Testosterone: Current Opinion and Controversy

Ravi Kacker, MD

Metrowest Urology
(508) 655 4422
Medical Office Building at Leonard Morse Hospital

Disclosures

- MHB Labs – President and CEO of Drug Development Start-up
- Veru Healthcare – Drug Development consulting

My Experience With Testosterone

- Andrology Fellowship BIDMC – 2014
- Research and Clinical Focus: Testosterone and Metabolism
- Examination papers alleging increased cardiovascular risk
- FDA Opinion and Advisory Committee
- SMSNA Expert Colloquium and White Paper on Adult Onset Hypogonadism
- AUA Crossfires Deabate

The New York Times

The Opinion Pages | EDITORIAL

Overselling Testosterone, Dangerously

NBC NEWS

Testosterone therapy linked to higher heart risk

Testosterone Treatment Lawsuits

Lawyers Reviewing Testosterone Therapy Heart Attack, Stroke and Wrongful Death Lawsuits for Men.

REQUEST A FREE CONSULTATION

Is Hypogonadism a Real Medical Condition?

What Causes it?

Who Should Be Treated?

TABLE 1. Clinical Signs, Symptoms, and Conditions Consistent With Adult-Onset Hypogonadism and Low Testosterone Levels[1,11,85,86]

Most specific signs/symptoms	More general signs/symptoms	Conditions commonly associated with low testosterone level and adult-onset hypogonadism
Reduced sexual desire & activity	Decreased energy, motivation, initiative	Type 2 diabetes
Decreased spontaneous erections	Delayed ejaculation	Metabolic syndrome
Erectile dysfunction	Reduced muscle bulk & strength	Chronic obstructive lung disease, obstructive sleep apnea syndrome
Hot flushes/sweats	Diminished physical or work performance	End-stage renal disease, hemodialysis
Decreased testicle size	Mild anemia (normocytic, normochromic)	Osteoporosis
Loss of pubic hair, reduced shaving requirement	Depressed mood, irritability	Human immunodeficiency virus–associated weight loss
Increased body mass index, visceral obesity	Poor concentration & memory	History of infertility, cryptorchidism, pituitary disease, delayed puberty
Height loss, low trauma fractures, reduced bone mineral density	Sleep disturbances, sleepiness	Treatment with opioids or glucocorticoids

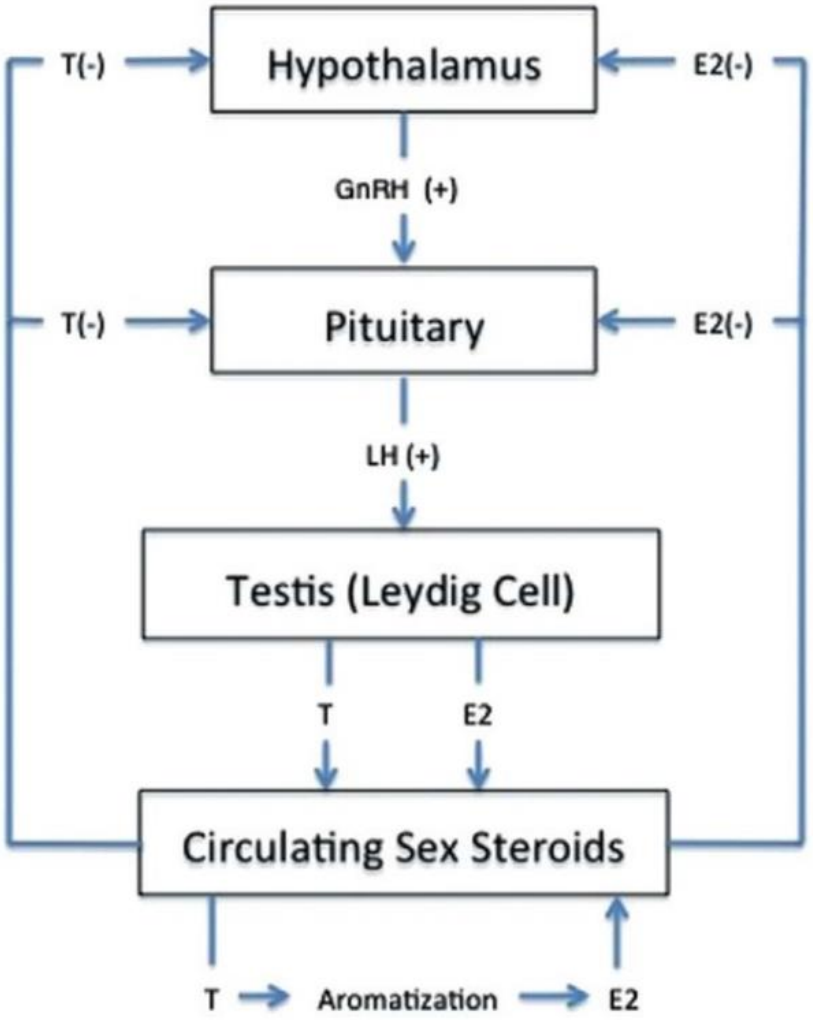
Adult-Onset Hypogonadism, Mayo Clinic Proc, July 2016

Consistent syndrome despite age, type of hypogonadism, clinical setting.

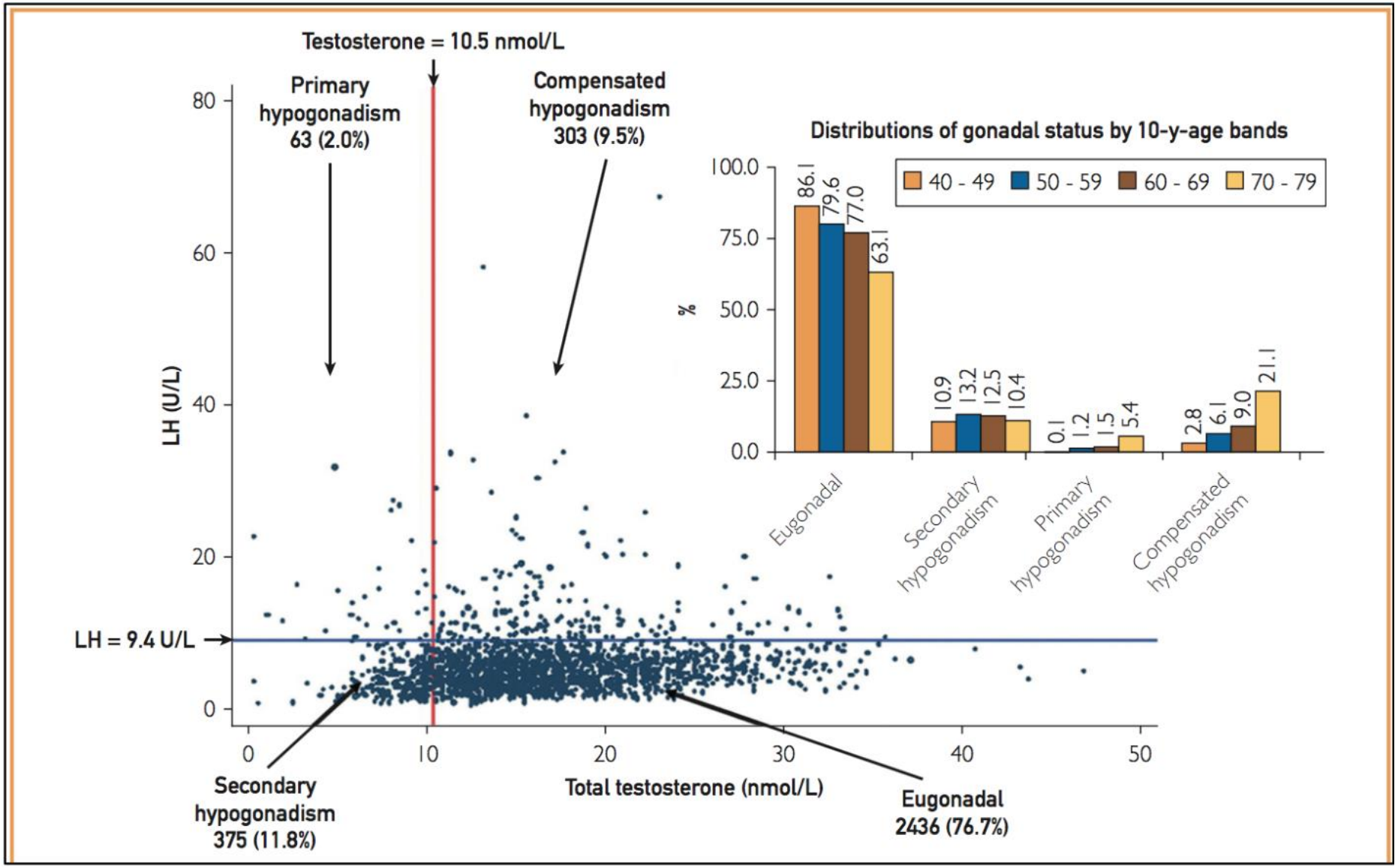
Syndrome can be created by reducing T and is reversed by naturally or pharmacologically increasing T

- Primary Hypogonadism (testicular failure)
  - Low Testosterone despite high gonadotropins
  - Testicular hypofunction, atrophy or loss

- Secondary Hypogonadism (hypogonadotrophic hypogonadism)
  - Low or normal gonadotropins with low T levels
  - Several conditions



Kacker, Journal of Sexual Medicine, 2012

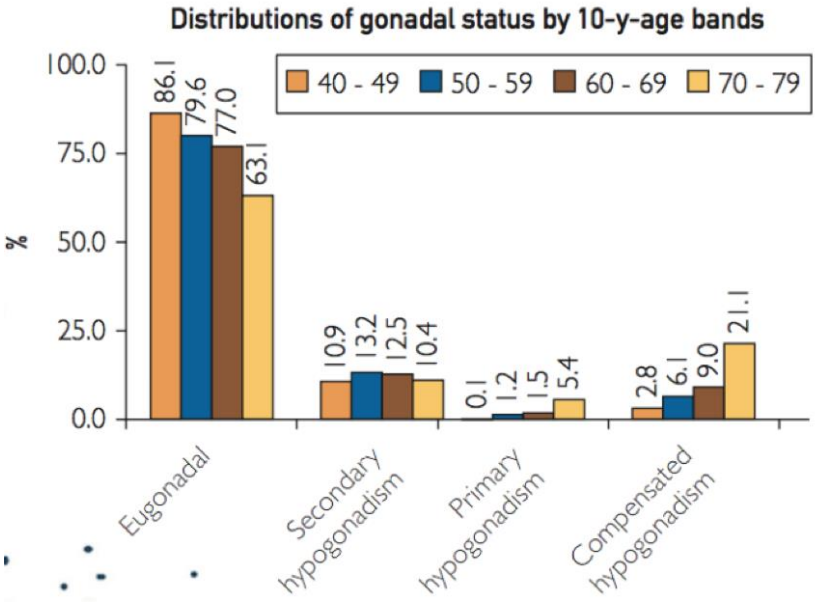


European Male Aging Study: Tajar, J Clin Endoncrinol Metab, 2010

Population based study of community dwelling men:
Prevalence of (biochemical hypogonadism) is 13.8%
Most hypogonadism is secondary (11.8% vs 2.0% primary)

Age and Hypogonadism

- Both primary and compensated hypogonadism increase with age.
- Why do some men compensate for testicular hypofunction failure and why do others not?
- Secondary hypogonadism does not increase with age



Something is suppressing gonadotropins and testosterone for MOST men with hypogonadism

Potential Drivers of Secondary Hypogonadism

Comorbidities	Drugs/Medications	Behaviors/Lifestyle
Obesity	Steroids	Sleep Disturbances
OSA	Opioids	Stress
Depression/Anxiety	Spironolactone	Long Commutes
DMII	Drugs that elevate SHBG (Insulin, Antipsychotics)	Smoking
HTN		

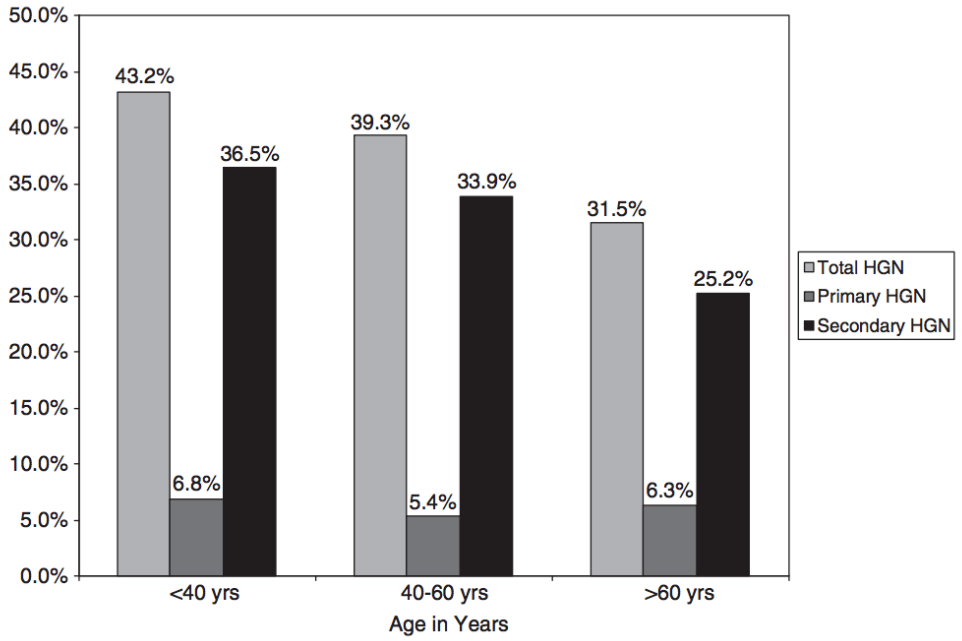
Complex Picture:

- Not every correlation with low testosterone is actually a cause
- Some effects are clearly reversible (e.g. removal of offending medication)
- **Obesity, stressful lifestyle, and sleep disturbances** are very common among men presenting with low testosterone

Adult-Onset Hypogonadism, Mayo Clinic Proc, July 2016

The “Rat Race”: Stress and Hypogonadism

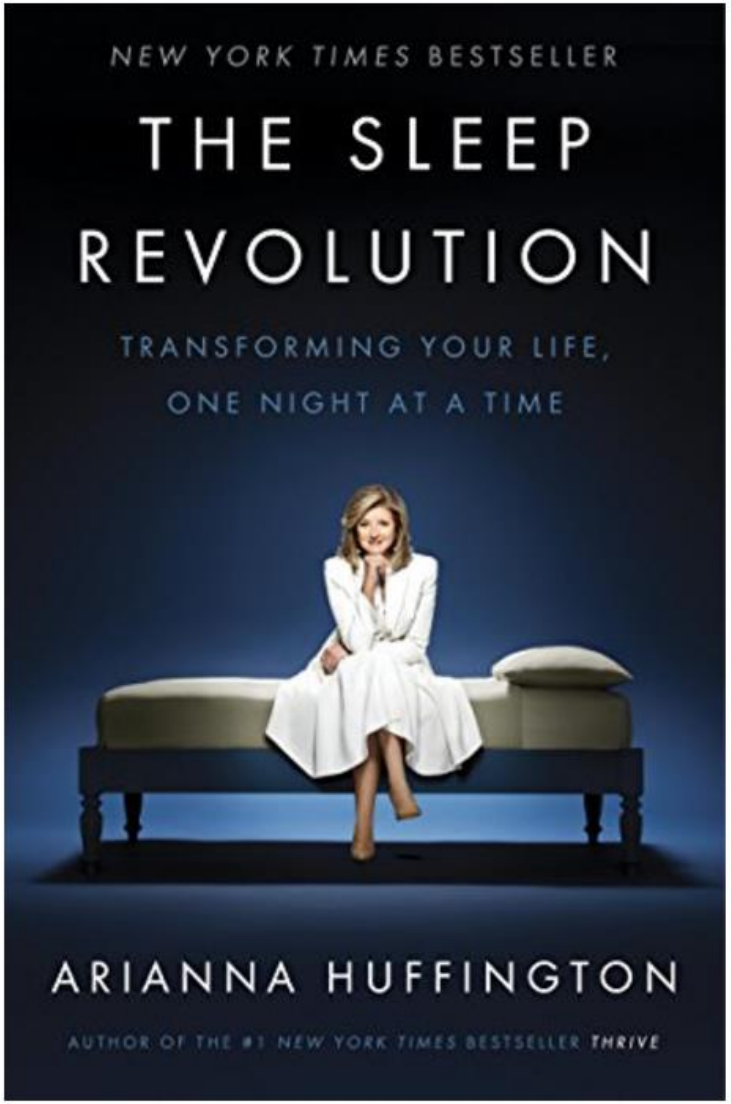
- 990 men to sexual medicine clinic in Massachusetts
- Men under age 60 were most likely to have hypogonadism
- “These men did not have overt clinical depression but typically were men who worked more than **50 or 60 h a week, often at more than one job**. Their jobs often involved **traveling great distances and/or long commutes**, along with meeting deadlines or quotas..”



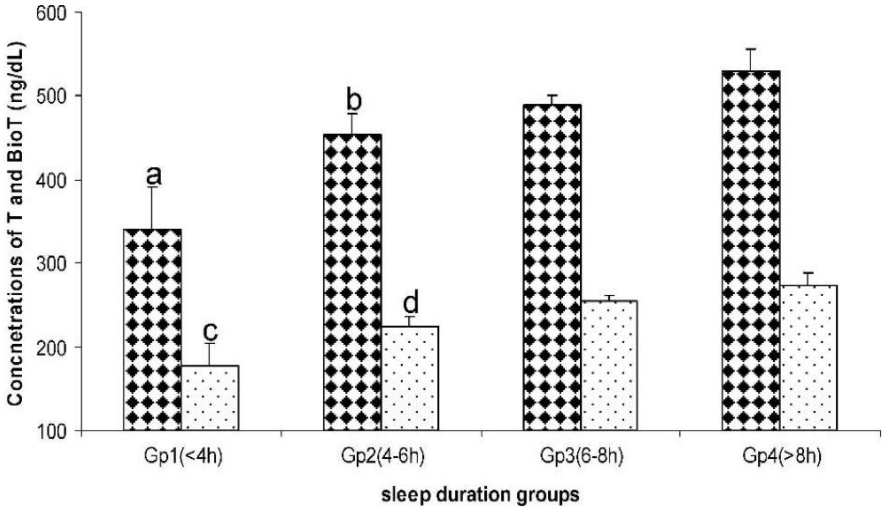
Traish, International Journal of Impotence Research, 2010

Sleep and Hypogonadism

- Widespread recognition of "epidemic" of sleep deprivation – books, start-ups, apps
- Blamed for fatigue, fogginess, lack of libido/sexual dysfunction, weight gain…. very similar to Low T
- Association between shift work, sleep deprivation, OSA and low testosterone



- Sleep duration during shift-work associated with T and BioT
- Decreased LH and T levels in men with OSA compared to healthy controls
- Men with non-standard have higher ADAM scores vs. men with shift work (Pastuzak, Urology, 2017)



531 Singaporean Chinese men age 29-72

Goh, J Androl, 2010

Treatment can be difficult:

- Inconsistent results on T levels with treatment of OSA
- Focus on “sleep hygiene”
- Emerging field of tech, medical device, sleep science

Testosterone Deficiency Can Be Reversible

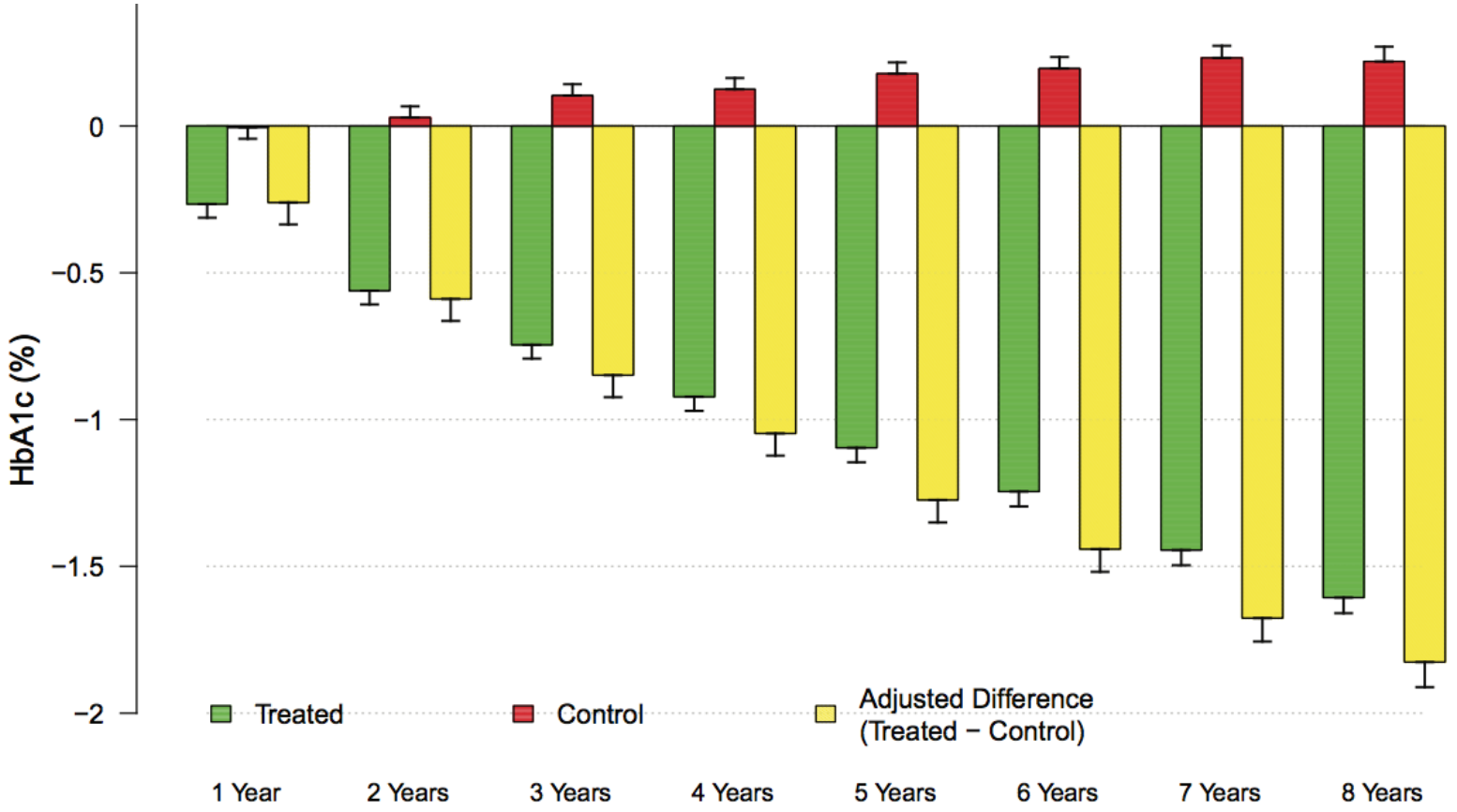
Table 2 Mean (95% CI) hormone changes by % weight change.

(n=2395)	**Mean testosterone change** (nmol/l)	**Mean FT change** (pmol/l)	**Mean SHBG change** (nmol/l)	**Mean LH change** (U/l)
Lost ≥15% (n=22)	5.75 (1.32, 10.18)*	51.78 (1.71, 101.85)*	14.77 (2.39, 27.15)*	2.21 (−0.58, 5.01)
Lost ≥10 to <15% (n=61)	1.96 (−0.47, 4.39)	−5.06 (−39.17, 29.06)	13.19 (7.06, 19.32)‡	0.34 (−1.51, 2.20)
Lost ≥5 to <10% (n=288)	0.28 (−0.22, 0.77)‡	−13.94 (−21.40, −6.48)	5.32 (3.40, 7.24)‡	0.87 (0.17, 1.60)
Within 5% (referent) (n=1554)	−0.33 (−0.79, 0.13)	−16.85 (−27.02, −6.68)	2.61 (1.06, 4.15)	0.16 (−0.05, 0.37)
Gained ≥5 to <10% (n=262)	−1.20 (−2.07, −0.33)*	−16.92 (−29.66, −4.18)	−1.26 (−2.90, 0.58)‡	−0.005 (−0.27, 0.26)
Gained ≥10 to <15% (n=69)	−1.89 (−3.14, −0.63)*	−16.55 (−46.45, 13.35)	−3.84 (−8.63, 0.95)‡	−0.26 (−1.10, 0.57)
Gained ≥15% (n=17)	−4.35 (−6.97, −1.73)*	−47.10 (−136.91, 42.72)	−8.41 (−18.73, 1.90)*	−0.004 (−1.00, 0.99)

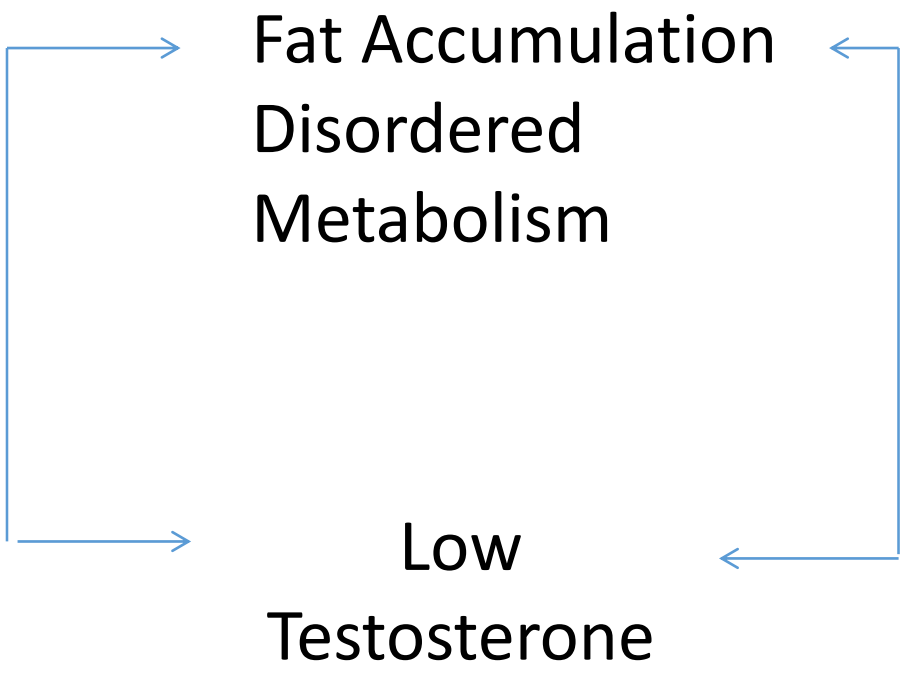
Significantly different from (referent): *P<0.05, ‡P<0.01. Models included the following covariates: baseline age and centre, changes in smoking status, alcohol consumption, comorbidities and physical activity. A total of 23 outliers with SHBG ≥120 nmol/l, LH ≥60 U/l or FT ≥800 pmol/l were excluded from the regression analysis.

- Longitudinal Data from EMAS: 2736 men age 40-79
- Weight loss increased T and LH but this only occurred in 22/2736 = 0.8%
- Improvement also seen in response to bariatric surgery (Corona, JCEM, 2013)

- When T is withdrawn, insulin resistance is detectable in serum within 48 hours (Pitteloud, Diabetes Care, 2005)
- Level 1b evidence – T therapy improves insulin sensitivity (Huefelder, J Androl, 2009)
- Long term effects of T therapy on IR and obesity continue for years (Traish, J Cardiovascular Cardiology Therapeutics, 2017)



Vicious Cycle



Low Energy
Fatigue
Insulin Resistance
Diabetes
Cardiovascular
Complications

Behavioral changes can sometimes reverse vicious cycle and achieve recovery "naturally" – but this is relatively rare.

Testosterone therapy can be a tool to reverse metabolic dysfunction

My Opinion: Try to encourage behavioral changes, but recognize that most fail. Consider treatment in those patients with severe metabolic dysfunction.

When Should Hypogonadism Be Treated?

Biochemical Evaluation of Hypogonadism

- Remains controversial
- Total T cut-offs include 250, 300, 350 ng/dL (Morgentaler, Mayo, Clinic Proc, 2016)
- SHBG and Free T complicate picture
- Polymorphisms in AR responsiveness exist in population (Zitzman, Nat Clin Pract Urol, 2007)

- Some men with low total T levels may not actually be *deficient* of T
- Some men with normal total T levels may still be T deficient!

TABLE 2. Conditions in Which Serum T Level Measurement Is Suggested[1,11,86]
Infertility
Osteoporosis, low trauma fracture
Type 2 diabetes
Glucocorticoids, ketoconazole, opioid or other medications that affect T metabolism or production
Moderate to severe chronic obstructive pulmonary disease
Sellar mass, radiation to the sellar region, or other diseases of the sellar region
End-stage renal disease, maintenance hemodialysis
Human immunodeficiency virus–associated weight loss

Adult-Onset Hypogonadism, Mayo Clinic Proc, July 2016

My Opinion/Practice: Diagnosis should be on the basis of *some* biochemical evidence of deficiency **combined** with several signs and symptoms of T deficiency. It may be reasonable to offer treatment to select men with normal total T. Not everyone with low total T needs treatment!

Benefits of Treatment

Time to see benefits may be long and require appropriate dosage. Some studies show only modest benefits (notably T –trial). Benefits from topical therapy lag behind injectable therapy.

Longer-term studies support assertion that T therapy leads to:

- Increases in muscle mass/strength
- Improvement in bone density
- Improvements in libido/sexual satisfaction
- Improvements in erectile dysfunction
- Improvement in abdominal weight, insulin sensitivity
- Observational studies: nearly 50% reduction in all cause mortality

Review of benefits of treatment:
Morgentaler, Mayo Clin Pro, 2016

Risks of Treatment

- Polycythemia/erythrocytosis
  - Hepcidin underlies effect
  - Patients on injectable T may be at greater risk (unpublished data)
  - Some patients may need periodic phlebotomy to keep HCT<54
- Suppression of endogenous production => infertility
- Acne/Oily Skin
- Breast Symptoms/Gynecomastia

Concerns about: abuse/dependence

Rhoden, NEJM, 2004

Cardiovascular Disease	Prostate Cancer

• Vast majority of papers on T and CV risk support safety and benefit of T
 	
• A few recent high-profile papers have raised concern around risk:
  • Statistical errors
  • Use of questionable statistical endpoints
 	
• Concern persists around signals of unclear clinical significance: non-calcified plaque, palpitations, diastolic BP (none consistent)
 	
• Absence of widespread problems despite concerns and medicolegal focus
	• Historical concern – lowering T still main treatment of metastatic prostate cancer!
	
	• Rise of T levels above "saturation point" do not appear to encourage prostate cancer.
	
	• Higher testosterone levels not associated with increased prostate cancer risk.
	
	• Lack of harm in patients after prostatectomy, radiation therapy
	
	• T given to men on active surveillance for prostate cancer – no pathologic progresson on serial biopsies.

<u>My Opinion/Practice:</u> • Cardiometabolic benefits appears to significantly outweigh risk • Important to monitor hematocrit	<u>My Opinion/Practice:</u> • Will offer T to symptomatic men who have had definitive treatment for PCa or low risk disease • Experimental for PCa in metastatic disease (under consent or IRB) • Appropriate to consider in palliative cases

Warnings on potential cardiovascular and prostate risk persist on FDA label for all T products

Key References for CV and PCa Risk of T therapy

- Public Citizen petition denial response from FDA CDER to Public Citizen. Regulations. gov website. http://www.regulations.gov/#!documentDetail;D1/4;FDA-2014-P-0258-0003. Published July 16, 2014. Accessed December 27, 2015
- Khera, et al. Adult Onset Hypogonadism, Mayo Clinic Proceedings, July 2016; 91 (7): 908-926
- Kacker, et al. Can Testosterone Therapy be Offered to Men on Active Surveillance for Prostate Cancer? Preliminary Results. Asian Journal of Andrology, 2016; 18(1)
- Miner, et al. The state of testosterone therapy since the FDA's 2105 labeling changes: indications and cardiovascular risk. Clin Endocrinology, 2018

Treatment with Testosterone

- Topical Treatments:
  - Patches
  - Gels
- Injectable Testosterone
  - Testosterone cypionate
  - Testosterone undecanoate
- Implants: Testosterone pellets

- Increasing complexity of insurance approvals.
- Self-injection with generic testosterone cypionate is least expensive and highly effective

Treatment of Secondary Hypogonadism

- Goal – increase testicular production by stimulating or administering gonadotropins
- Useful for patients who wish to maintain fertility, testicular function, or where there are concerns about abuse or dependence

Human Chorionic Gonadotropoin

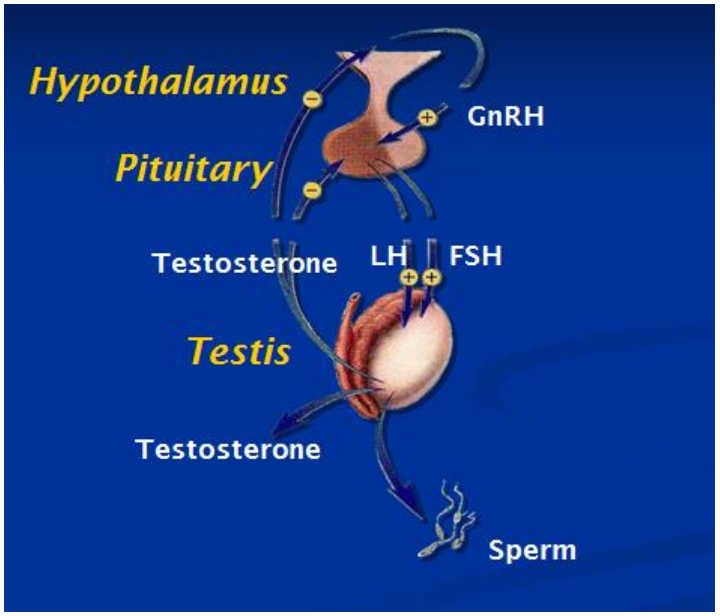
- FDA approved
- Injection 3x per week

Clomiphene Citrate (Selective Estrogen Receptor Modulators)

- Off label Oral medication
- Limited symptomatic benefit – estrogens important to male sexual function, bone density.

Physiology of hCG

- Best known as serum marker for pregnancy – several roles in physiology
- Produced by syncytiotrophoblast cells found in placenta and in gonads
- hCG mimics actions of LH to stimulate endogenous testosterone production
- Binds to same receptor as LH on fetal and adult testicular Leydig cells



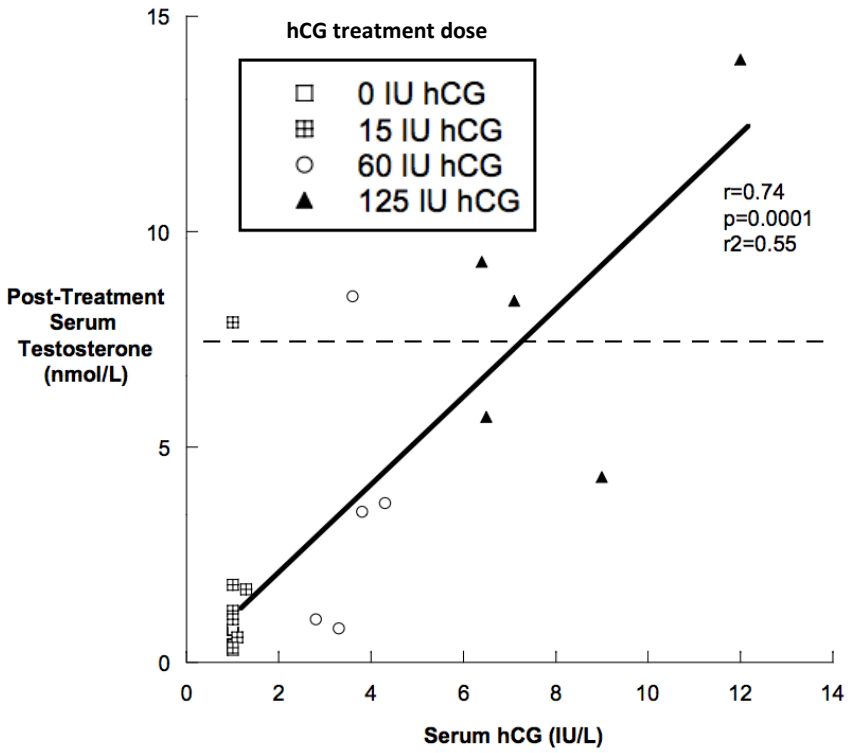
hCG and Testosterone

Liu et al, JCEM, 2002:

- Double-blind Randomized Controlled Trial: 40 men with androgen deficiency treated with hCG injections twice weekly or placebo
- Stable increase in serum testosterone levels within the normal range after 3 months of treatment

Roth et al, JCEM, 2010:

- 37 healthy men received a GnRH antagonist and were treated with low doses of hCG daily or Testosterone gel for 10 days
- Dose-response relationship between hCG and serum testosterone levels



Linear dose response relationship between low-dose hCG and serum T
Adapted from Roth et al, JCEM, 2010

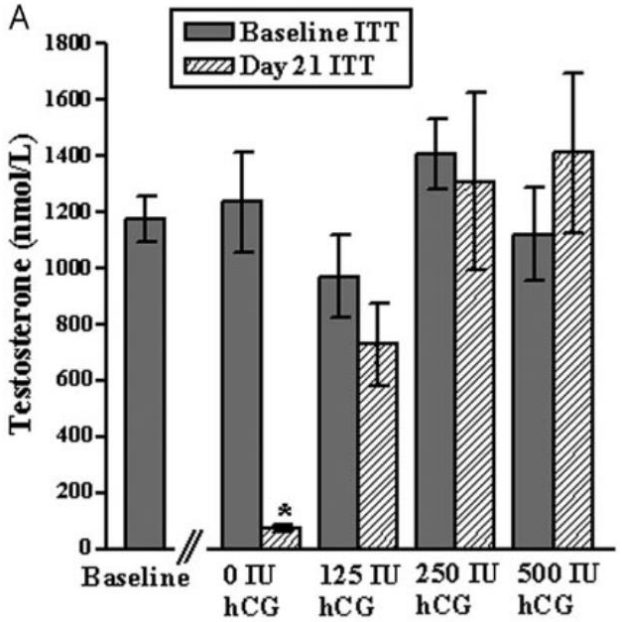
Liu et a.l J Clin Endocrinol Metab. 2002 Jul;87(7):3125-35.
Roth et al. J Clin Endocrinol Metab. 2010 Aug;95(8):3806-13

hCG Preserves Fertility and Intra-Testicular Testosterone Production in Men on Testosterone Therapy

Table 3. *Semen analysis in 7 patients with transdermal and 19 with injectable TRT*

TRT	Mean ± SD Sperm Count/Million		Mean ± SD % Motility	Mean ± SD FP
	Total	Motile		
Before:				
Transdermal	35.5 ± 28.3	43.6 ± 70	42.2 ± 10.2	2.3 ± 0.1
Injectable	33.7 ± 38	49.8 ± 44	51.3 ± 10	2.4 ± 0.3
p Value	0.08	0.6	0.93	0.14
After:				
Transdermal	30.8 ± 15	37 ± 36	47 ± 20.7	2.7 ± 0.6
Injectable	30.6 ± 26.8	46.7 ± 39	51.3 ± 13	2.4 ± 0.3
p Value	0.99	0.64	0.68	0.22

- 26 men treated with daily TRT gel or weekly T injections
- HCG 500 IU every other day
- Follow-up 6.2 months
- After 6 months, there was only a slight decline in sperm density and motility (p>0.05)



- 29 normal healthy fertile men
- Randomized to receive testosterone enanthate 200mg per week plus hCG at a doses of 0, 125, 250, or 500IU twice weekly
- Despite supraphysiologic doses of T, high levels of intra-testicular testosterone were maintained with administration of low-dose hCG

Hsieh et al. J Urol. 2013 Feb;189(2):647-50
Coviello et al. *J Clin Endocrinol Metab*, 90(5):2595-2602, 2005.

Questions/Discussion