATED HEMOCRIT

ANDROGEN PREPARATIONS

- ORAL
- BUCCAL
- PARENTERAL
- TRANSDERMAL PATCH
- TRANSDERMAL GEL

Testosterone Enanthate 250 mg Administered IM Every 3 Weeks



Behre HM et al. In: Testosterone: Action, Deficiency, Substitution. Berlin, Germany: Springer-Verlag; 1996:329-348

ANDROGEN PREPARATIONS

TRANSDERMAL PATCH

- Testoderm (scrotal) - Delivers 4-6 mg testosterone daily
- Testoderm TTS (arm/torso/thigh skin) Delivers 5 mg testosterone daily
- Androderm (arm/torso/thigh skin) Delivers 2.5-5 mg testosterone daily

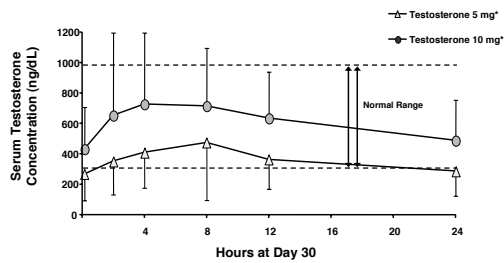
ANDROGEN PREPARATIONS

TRANSDERMAL GEL

- ANDROGEL OR TESTIM 1%
(ARM/TORSO SKIN)
5 G/DAY

Testosterone 1% Gel

Testosterone Concentration (Day 30)



Steidle C, et al. *J Clin Endocrinol Metab.* 2003;88:2673.

*Approx. delivered testosterone dose

CLOMIPHENE CITRATE

WORKS WHEN LH IS LOW

EFFECTIVE AS A Q O D PILL (25 – 50 mg)

MINIMAL SIDE EFFECTS

DOES NOT SUPPRESS SPERMATOGENESIS

CHECK SERUM T IN 2-3 WEEKS

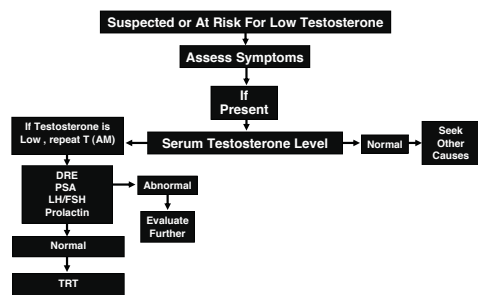
Rajfer J; Personal experience

TRT : NOT RECOMMENDED

hCG, DHEA, DHEAS, DHT

http://www.uroweb.org/fileadmin/user_upload/Guidelines/14%20Hypogonadism.pdf

Diagnosis and Treatment Algorithm for Testosterone Deficiency



DRE=Digital Rectal Exam, PSA=Prostate Specific Antigen, TRT=Testosterone Replacement Therapy, LH=Luteinizing Hormone, FSH=Follicle Stimulating Hormone.

Patient Monitoring with Testosterone Replacement Therapy

Baseline, Pre-therapy:	Testosterone levels Hgb and Hct PSA level DRE IPSS
Day 30:	Testosterone levels
Day 90:	Hgb and Hct PSA level DRE IPSS
Repeat Day 90 Measures:	Month 9 and every 6-12 months thereafter

Hgb=Hemoglobin, Hct=Hematocrit, PSA=Prostate-Specific Antigen, DRE=Digital Rectal Exam, IPSS=International Prostate Symptom Score.

LOH

LOH: underdx. & undertx

LOH is a syndrome characterized primarily by:

- (1) The easily recognized features of **diminished sexual desire (libido) and erectile quality** and frequency, particularly nocturnal erections.
- (2) Changes in **mood** with concomitant **decreases in intellectual activity, cognitive functions, spatial orientation ability, fatigue, depressed mood and irritability.**
- (3) **Sleep disturbances.**
- (4) **Decrease in lean body mass** with associated diminution in muscle volume and strength.
- (5) **Increase in visceral fat.**
- (6) **Decrease in body hair and skin alterations.**
- (7) **Decreased bone mineral density** resulting in **osteopenia, osteoporosis** and increased risk of bone fractures.

Ref: ISA*, ISSAM**, and EAU recommendations
http://www.uroweb.org/fileadmin/user_upload/Guidelines/14%20Hypogonadism.pdf

**A Ten-Year Safety Study of the Oral
Androgen Testosterone Undecanoate**

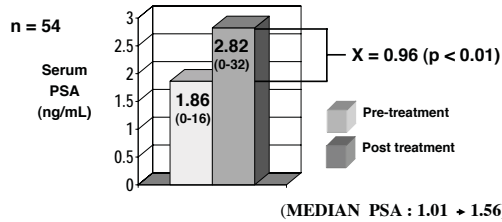
N = 33/35 men followed for 10-year minimum; 8/33 >50 y age

- No gynecomastia
- No liver abnormalities
- No prostate abnormalities
- 2/8 > 50y age showed slight decrease in urine flow
- Levels of T remained stable
 - No liver enzyme activation

REF: Gooren. J Androl. 1994; 15: 212-215.

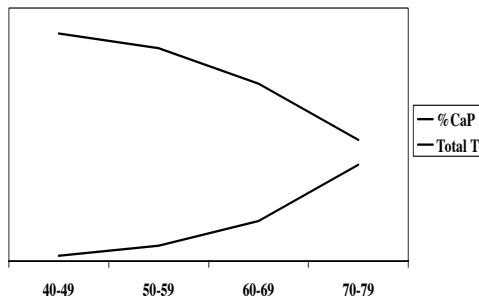
**Effect of Testosterone Supplementation
on Serum PSA**

Dose = 200-300 mg, Q2-4wks Mean F/U = 30.2 mos
6 biopsies (11%), 1 PCa Mean Age = 60.4 yrs



Gerstenbluth RE, et al. J Androl. 2002; 23:922-926.

CaP Prevalence Increases as T Levels Decline



**Case series: reports of clinically apparent
tumor diagnosed in men while on TRT**

	TRT (months)	Patients	Prostate Cancer
Hajjar, 1997	24	45	-
Sih, 1997	12	17	-
Dobs, 1999	24	66	3
Snyder, 1999	36	54	1
Snyder, 2000	36	18	0
Wang, 2000	6	76	0
Kenny, 2001	12	34	0
Wang, 2004	36	123	3
Total		433	7 (1.6%)

**Effects of Exogenous Testosterone on PSA
Levels**

166 hypogonadal men
3 years of 1% testosterone gel
mean PSA increase of 0.37 ng/ml
3 men diagnosed with cancer (1.8%)

**NOTE: THE PSA RISE OCCURS IN THE
FIRST 6 MONTHS OF TREATMENT AND
REMAINS STABLE THEREAFTER**

Swerdlloff et al. Aging Male 2003;6:207

**Is the incidence in Hypogonadal men
different?**

- 345 “hypogonadal” men (<300 ng/dl)
 - PSA ≤ 4: 15% positive biopsy
 - Markedly suppressed T level: 20% positive biopsy
 - Low T and PSA ≥ 2.0: 30% positive biopsy
- Is this any different than the “baseline” established in PCPT?

Rhoden & Morgentaler. JUrol,2003

**High Levels of Circulating Testosterone Are Not
Associated With Increased Prostate Cancer Risk:
A Pooled Prospective Study**

- N = 708 men (Finland, Norway, Sweden) with prostate cancer
- N = 2,242 men without prostate cancer
- Mean lag time from blood draw to diagnosis was 14 years.
- Decrease in risk of prostate cancer for increasing levels of:

Total Testosterone	OR	0.80
SHBG	OR	0.76
Free Testosterone	OR	0.82

Statlin, et al. Int J Cancer 2004; 108: 418-424

**Testosterone Replacement in Hypogonadal
Men With
Prostatic Intraepithelial Neoplasia (PIN)**

75 hypogonadal men (TT <300ng/dL) after 12 mo TRT

	<u>With PIN</u>		<u>Without PIN</u>
	PSA		
Before TRT	1.49		1.53
After TRT	1.82		1.78
	Biopsy for ↑ PSA		
Bx +	1		0
Bx -	2		4

Overall, one cancer in 75 men (1.3%). No sig difference with PIN

Rhoden et al. J Urol. 2003; 170: 2348-2351

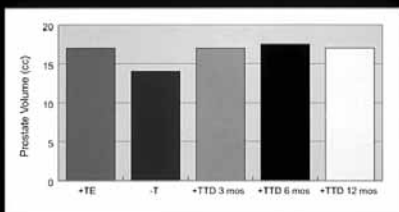
EFFECTS OF TRT ON PROSTATE

- PBO (n = 19) vs T (n = 21: TE 150 mg/2 wk) x 6 mo., TRUS + Bx @ baseline and 6 mo.
- T: 282 → 640 ng/dl (@ 6 mo); no diff PBO
- No increased CA with T tx
- No difference in pT or pDHT with TRT
- No change in PSA, genes for prostate growth

44-78y

REF: Marks et al., JAMA 2006;296:2351-61

Mean Prostate Volume +/- Treatment With Testosterone Enanthate (TE) or Transdermal Patch (TTD)



TRT and PSA

T trials have *inconsistently* shown a rise in PSA- the mean increase has been 0.3-0.43 ng/mL.

Study	Duration mo	Increase in PSA	
		Placebo	Testosterone number/t
Hajjar et al. (1997) ¹⁰	24	-	-
Sih et al. (1997) ⁹	12	0/15	0/17
Dobs et al. (1999) ¹¹	24	-	3/33
		-	0/33
Snyder et al. (1999) ⁸	36	7/54	13/54
Snyder et al. (2000) ⁶	36	-	-
Wang et al. (2000) ²⁰	6	-	0/76
		-	1/73
		-	4/78
Kenny et al. (2001) ⁷	12	3/33	8/34

Duval reported no significant PSA changes in 50 men treated for over 5 years. (Aging Male, 2001)

TRT and BPH?

- Results of studies are conflicting or insignificant
- No well-designed study yet done
- What we have so far:
7 studies of 3-36 months' duration conclude:
 - Prostate volume No change
 - IPSS No change
 - Average urine stream No change

Gettman M, et al. AUA Update Series 2001

• *Despite decades of research there is no compelling evidence that T has a causative role in prostate cancer, that men with higher T levels are at greater risk of prostate cancer or that treating hypogonadal men with androgens increases the risk of converting the biological behaviour of prostate cancer*

T & SLEEP APNEA

THERE IS LACK OF EVIDENCE TO SUPPORT ANY LINK BETWEEN OSA AND TRT

REF: Hanafy HM J Sex Med 4:1241-6, 2007.

ANDROGENS AND CV SYSTEM

Age = 51 y, n = 25 in each group; case control study for plasma total T; no TRT.

- **Lipid metabolism**
- **Insulin sensitivity**
- **Coagulation factors**
- **Vascular responsiveness**

DATA ARE INCONCLUSIVE AT THIS TIME

Simon D. JCEM 82:682-685, 1997

Androgens And Coronary Artery Disease

- 430 references
- "Cross-sectional data have suggested coronary heart disease can be associated with low T in men"
 - But no independent association in prospective studies
- "Based on current evidence, the therapeutic use of T in men need not be restricted by concerns regarding cardiovascular side effects"
- Hypoandrogenemia in men are associated with:
 - Visceral obesity
 - Insulin resistance
 - Low HDL cholesterol
 - Elevated: Triglycerides, LDL cholesterol

Wu and von Eckardstein. Endocrine Reviews. 2003; 24: 183-217

Effects of Testosterone on Serum Lipid Profile in Middle Aged-Men: A Meta-Analysis

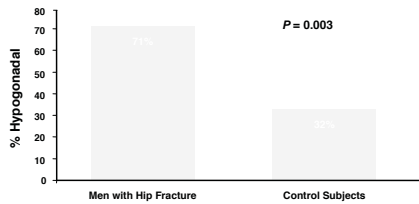
Hypoandrogenemia in men are associated with:
 Visceral obesity
 Insulin resistance
 Low HDL cholesterol
 Elevated: Triglycerides, LDL cholesterol

- Review of randomized- controlled trials (#29) OF TRT
- n = 1,083
- Mean age 64.5 yrs
- **Total and LDL chol ↓**
- **HDL Chol mixed:**
 - Small ↓, esp. in men with higher testosterone
 - Do not give supraphysiological levels

Islidori, et al. Clinical Endocrinology 2005; 63: 280-293

Hip Fractures in Aging Males

Increased Hypogonadism With Hip Fractures



Jackson JA et al. Am J Med Sci. 1992;304(1):4-8.

**Elderly Population >65
% of the Total**

Continents	1950	2000	2025	2050
Europe	8.2	14.6	20.2	25.8
North America	8.2	12.4	18.5	21.5
Latin America	3.7	5.4	9.6	16.7
Asia	4.1	5.8	9.6	15.9
World	5.2	6.8	10.0	15.1

U.N. Data

Conclusions

Testosterone Therapy is Safe In:

- Benign prostate disease (BPH)
- Risk of prostate cancer
 - Men receiving testosterone therapy
 - Men with high normal levels of T
 - Men at higher risk for prostate cancer (PIN)
- Effect on lipids and cardiovascular disease

Low Testosterone May Be Unsafe For:

- Incidence of prostate cancer
- Prognosis of prostate cancer
- Prevention of cardiovascular disease
- Prevention of osteoporosis / fractures
- Overall longevity ?