Point-Counterpoint: Late Onset Hypogonadism (LOH)

We are Under-diagnosing and Treating Men with LOH

~ Jacob Rajfer, MD

LOH is a Non-existent Disease

~ Robert E. Donohue, MD

Late Onset Hypogonadism

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

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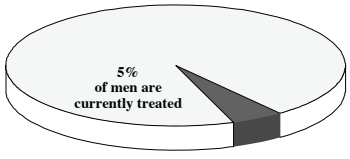
PREVALENCE OF HYPOGONADISM

4 TO 5 MILLION MEN WITH HYPOGONADISM



US Food and Drug Administration Updates. Skin patch replaces testosterone. Available at: http://www.fda.gov/fdac/departs/196_upd.html. Accessed January 19, 2004.

LOH : why is it under tx?

FEAR OF ADVERSE EVENTS

1. PROSTATE CANCER
2. BPH / LUTS
3. SLEEP APNEA
4. C V EVENTS
5. NO DATA TO SUPPORT ↓ MORTALITY

ARE THESE FEARS APPROPRIATE?

The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate

In men with metastatic prostate carcinoma to bone:
Acid phosphatase:

- **Rose in 3 men after testosterone injection**
- **Decreased in 3 men after estrogen administration**
- **Decreased in 8 men after castration**

Since low T causes prostate cancer to shrink, it has been assumed that higher T causes prostate cancer to grow. There are little data to support this.

REF: Huggins, Hodges. *Cancer Research* 1941; 1: 293-297.

Are Serum Hormones Associated With The Risk Of Prostate Cancer?
Prospective Results From The Massachusetts Male Aging Study

- **N = 1,576 men - Approximately 8 year follow-up**
- **70 men (4%) developed prostate cancer**
  - **Correlated positively with PSA levels**
- **No correlation with:**
  - **Total testosterone**
  - **Free testosterone**
  - **SHBG**
  - **Androstenedione**
  - **Estradiol**

Mohr, et al. Urology 2001; 57: 930-935

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

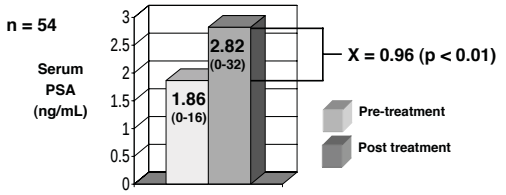
N = 33/35 men followed for 10-year minimum; 8/33 >50 y age

- **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

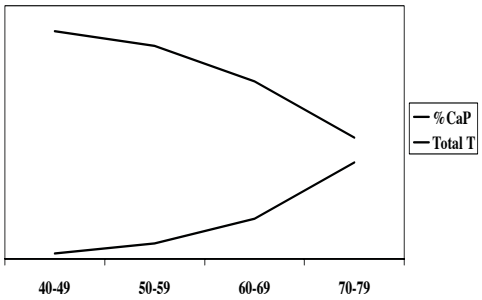
Dose = 200-300 mg, Q2-4wks
6 biopsies (11%), 1 PCa
Mean F/U = 30.2 mos
Mean Age = 60.4 yrs



(MEDIAN PSA : 1.01 → 1.56)

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

Swerdloff 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, Sweeden) 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**

Stattin, 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

	With PIN	**Without PIN**
	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

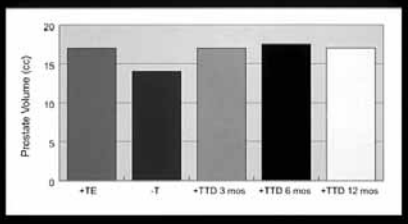
EFFECTS OF TRT ON PROSTATE

- **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	Increase in PSA	
		Placebo	Testosterone
	mo		*number/t*
Hajjar et al. (1997)[32]	24	–	–
Sih et al. (1997)[9]	12	0/15	0/17
Dobs et al. (1999)[11]	24	– –	1/33 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

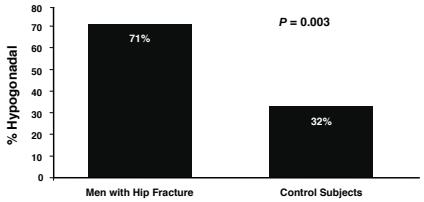
- Review of randomized- controlled trials (#29) OF TRT
- n = 1,083
- Mean age 64.5 yrs

- Total and LDL chol ↓
- HDL Chol mixed:
  - Small ↓, esp. in men with higher testosterones
  - Do not give supraphysiological levels

Isidori, 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 ?