Navigating Testosterone Replacement Therapies & Risks

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From pop culture to controversy

- Outline:

- We will walk a little through history

- T related myths
- How to diagnose low T
- What are the risks and benefits
- Recent clinical trials

T, the new normal

- http://www.ironmanmagazine.com/testosterone-the-new-normal/
- Normal range ‘for young men should be 600-700 plus’
- ‘There is a stigma for young men, they should be encouraged to talk about it’
- Apparently stress and hard work can cause low T
- ‘T will help you lose weight’

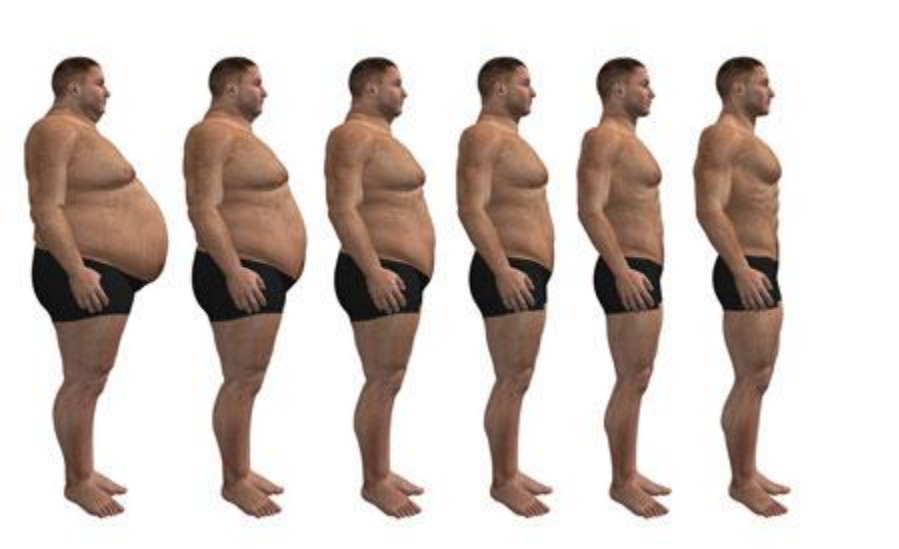
Apparently, this is how we must look

And we do not want to look like this

Often quoted Symptoms of low T

- Erectile dysfunction (impotence: inability to develop or maintain an erection)
- Fatigue (lack of energy)
- Muscle mass and strength (reduced)
- Body fat (increased)
- Back pain
- Osteoporosis development (reduced bone mass/density and increased risk of fracture)
- Heart attack risk (higher incidence of sudden death)
- Cholesterol (high: especially LDL/HDL ratio)
- Refractory period increased (time it takes to have sex again)
- Sperm count (reduced fertility)
- Gynecomastia (development of male breasts)
- **MENTAL SIGNS AND SYMPTOMS**
- Libido decreased (lowered sex drive)
- Brain fog (difficulty concentrating)
- Memory problems
- **EMOTIONAL SIGNS AND SYMPTOMS**
- Depression (sadness, hopelessness, despair)
- Motivation and ambition (decreased)
- Irritability (increased anger, agitation, or loss of patience)

So what is happening, does T help the men to left?



Or is it caused by the men on the right, vs aging itself

Now the endocrine part

- 2015: (FDA) held a hearing and issued a statement
- Health care professionals should make patients aware of the possible increased cardiovascular risk
- Thrombo-embolic risk
- Abuse, dependence risk

AACE practice guideline 2015

- The link for CV risk is weak
- If there is an unequivocally low T, a man should be considered for TRT
- extra cautious in the symptomatic elderly and frail
- More data are needed
  - https://www.aace.com/files/position-statements/ep14434ps.pdf

Where to start with this? -symptoms-

Incomplete or delayed sexual development, eunuchoidism
Reduced sexual desire (libido) and activity
Decreased spontaneous erections
Breast discomfort, gynecomastia
Loss of body (axillary and pubic) hair, reduced shaving
Very small (especially <5 ml) or shrinking testes
Inability to father children, low or zero sperm count
Height loss, low trauma fracture, low bone mineral density
Hot flushes, sweats

Less specific signs and symptoms

Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, dysthymia
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild anemia (normochromic, normocytic, in the female range)
Reduced muscle bulk and strength
Increased body fat, body mass index
Diminished physical or work performance

Do measure T when: symptoms, + the following, or if high index

Hx Pituitary ds
Patients on glucocorticoids or opioids
HIV-associated weight loss
End-stage renal disease and maintenance hemodialysis
Moderate to severe chronic obstructive lung disease
Infertility
Osteoporosis or low trauma fracture, especially in a young man
Type 2 diabetes mellitus, uncontrolled

Diagnostic work up

- Obtain 8 AM Testosterone, total
- Confirm with a repeat 8 AM total and free Testosterone, with LH and FSH
- In cases of low normal or low LH and FSH get a fasting Prolactin and ferritin/ iron studies
- BECAUSE WE MUST KNOW IF CAUSE IS CENTRAL
- Do not draw during (sub)acute illness (it will be low)
- Semen analysis – when appropriate

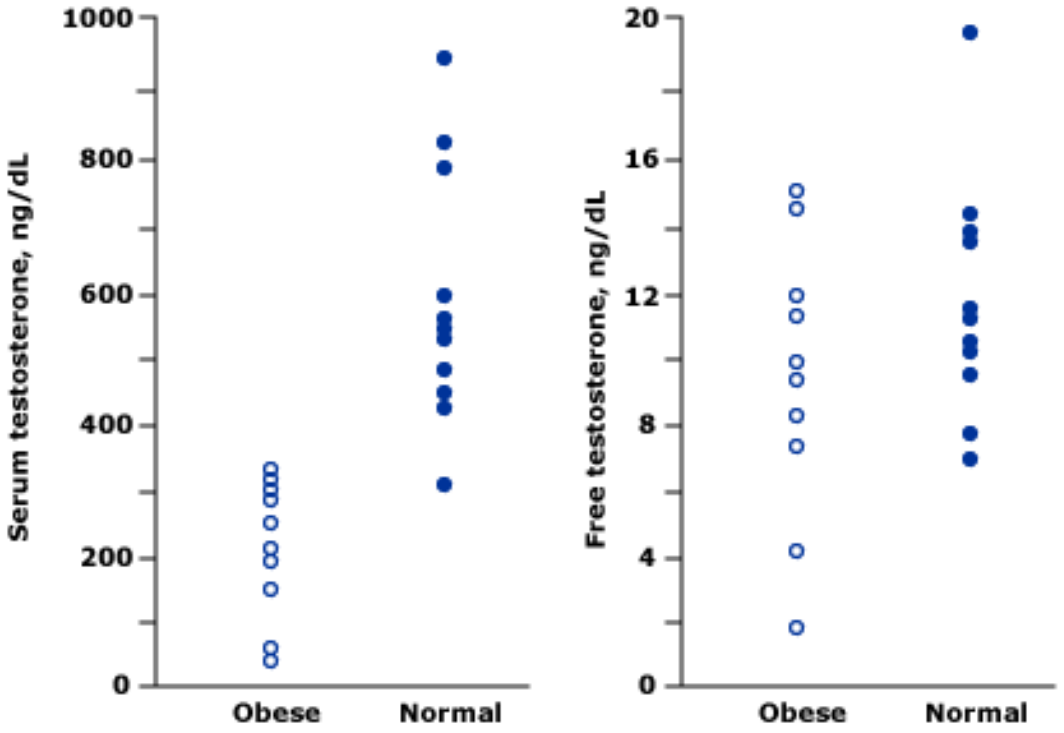
Conditions that affect results

- Time of day
- Sleep cycle, shift work, time zone travel
- Abnormal sleep
- Acute, subacute illness
- The type of assay, the type of assay, the type of assay
- Over the counter meds (NO explode, others)
- Steroids, recent T exposure
- Cannabis, opioids

Conditions that affect results

- SHBG affects total T more then Free T
- Increased SHBG : aging, hyperthyroidism, high estrogen concentrations, liver disease, HIV, antiseizure drugs
- Decreased SHBG : central obesity, insulin resistance, type 2 diabetes, hypothyroidism, growth hormone excess, exogenous androgens/anabolic steroids, glucocorticoids, progestins, nephrotic syndrome

Serum testosterone concentrations in obesity



Obesity is characterized by a reduction in serum total testosterone concentration (left panel) but a normal serum free testosterone concentration (right panel) due to decreased SHBG.

SHBG: sex hormone-binding globulin.

Data from Glass AR, Swerdloff RS, Bray GA, et al. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. J Clin Endocrinol Metab 1977; 45:1211.

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Evaluating the cause: Key issues

- 1e **Hypogonadism (high FSH/ LH)**
- Karyotype esp if social or learning issues, tall

- 2nd **hypogonadism (normal or below normal FSH/LH**)
- Iron studies
- Sleep study
- ? MRI pituitary (not if sleep apnea, very obese, DM uncontrolled, and T is >>150)
- Take history : Over the counter, drug use

Causes of primary hypogonadism in males

Congenital abnormalities
Klinefelter syndrome
Other chromosomal abnormalities
Mutation in the FSH and LH receptor genes
Cryptorchidism
Varicocele
Disorders of androgen synthesis
Myotonic dystrophy
Acquired diseases
Infections, especially mumps
Radiation
Alkylating agents
Suramin
Ketoconazole
Glucocorticoids
Environmental toxins
Trauma
Testicular torsion
Autoimmune damage
Chronic systemic illnesses
Hepatic cirrhosis
Chronic renal failure
AIDS
Idiopathic

FSH: follicle-stimulating hormone; LH: luteinizing hormone: AIDS: acquired immunodeficiency syndrome.

Causes of hypogonadotropic (secondary) hypogonadism

Acquired
Tumors
Benign tumors and cysts
Craniopharyngiomas
Germinomas, meningiomas, gliomas, astrocytomas
Metastatic tumors (breast, lung, prostate)
"Functional" gonadotropin deficiency
Chronic systemic disease
Acute illness
Malnutrition
Hypothyroidism, hyperprolactinemia, diabetes mellitus, Cushing's disease
Anorexia nervosa, bulimia
Post-androgen abuse
Infiltrative diseases
Hemochromatosis
Granulomatous diseases
Histiocytosis
Head trauma
Pituitary apoplexy
Drugs - Marijuana
Congenital
Isolated GnRH deficiency
Without anosmia
Kallmann syndrome
Associated with adrenal hypoplasia congenita
GnRH deficiency associated with mental retardation/obesity
Laurence-Moon-Biedl syndrome
Prader-Willi syndrome
Idiopathic forms of multiple anterior pituitary hormone deficiencies
Congenital malformations often associated with craniofacial anomalies

GnRH: gonadotropin-releasing hormone.

Benefits from T – conflicting data!

- Sexual function
- Muscle mass and function
- Lower fat mass
- Typically not a lower body weight
- Bone density – takes a few years to emerge
- May be on mood and cognition

- Depends on cause and severity! Usually symptoms attributable if T < 150
- Several studies: it is only 2% of 'low T men'

Contra-indications

- Prostate cancer, severe prostatism
- Polycythemia
- Active ASCVD disease
- Active Thrombo-embolic disease
- Certain psychiatric conditions
- Untreated severe sleep apnea
- Breast cancer
- Uncontrolled CHF
- Fertility wish

Whom to treat

- Not all older men with low T
- Look really hard for reversible cause
- Look really hard for underlying cause
- Treat underlying cause even if it does not improve T
- Think about fertility

- Typically: known testicular or pituitary cause and T is < 150, probably men on opioids or steroids and T is < normal range, rest is ?

How to monitor

- CBC every 3-12 months
  - Phlebotomy if HCt> 50, hold and lower T if HCt>54
  - ? Use 81 mg a day ASA??? (I do first 6 months)
- PSA
  - After 1 year, PSA may increase by 1.2
  - After that velocity should be < 0.5/ year
- DRE
- Liver panel every 3-12 months
- Skin for acne
- Breasts for Gynecomastia

What preparation to use

- T cypionate 200 mg/mL cheapest option
  - 50-100 mg IM weekly or 100-200 mg every 2 wks
- Gels
  - More even absorption yet not uniformly
  - Expensive
  - Likely safer!
- Patch, scrotal or non scrotal out of favor
- Pellets, not a lot of experience how to monitor
- T undecanoate – not –yet – available (very LA)

Back to the risks: Meta-analysis

- There was no increase in the rates of death, myocardial infarction (MI), revascularization procedures, or cardiac arrhythmias as compared with the placebo-nonintervention groups. None of these trials, however, was powered to show a difference in these end points
  - J Clin Endocrinol Metab. 2010;95:2560-2575
- we do not have definitive studies demonstrating efficacy or risk for treating men with these conditions. The IOM committee agrees that the risk/benefit ratio of TRT is not well established in aging-associated hypogonadism

More recent clinical trials

- 2016 Meta-analysis
  - http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162480
- The prescription of testosterone supplementation for low-T for cardiovascular health, sexual function, physical function, mood, or cognitive function is without support from randomized clinical trials

More recent:

- 2017 : NIH-supported trials of testosterone therapy in older men report mixed results (The Testosterone Trials), 7 ongoing studies
- *Hormone treatment improved bone strength and hemoglobin levels; may increase cardiovascular risk; had no effect on cognition*

More recent

- **Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone** Peter J. Snyder, MD[20]
- *JAMA*. 2017;317(7):708-716. doi:10.1001/jama.2016.21043
- **Conclusions and Relevance** Among older men with symptomatic hypogonadism, treatment with testosterone gel for 1 year compared with placebo was associated with a significantly greater increase in coronary artery noncalcified plaque volume, as measured by coronary computed tomographic angiography. Larger studies are needed to understand the clinical implications of this finding

Case studies 1

- 53 yo male
- BMI 24, Ht 6'2", lanky guy
- Symptoms
- T 232 (300-1000)
- Repeat same
- FSH LH 6 and 7 (2-8)

Case studies 2

- 47 yo male , sedentary work, no shifts
- Feels ok but always fatigued and low sex drive
- BMI 33
- DM2, A1c 8.5
- Exam nl
- T 256 (repeat same, nl > 300), FSH LH nl, Iron nl, HCt 51

Case studies 3

- 64 yo male
- Always tired and low sex drive
- Sleep apnea, stable CAD, smoker
- Treat if T 250?
- 200?
- 150?
- 100?
- 50?

Case studies 4

- 31 yo male
- Always tired and last year lower sex drive and some ED
- Shiftworker (gy), on opioids for LBP
- T is 220, also after repeat
- Just got married

Case studies 5

- 64 yo alcoholic male
- Symptoms
- BMI normal
- T 210 (>240), repeat same, free T is a bit low
- Iron studies normal
- FSH 12 (<10), LH 10 (<10)

Case 6, what is the diagnosis

- Male 66 yo, tired, ED
- T at 8 am was 371 (nl 7-50)

- Male age 85, tired, ED, T 1200 (nl 300-1000)

Conclusions

- Always verify result (8am!), and evaluate for cause
- Think Klinefelter, Hemochromatosis, external OTC's or opioids or cannabis, Think Risks
- Almost always treat if T < 150
- Almost never treat the aging male with metabolic syndrome type features and lowish T, get them to lose weight, pending more research
- ASA 81 mg! for 6 months

Low T is caused by the men on the right