

Testosterone & Aging

Is Replacement Therapy Indicated?

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What Happened?



Review: Sex Steroids in the Circulation¹

	Age	
	<u>25</u>	<u>85</u>
Testosterone	600	400 ng/dL
Dihydrotestosterone (DHT)	20-70	20-70
Androstenedione	100	50
DHEA	450	100
DHEAs	250,000	50,000

Sources of Testosterone

Testis	>95.0 %
Androstenedione	1.0 %
DHEA	0.6 %
DHEAs	?

Review: Sex Steroids in the Circulation

Testosterone

Total 260-1000 ng/dL

Free 50-210 pg/dL (1-2%)

Bound ~98%

SHBG

Strong binding 50-60% of total testosterone
No dissociation during tissue transit time

Albumin

Loose binding 40-50% of total testosterone

“Bioavailable” = Free + Albumin bound

Review: Sex Steroids in the Circulation

DHT

Significance of free DHT = ?

Strongly bound to SHBG

DHT is formed locally in peripheral target tissues by 5-alpha reductase

Androstenedione and DHEA

Loosely bound to albumin

Not bound by SHBG

DHEAs

Strongly bound to albumin

Androgenic and Physiologic Activity of Testosterone

Androgenic activity of testosterone & DHT is mediated through binding to the androgen receptor (AR)

AR has high binding affinity for testosterone & DHT
AR does not bind androstenedione, DHEA, DHEAs

Physiologic activity* of testosterone is mediated through Aromatization to estradiol** which binds to the estrogen receptor

* Estrogen functions in feed back regulation of LH, spermatogenesis, bone homeostasis, lipid metabolism, cardiovascular physiology

** Male estrogen ~20-30 pg/mL, 80% from aromatization, 20% from testis

Mechanisms of Testosterone Decline with Age

Testis¹

- ↓ Volume 30%
- ↓ Number Leydig cells →
 - ↓ Testosterone secretion

Neuroendocrine regulation²

- Loss of GnRH timing release →
 - ↓ LH signaling to Leydig cells →
 - ↓ Testosterone secretion

Increased SHBG³

- ↓ Nonspecific bound fraction of testosterone →
 - ↓ Bioavailable testosterone

¹Mulligan T, Iranmanesh A, Veldhuis JD. J Clin Endocrinol Metab 2001;86:5547

²Deslypere JP, et al. J Clin Endocrinol Metab 1987;64:68

³Mechanism = Unknown. ↑ binding generally leads to ↑ production & maintenance of an available hormone fraction. Further, ↑ adipose tissue is negative regulator of SHBG

Progression of Androgen Deficiency in Aging Males

Age-related decline begins ~30-40 years of age^{1,2}
at approximately 1.2% per year

Average testosterone at age 75 compared to age 25³

Total	↓ 35%
Bioavailable	↓ 50%

However, realize many males in the 7th & 8th decade have normal testosterone levels

¹ Harman SM et al. J Clin Endocrinol Metab 2001;86:724

² Feldman HA, et al. J Clin Endocrinol Metab 2002;87:589

³ Ferrini RL, Barrett-Connor E. Am J Epidemiol 1998;147:750

Prevalence of Androgen Deficiency?

Estimates are based on arbitrary cut points for total or free compared to lower limit of young males

<u>Cut-Point</u>	<u>Prevalence</u>
250 ng/dL total	8% ¹
320 ng/dL total	20% ¹
50 pg/dL Free	33% ²

Ill-defined terminologies:

Late Onset Hypogonadism (LOH)³

Andropause³

Syndrome of Male Hypogonadism⁴

Partial Androgen Deficiency in Aging Male (PADAM)⁴

Middle-Age Crisis⁵

Testosterone Deficiency Syndrome (TDS)⁵

¹ Tenover JL. Mayo Clin Proc 2000;75(Suppl):S77

² Morley JE et al. Metabolism 2002;51:554

³ Bassil, Nazem et al. Therapeutics and Clinical risk Management 2009;5:427-448

⁴ Hernandez et al. Postgraduate Medicine 2008;120(4):73

⁵ Delev et al. *Folia Medica* 2009;51(1):15

Problems Defining Androgen Deficiency in Aging Males

Factors other than age may be important determinants of androgen status

Acute or chronic disease

Medications

Obesity

Diabetes

ETOH

Qu: Does age-related decline constitute a true deficiency state worthy of replacement therapy?

Diagnosis of Hypogonadism in Older Males

- Presence of signs/sx of testosterone deficiency
- Questionnaires:
 - Androgen Deficiency in Aging Male (ADAM)
 - Aging Male Symptoms Scale
- Lab and physical exam

Clinical Associations with Decreased Testosterone

Age-related declines in testosterone have the same clinical features as hypogonadism:

- ↓ libido
- ↓ virility
- ↓ sexual activity
- ↓ energy
- ↓ cognitive function
- ↓ bone mineral density
- ↓ muscle mass
- ↑ adiposity
- ↑ insulin resistance
- ↑ erectile dysfunction (not common)
- ↑ insomnia, nervousness, hot flashes

ADAM Questionnaire

Do you have a decrease in sex drive?

Do you have a lack of energy?

Do you have a decrease in strength and/or endurance?

Have you lost height?

Have you noticed a decreased enjoyment of life?

Are you sad and/or grumpy?

Are your erections less strong?

Has it been more difficult to maintain your erection throughout sexual intercourse?

Are you falling asleep after dinner?

Has your work performance deteriorated recently?

Evaluation of Hypogonadism in Older Men

R/O Anemia
Hypertension
Renal and hepatic disease
urogenital disease

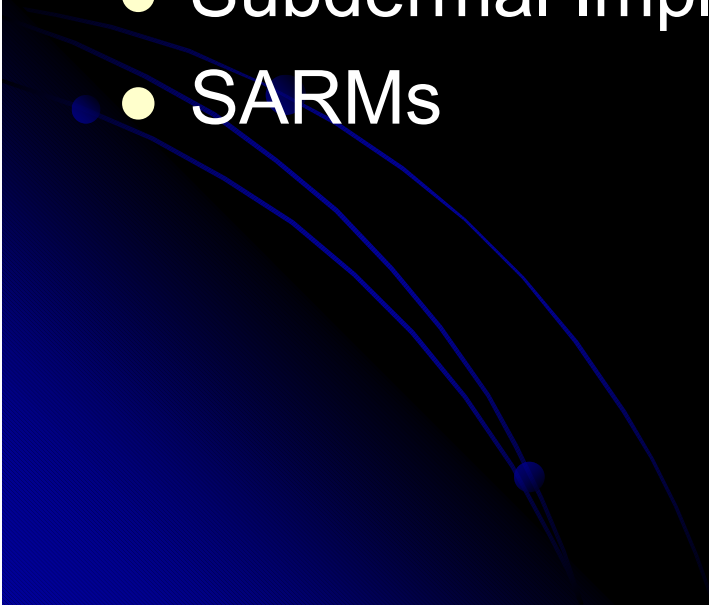
Lab: CBC
CMP
PSA
Testosterone total & free
LH
(PRL if total testosterone <150 ng/dL)

Miner MM et al, Postgraduate Medicine 2008; 120(3):130

Bassil, Nazeem et al. Therapeutics and Clin Risk Management 2009;5:427

The Endocrine Society. Summary from 2nd Annual Andropause Consensus Meeting 2001;1-5

Treatment Options

- Oral Agents (hepatotoxicity)
 - Intramuscular Injection
 - Transdermal Systems
 - Sublingual and Buccal
 - Subdermal Implants
 - SARMs
- 

Contraindications to Testosterone Replacement Therapy

BPH with significant sx (IPSS > 19)¹

Prostate nodules/indurations¹

Unexplained ↑ PSA¹

Prostatic CA¹

Breast CA²

Erythrocytosis (Hct > 50)³

Unstable CHF³

Severe untreated sleep apnea³

¹ Wang et al. *Eur J Endocrinol* 2008;159:507-14

² Bhasin et al. *J Clin Endocrinol Metab* 2006;91:1995

³ Bassil, Nazeem et al. *Therapeutics and Clin Risk Management* 2009;5:427



Testosterone
shots? Why, I'm
only 24

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #1

Will testosterone increase lean body mass and decrease fat mass?

Katznelson L, et al. *Eur J Endocrinol* 2006;155:867

Miner MM, et al. *Int J Clin Pract.* 2007; 61(4):622-32

Stanworth RD, et al. *Clin Interventions in Aging* 2008;3(1) 25-44

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #2

Will testosterone increase strength and does it increase bone mineral density

Katznelson L, et al. *Eur J Endocrinol* 2006;155:867

Miner MM, et al. *Int J Clin Pract* 2007; 61(4):622

Tracz, MJ, et al. *J Clin Endocrinol Metab* 2006;91(6):2011

Stanworth RD, et al. *Clin Interventions in Aging* 2008;3(1):25

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #3

Will testosterone improve a patient's perception of quality-of-life? Does it improve sexual desire, function and performance?

Emmelot-Vonk MH, et al. JAMA 2008;299(1):39
Miner MM, et al. Postgraduate Medicine 2008;120(3):130

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #4

Does testosterone improve cognitive function?

Emmelot-Vonk MH, et al. JAMA 2008;299(1):39

Cherrier MM, et al. Psychoneuroendocrinology 2007;32:72

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #5

Does low testosterone increase the risk of anemia?



Ferrucci L, et al. Arch Intern Med 2006;166(13):1380

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #6

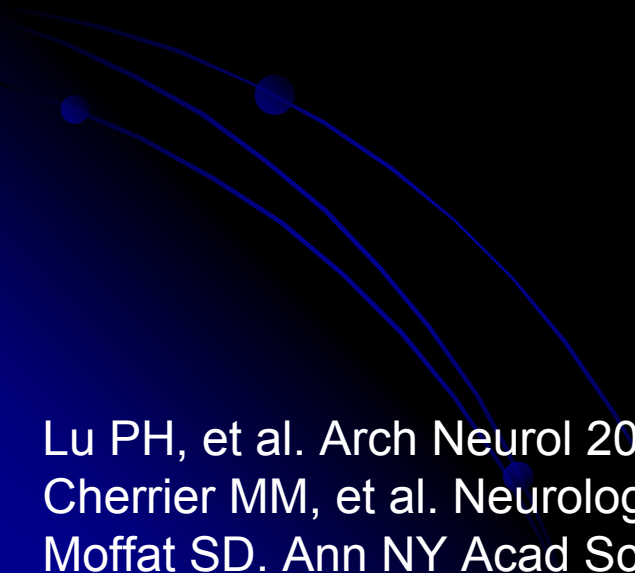
Does testosterone replacement have an adverse effect on the prostate? Does it cause cancer?

Marks LS, et al. JAMA 2006;296:2351

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #7

Is there a role for testosterone replacement in patients with mild Alzheimer disease?



Lu PH, et al. Arch Neurol 2006;63(2):177
Cherrier MM, et al. Neurology 2005;64:2063
Moffat SD. Ann NY Acad Sci 2005;1055:80

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #8

Is there any association between low testosterone and mortality?



Shores MM, et al. Arch Intern Med 2006;166(15):1660

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #9

Does aromatase inhibition increase testosterone levels?

Burnett-Bowie SM, et al. Clinical Endocrinology 2009;70(1):116

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #10

What are the effects of DHEA in elderly women and DHEA or testosterone in elderly men?

Nair KS, et al. N Engl J Med 2006;355:1647



Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu. #11

What are the effects of testosterone therapy on fuel metabolism?

Insulin resistance

Glucose

Lipids

Miner, MM, et al. Postgraduate Medicine 2008;120(3):130

Stanworth RD, et al. Clin Interventions in Aging 2008;3(1):25

Will Testosterone Replacement Therapy Reverse Age-Related Declines?

Qu #12

Are there any cardiovascular risks of low testosterone levels?

Edith, that damn neighbor
who's always shoot'in
testosterone is at it again

