

# LOH is a non-existent disease

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## Hypogonadism

Hypogonadism in men is a clinical syndrome that results from the failure of the testis to produce physiologic levels of Testosterone and the normal levels of spermatozoa due to disruption of one or more levels of the HPG axis.

## Disease

Any deviation from or interruption of the normal structure or function of any part, organ or system, or combination thereof, of the body that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology and prognosis may be known or unknown

## Syndrome

A set of symptoms which occur together; the sum or signs of a morbid state,

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## Hypogonadism

sub-categories

Rx young males with Androgen deficiency with T

Rx Sexual disfunction with T

Older men with lower serum T

Chronic illness and lower serum T

Glucocorticosteroid treated men

## Hypogonadism

serum Testosterone

< 325 ng/dL

60's            20%

70's            30%

80's            50%

Baltimore Longitudinal Study of Aging 2001

## Hypogonadism

serum Testosterone

secondary; not primary

[role of obesity ?]

LH      9.4 to 13.8   15yrs

FSH    14.1 to 27.4

New Mexico Aging Process 1997

LH      0.9% / year

FSH    1.3% / year

Massachusetts Male Aging Study 2002

## Hypogonadism

serum Testosterone

total

free

bound to albumin

SHBG

bio-available free + albumin

Am Soc Repro Med, F&S 86, S236, 2006

## Hypogonadism

benefits of therapy  
older men

long term benefit in  
conditions of concern  
to patient and MD ?

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## Hypogonadism

serum total Testosterone  
assay is widely available  
bio-available and free\* T levels  
are not widely available;

\*free - challenged assay

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## Hypogonadism

total Testosterone  
free Testosterone index\*  
total Testosterone / SHBG

\* bio-available Testosterone

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## Hypogonadism

consensus  
androgen replacement candidates  
hormonal criteria, No  
clinical criteria, No  
additional studies to elucidate  
patients who might benefit from  
androgen replacement

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## Hypogonadism

Endocrine Society

Testosterone total

< 200 ng / dL; treat

200 – 400 ; beneficial ??

> 400 ng / dL; unlikely to benefit

Bhasin JCE&M; 91: 1995, 2007

## Hypogonadism

Endocrine Society

measure LH when serum

Testosterone low, < 150 ng / dL

if LH normal or low

order Prolactin,

pituitary MRI,

## Hypogonadism

candidates

clinical manifestations of ADAM

osteopenia,

low libido,

muscle mass

E quality,

strength down,

irritability,

stamina

impaired

energy down,

cognition,

## Androgen Deficiency suggestive

sexual development

infertility

libido and activity

height loss

decreased erections

muscle bulk/

breast discomfort

strength less

gynecomastia

hot flashes

loss of body hair

sweats

shrinking testes



## Hypogonadism

**candidates**

**Testosterone concentration below which T administration improves outcome is unknown and may vary patient to patient and among target organs**

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## Hypogonadism

**candidates**

**available evidence does not support the use of an arbitrary threshold for T below which clinical androgen deficiency occurs and that confirms the diagnosis of hypogonadism.**

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## Hypogonadism

**candidates**

**threshold Testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur is not known !**

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## Hypogonadism

**concensus**

**androgen replacement candidates hormonal criteria, No clinical criteria, No additional studies to elucidate patients who might benefit from androgen replacement**

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### Hypogonadism

**Sex Hormone Binding Globulin**  
**increases with age**  
**decline in bio-available**  
**Testosterone with normal aging is**  
**greater than for total Testosterone**

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### Sex Hormone Binding Globulin

<b>decreased</b>	<b>increased</b>
<b>obesity</b>	<b>aging</b>
<b>nephrotic Syn</b>	<b>cirrhosis</b>
<b>hypothyroidism</b>	<b>hyperthyroidism</b>
<b>steroids,</b>	<b>anticonvulsants</b>
<b>progestins</b>	<b>estrogens</b>
<b>androgens</b>	<b>HIV infection</b>

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### Hypogonadism

**bio-available Testosterone**  
**epidemiological studies**  
**bone mineral density**  
**sexual function**  
**cognition**  
**metabolites**  
**Estrogen bone; DHT prostate**

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### Hypogonadism

<b>libido</b>	<b>osteopenia</b>
<b>potency</b>	<b>osteoporosis</b>
<b>fatigue</b>	<b>lipid profile</b>
<b>strength loss</b>	<b>cholesterol</b>
<b>muscle loss</b>	<b>triglycerides</b>
<b>weight gain</b>	<b>LDL, VLDL</b>
<b>anemia</b>	<b>HDL</b>

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## Hypogonadism

initial evaluation

breast

heart

lungs

rectal                    23,580 rectal tumors

CBC, PSA

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## Hypogonadism

No evidence that clinical response depends on Testosterone form.

Benefits relate to level achieved !

endogenous / exogenous

goal – raise T over pretreatment

values but not exceeding levels of

normal young adult males

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## Hypogonadism

normal range

Testosterone 300 ng / dL\*

free Testosterone 50 pg / dL

\* Use your reference laboratory

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## Hypogonadism

lack on consensus on

1] case definition

2] extent to which androgen deficiency is an important health problem

3] lack of data on screening tools, population screening cannot be evaluated at present.

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### Hypogonadism

long term health consequences are unknown in two largest subsets of men with low Testosterone: 1] older men and 2] men with chronic diseases Impact, untreated, on mortality is unclear.

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### Hypogonadism

dehydro-epiandrosterone, DHT 50 – 100 mg does not increase serum T androgen deficiency benefit ???

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### Hypogonadism

replacement side effects IM pain, mood swings, elevated hematocrit, patch scrotal site irritation non-scrotal “ , urticaria gel skin irritation

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### Hypogonadism

measure Testosterone IM T 350 – 700 ng / dL controversial –at 8 AM best patch T 3 to 12 hours gel T 1 to 2 weeks buccal T before fresh tablet

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## **Testosterone trials**

**testosterone – young men  
Improvement in overall sexual activity, sexual thoughts and fantasies, attention to erotic stimuli, frequency and duration of nighttime erections, hair growth, increases in fat-free mass, muscle strength, decrease in fat mass.**

## **Testosterone trials**

**Bone mineral density increases but effect on fracture risk is unknown. T improves positive and reduces the negative aspects of mood, improves energy and sense of well-being, and some studies report improvement in visuospatial cognition and verbal memory.**

## **Testosterone trials**

### **recommendations**

**The recommendations to treat young, healthy, hypo-gonadal men with T places a higher value on alleviating hypo-gonadal symptoms and other benefits , and lower value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.**

## **Testosterone trials**

**testosterone - older men  
There are no randomized, placebo- controlled trials of T therapy on depression, cognition, fracture fragility, quality of life and cardiovascular outcomes; libido improved but no significant improvement in self-reported erectile function.**

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**Testosterone trials**

bone mineral density [ BMD ]  
Inconsistent and imprecise data  
@ 1 year - insignificant  
longer trials – 1 to 3 years  
lumbar BMD 2% increase  
femoral neck, No

**Testosterone trials**

bone fracture  
No trial reporting the effect of  
Testosterone on bone fractures  
was reported.

**Testosterone trials**

body composition  
Significantly greater increase  
in LBM [ lean body mass ] and  
reduction in fat mass.  
Body weight change did not  
differ significantly.

**Testosterone trials**

muscle strength and physical  
function  
Greater improvement in grip,  
lower extremity strength but  
measures of physical function  
were inconsistent .

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### Testosterone trials

**11 randomized clinical trials,  
474 men  
muscle strength  
larger effects for lower  
extremity muscle strength than  
upper extremity - injected >topical**  
Ottenbacher J Am Ger Soc 54: 1666, 2006

### Testosterone trials

**sexual function  
Two placebo- controlled trials  
on overall sexual satisfaction  
yielded imprecise results.**

### Testosterone trials

**sexual function  
17 trials - 862 men  
low T; moderate, non-significant  
and inconsistent effect of T on  
satisfaction with erectile function;  
large effect on libido  
none on sexual satisfaction**

### Testosterone trials

**sexual function  
17 trials - 862 men  
low normal and normal T  
small satisfaction of EF effect  
moderate, non-significant libido  
no effect sexual satisfaction**  
Bologa Mayo CI Pro 82: 20, 2007

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## **Testosterone trials**

### **quality of life**

The results were imprecise and inconsistent across trials.

There was improvement in physical function domain.

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## **Testosterone trials**

### **depression**

Three randomized T trials for 3 months or longer showed no significant effects on depression. Inconsistent and imprecise results limit the inferential strength.

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## **Testosterone trials**

### **cognition**

Three placebo-controlled randomized trials, one which studied men with Alzheimer's Disease and low Testosterone, reported imprecise effects on several aspects of cognition; none of which were significant after pooling data.

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## **Testosterone trials**

### **adverse outcomes**

19 randomized trials

### **Prostate Events**

Rates of prostate Ca, PSA > 4 ng and prostate biopsies were numerically higher but not significantly higher.

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## Testosterone trials

adverse outcomes

Erythrocytosis

T treated men were four times as likely to experience a rise in hematocrit above 50%.

## Testosterone trials

adverse outcomes

The frequency of cardiovascular events, sleep apnea or death did not differ significantly between groups.

## Cardiovascular risk

30 trials; 1642 men

Low Testosterone

inconsequential changes in BP and glycemia; lipid profile shows

Cholesterol [-0.22],

HDL [-0.04],

LDL [ 0.06]

Trig [-0.27]

## Cardiovascular risk

30 trials; 1642 men

Currently available evidence weakly supports the inference that T use in men is not associated with important cardiovascular effects. We need large, randomized, clinical trials of men at risk for CVD.

Haddad Mayo CI Pro 82: 29., 2007

### **Testosterone trials**

adverse outcomes  
Lipid profiles  
5 trials reported insignificant changes in major lipid fractions.  
Cholesterol - 4mg/dl  
HDL - 6 mg/dl  
triglycerides - 9 mg/dl

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### **Testosterone trials**

HIV infected men  
Low T yielded weight loss\*, lean body mass\*, AIDS wasting\*  
AIDS progression, depression\* and loss of muscle mass\*, mood\*\*  
exercise capacity, and QoL\*\*. \* Improved \*\* minimal to none

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### **Testosterone trials**

gluco-corticoid- treated men  
5 – 7.5 mg Prednisone or >  
changes in muscle mass and BMD  
bronchial asthma and COPD  
greater gain in LBM and decrease in fat mass; increase in lumbar, +/- femoral BMD; no fracture data

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### **Testosterone trials**

gluco-corticoid- treated men  
higher value on potential benefit and lower value of avoiding adverse events, burdens of T administration, monitoring and cost and long term safety

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## Testosterone trials

summary – older men  
small sample size, healthy men,  
normal or low T, asymptomatic,  
Insufficient power to detect  
meaningful gains in outcomes or  
changes in cardiovascular or  
prostate event rates

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## Testosterone trials

recommendations  
The recommendations not to  
treat older men with age-related  
decline in T place a lower value  
on unproven, beneficial events  
of T and higher value on  
avoiding burdens of T dosing,  
monitoring and cost with ? long-  
term safety.

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### Testosterone trials

#### recommendations

The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

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### Testosterone trials

#### recommendations

The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

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### Testosterone trials

#### recommendations

The recommendations not to treat older men with age-related decline in T place a lower value on unproven, beneficial events of T and higher value on avoiding burdens of T dosing, monitoring and cost with ? long-term safety.

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### Prostate Biopsy

transition zone biopsies  
suspicious; PSA rise, velocity +,  
negative biopsies,  
negative repeat biopsies,  
negative 12 or + core biopsies,  
biopsy TZ and anterior, separate  
specimens from repeat PZ cores

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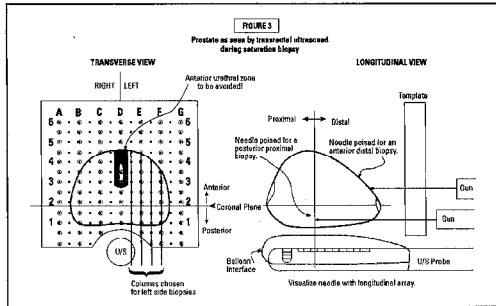
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## Prostate Biopsy

146 patients

PNBx	Saturation Bx
12 cores	59 [17-124]
1 positive	2 [0-19]

## Prostate Biopsy

technique

combination

TRUS-guided transrectal biopsies  
for diagnostic biopsies

TRUS-guided perineal biopsies for  
saturation biopsies

## Prostate Biopsy

146 patients

PNBx	Saturation Bx	
Gleason		
1	5 0	
119	6 62	
12	7 49	
0	8 5	
14	neg 30	

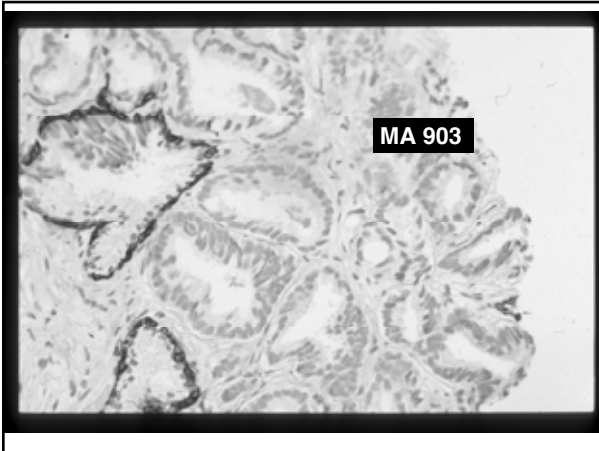
## Thompson

Google

Prostate Cancer Risk Calculator

risk 44%

high grade 14%



## Racemase and P<sup>63</sup> stains

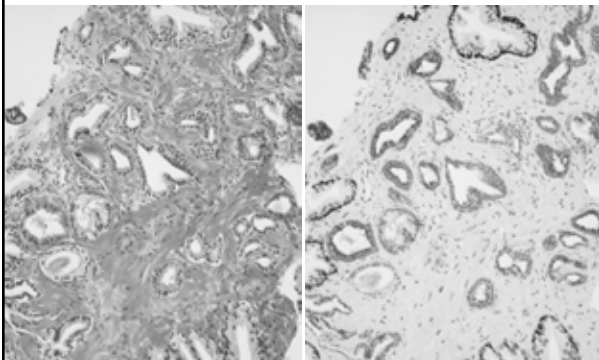
MA 903 - basal cell cytoplasm;  
benign, 2 layer prostate glands  
no basal layer = malignancy

Racemase - cytoplasmic epithelial  
cell; stains = malignancy

P<sup>63</sup> - basal cell nuclei, basal cells  
present, stain = benign gland

R +, P<sup>63</sup> - = Ca;

## AMACR + p63 in PCa



### Prostate Biopsy

43 patients  
 PNBx Saturation Bx  
 11 cores 61.8  
 1.5 positive 3.9

### Prostate Biopsy

43 patients  
 PNBx Saturation Bx  
 Gleason  
 41 6 24  
 2 7 10  
 0 8 7

### Prostate Biopsy

43 patients  
 PNBx Saturation Bx  
 43 unilateral 20  
 0 bilateral 16  
 0 negative 7

### Prostate Biopsy

43 patients  
 PNBx Saturation Bx  
 43 unilateral 20  
 0 bilateral 16  
 0 negative 7

## Prostate Biopsy

The future  
Djavan's technique  
Thompson's risk calculator  
tumor localization technique  
PCA 3

### Prostate Biopsy Oct 2000 – September 2007

percentage positive

#	pos / total	percentage
3 cores	106 / 433	24.4%
4 cores	115 / 407	28.2%
5 cores	152 / 449	33.8%
6 cores	154 / 418	36.8%
7 cores	128 / 364	36.2%

## Biopsy Results

technique altered  
7/01/07 to 11/28/2007; 41+ / 165, 25%  
technique corrected  
12/01/07 to 3/30/08; 77+ / 273, 28%  
technique re-corrected; re-re-corrected  
March 08 46%; October 08 50%  
April 08 41%;  
BUT 31 / 85 36% 4-6; 37 / 100 37% 7-9,08





