“Mens Health”
A Urologist’s Guide To Happiness

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OBJECTIVES

- Prostate cancer Biomarkers
- Indications for usage
- PSA variants
- Testicular function and Testosterone production
- Aging and effects on Testosterone production
- Indications for Testosterone Replacement Therapy

OBJECTIVES

- Risks/benefits of TRT
- Various formulations of TRT
- Correlation to Prostate cancer
- Controversies regarding TRT
- Mental Well-Being

Utility of Biomarkers for Prostate Cancer

- Useful for 4 main domains

1. Screening
2. Elevated PSA with prior negative biopsy
3. Pretreatment in men with new diagnosis
4. Postprostatectomy

Prostate Specific Antigen

- Serine protease protein
- Produced by prostate luminal epithelial cells (highly organ specific)
- Begins as a zymogen (preproPSA) ; cleaved into proenzyme (proPSA)
- Active form of PSA formed by cleavage of leader amino acid sequence of proPSA
- Functions to liquify semen via semenogelin and fibronectin

PSA

- Circulates in serum in bound (complexed PSA) and unbound (free PSA)
- 70-80% bound to one of three enzymes

1. alpha 1 antichymotrypsin (most common)
2. alpha 2 macroglobulin
3. alpha 1 protease inhibitor

PSA

- Becomes detectable at puberty
- On a per cell basis, PSA expression similar btw benign and malignant cells
- Men with BPH- rate of change of psa is 0.07 to 0.27 ng/mL per year
- Without BPH- 0.04 ng/mL per year change
- Elevated PSA levels occur due to disruption of cellular architecture (inflammation, biopsy , cancer)

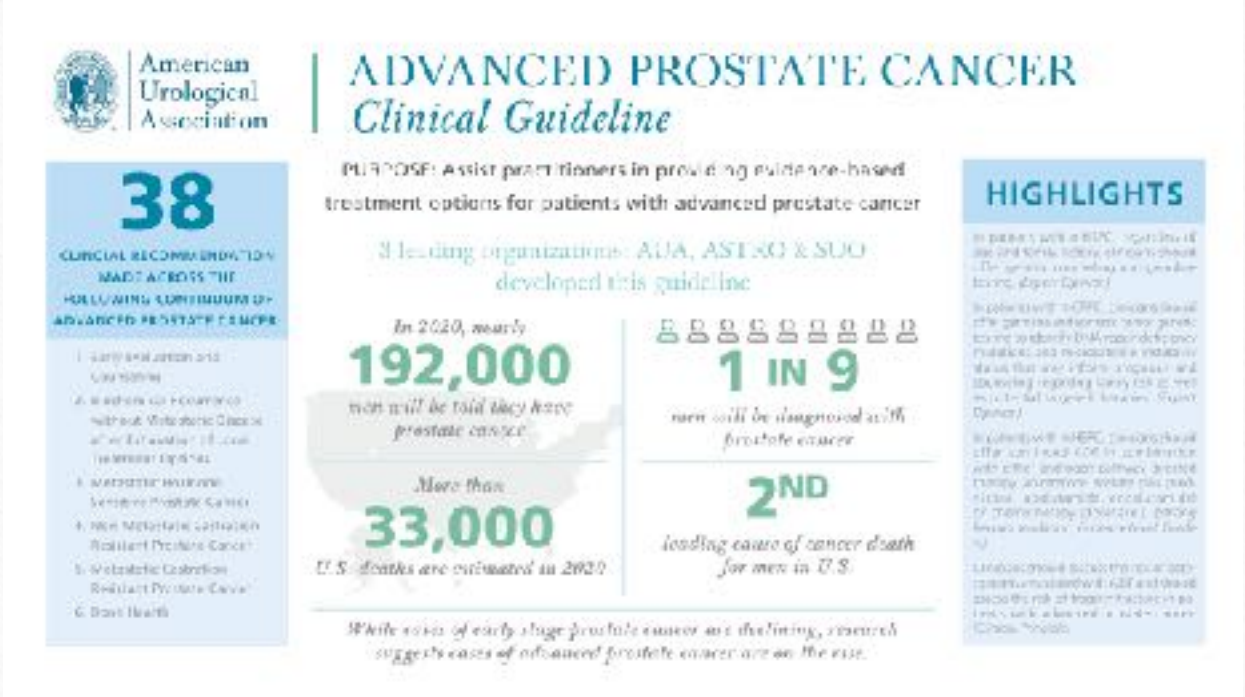
Age Adjusted PSA

AGE-BASED RANGES FOR PSA IN AMERICAN MEN ACCORDING TO RACE (NG OF PSA/ML)

Age	Whites	Blacks	Latino	Asian
40-49	0.0 – 2.4	0.0 – 2.4	0.0 – 2.1	0.0 – 2.0
50-59	0.0 – 3.6	0.0 – 4.2	0.0 – 4.3	0.0 – 4.5
60-69	0.0 – 4.5	0.0 – 5.5	0.0 – 6.0	0.0 – 5.5
70-79	0.0 – 5.2	0.0 – 6.6	0.0 – 6.6	0.0 – 6.8

Adapted from Morgan et al, 1996; DeAntoni et al, 1998 (average upper range taken for Whites and Blacks)

American Urological Association



AUA Screening Guidelines

- The Panel recommends against PSA screening in men under age 40 years. (Recommendation; Evidence Strength Grade C)
- The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C)
- For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of reducing the rate of metastatic prostate cancer and prevention of prostate cancer death against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B)

AUA Screening Guideline

- To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. As compared to annual screening, it is expected that screening intervals of two years preserve the majority of the benefits and reduce overdiagnosis and false positives. (Option; Evidence Strength Grade C)
- The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C)

FreePSA

- Usually 5-45% of PSA is inactive as freePSA
- Useful with psa ranging btw 4-10ng/mL
- Used to assess likelihood of prostate cancer on biopsy

Prostate Specific Membrane Antigen

- Biomarker for prostate cancer
- Predominately expressed in prostate secretory acinar epithelium
- Also found in CNS and intestine
- Used for targeted imaging to detect recurrent prostate cancer

Prostate Cancer Antigen 3

- Urinary biomarker for prostate cancer detection
- First urine after prostate manipulation (first 20-30mL)
- Useful in patient with negative first biopsy
- In contrast to PSA, PCA3 is independent of prostate size
- Cut off value of 35

4K score

- Multikallekrein panel (2008)
- Comprised of fPSA, tPSA, intact PSA, hK2
- Can accurately predict prostate cancer in men with PSA 3 or greater

Prostate Health Index

- Multiplex diagnostic serum assay
- Combines free and total psa along with proPSA forms
- Increase yield of biopsy and reduce unnecessary biopsies
- Men 50 years of age and older with negative DRE and PSA btw 4-10

USPSTF

- USPSTF's 2008 and 2012 grade "D" recommendations, PSA testing declined in the U.S. by 25–30%, significantly reducing overall PCa incidence rates and precluding early PCa detection in many patients.
- In May, 2017, the Task Force backed away from its grade "D" recommendation and issued a draft recommendation that clinicians inform men aged 55 to 69 years about the potential benefits and harms of PSA screening

Prostate Cancer Screening Trials

- PLCO trial: 76,683 volunteers
- Men randomized to intervention arm had a higher prostate cancer incidence (RR =1.12; 95% CI = 1.07 to 1.17) but no reduction in prostate cancer mortality (RR =1.09; 95% CI = 0.87 to 1.36)
- Equal proportions of men in control (34.3% once and 9.8% two or more times) and screening arms (34.6% once and 9.4% two or more times) had undergone PSA testing within 3 years preceding recruitment in the trial
- those having undergone pre-recruitment screening had 25% lower prostate cancer death rates than those who did not
- 50% of control arm were screened with psa during study at year 6 (corrected to almost 90% after statistical analyses)

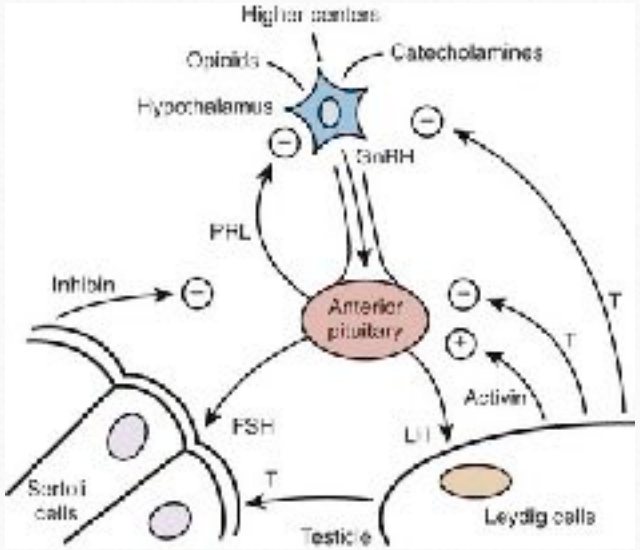
- ERSPC: 161,394 volunteers
- 21% reduction (rate ratio, 0.79; 95% CI 0.68 to 0.91; P=0.001) in death from prostate cancer in a pre-defined subgroup of men aged 55–69 years after 11 years of follow up

Does Screening Lead to Decrease Mortality?

- Alex Tsodikov, PhD, et al; Ann Intern Med. 2017 Oct 3; 167(7): 449–455. Conducted statistical analysis from the PLCO and ERSPC relating to mean lead time (MLT)
- MLT defined as the average time by which diagnosis is advanced by screening relative to the date of diagnosis without screening
- Under a common effect of screening, all approaches indicated strong evidence that a longer MLT was associated with a lower risk of prostate cancer death after accounting for differential baseline risks of prostate cancer death between trial settings and participant age at randomization (P=0.0027–0.0032)
- These analyses showed that screening was estimated to confer a 7–9% lower risk of prostate cancer death per year of MLT.
- this would translate into an estimated 25–31% and 27–32% reduction in the expected risk of prostate cancer death in the setting of screening as performed in the ERSPC and PLCO intervention arms, respectively, over 11 years of follow-up relative to no screening

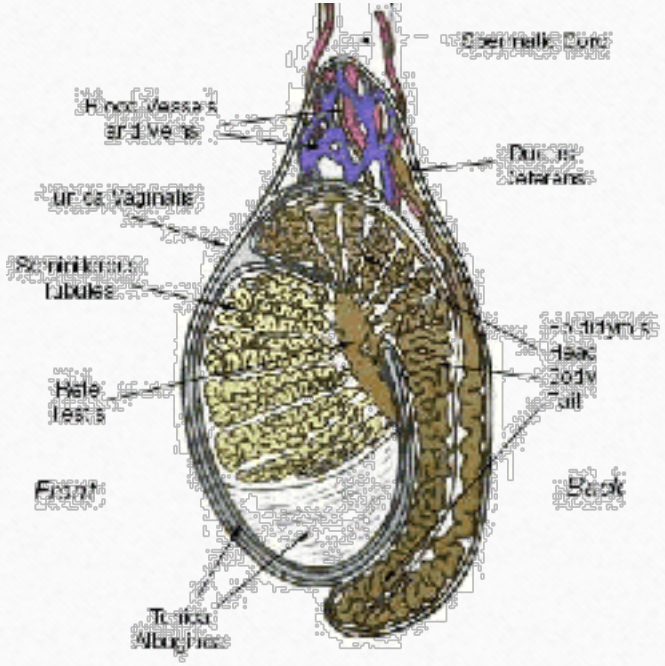
A few of the beauties of WV

Testicular function



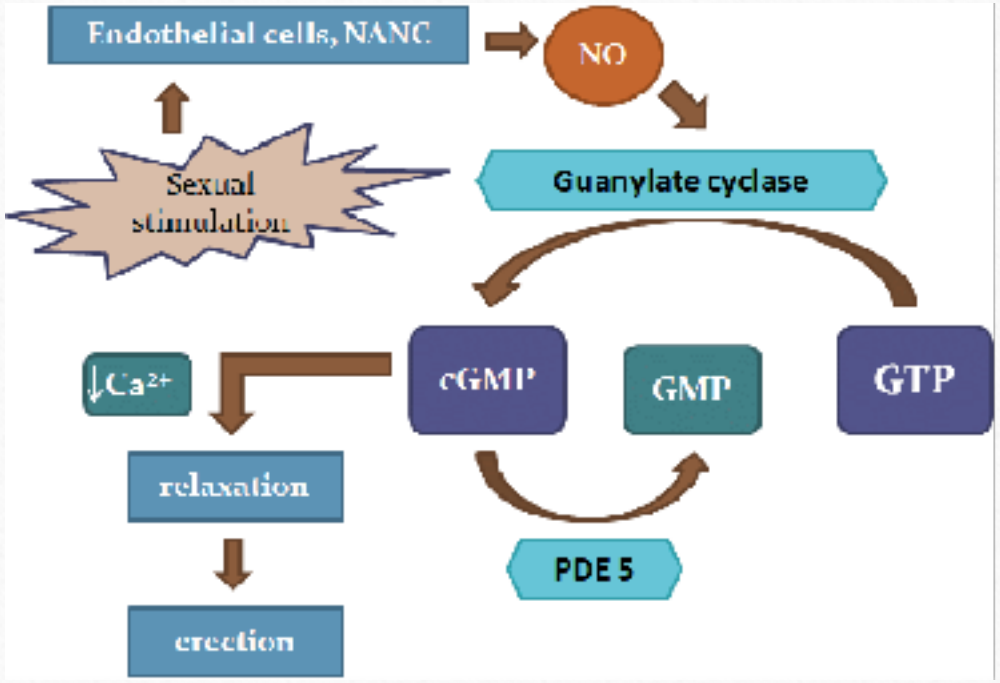
- Leydig cells responsible for steroidogenesis
- Seminiferous tubules produce spermatozoa
- Normal T production is 5g/day
- 2 main androgens produced: DHT and estradiol

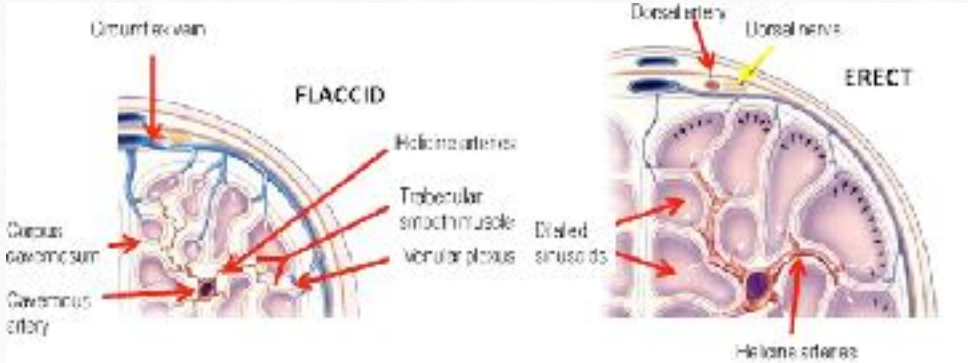
Testicular Function



- FSH works on Sertoli cells in seminiferous tubules
- Initiates sperm production
- Inhibin- stimulated by FSH (neg feedback)
- Activin – stimulates FSH production

Erectile Mechanisms





Contraction

Noradrenaline
Endothelins
Angiotensin II
Serotonin
Prostanoids ($PGF_{2\alpha}$, TXA_2)
Tumor Necrosis Factor-α

Relaxation

Acetylcholine
Dopamine
ATP
Adenosine
VIP and related peptides
Adrenomedullin, CGRP
Prostanoids (PGE_2)
Endocannabinoids

Testosterone

- Majority is bound to albumin (54-68%)
- Less bound to SHBG (30-44%)
- Rest is unbound or free Testosterone
- When SHBG binds T it renders it unavailable
- Albumin bound T and free T are termed bioavailable

Testosterone

- Metabolism important to maintain proper balance btw production
- Occurs primarily in liver
- Extratesticular aromatization to estradiol
- T 1/2 of testosterone in plasma is 12 minutes
- Estrogen acts either synergistically or antagonistically
- Bioavailable estrogen and T strongly associated with high bone turnover, low BMD, and risk of osteoporotic fractures
- Imbalance of the T:E ration likely responsible for impaired glucose tolerance and insulin resistance

Testosterone

- Gives rise to DHT through 5 alpha reductase
- DHT responsible for normal sexual development and virilization in men
- When combined with transactivation of AR leads to prostate gene transcription and growth
- 2 types of 5 Alpha reductase

1. Type 1 – localized in non genital skin, liver, brain, prostate, and testis
2. Type 2 – mainly active in classic androgen-dependent tissues such as epididymis, genitalia, SV, testis, and prostate (also in uterus, liver, breast, placenta, and hair follicles)


I CALL MY TESTICLES WONKAS
CUZ THEY ARE BETWEEN MY WILLY AND MY CHOCOLATE FACTORY
makeameme.org

Androgen Deficiency (Hypogonadism)

- A result of either testicular failure (primary AD) or disruption of the hypothalamic-pituitary-gonadal axis (secondary AD)
- GnRH main affect on LH and FSH
- Hormone stimulation can restore levels in secondary AD

Primary Hypogonadism

Causes of primary hypogonadism

Congenital	Acquire disorders	Systemic disorders
Klinefelter syndrome (XXY)	Bilateral surgical castration or trauma	Chronic liver disease
Myotonic dystrophy	Orchitis	Malignancy (Lymphoma, testicular cancer)
Uncorrected cryptorchidism	Drugs (Spironolactone, ketoconazole, abiraterone, enzalutamide, alcohol, chemotherapy agents)	Chronic kidney disease
Noonan syndrome	Ionizing radiation	Sickle cell disease
Bilateral congenital anorchia		Aging
Polyglandular autoimmune syndrome		Spinal cord injury
Testosterone biosynthetic enzyme defects		Vasculitis, infiltrative disease (Amyloidosis, leukemia)
Congenital adrenal hyperplasia		
Complex genetic syndromes		
Down syndrome		
Luteinizing hormone receptor mutation		

Which stage do you feel?

Hypogonadism

- "a biochemical syndrome associated with advancing age and characterized by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgen. It may result in significant alterations in the quality of life and adversely affects the function of multiple organ systems."
- Progressive decline in testosterone and sperm production with aging
- At 7th decade men have 35% lower T levels than young men
- Volume and length of testicles decreases
- Circulating LH concentrations do no decline as men age although affects on tissue seen
- Diurnal variation of T secretion lost in elderly
- Normal pulsatile GnRH release replaced by irregular pulses (less effective)

Hypogonadism

- T levels in men >40 YOA decrease at a rate of 1-2% per year
- Using 300ng/dL as cutoff for AD, overall prevalence estimated around 40%
- Prevalence of AD associated with systemic disease is higher than for the normal aging process
- Functional androgen receptor critical for actions of androgens

Systemic Illnesses Associated with AD

- Burn injury
- Traumatic brain injury
- Respiratory illness
- Surgical stress
- Chronic opioid exposure
- HIV
- Chronic liver disease
- Diabetes
- Stroke
- Myocardial infarction
- Sepsis
- Cancer
- Chronic renal failure
- Rheumatoid arthritis
- Obesity

Hypogonadism

Table 3. Signs and Symptoms of Hypogonadism

Signs of Hypogonadism	Symptoms of Hypogonadism
Incomplete sexual development	Reduced libido and activity
Gynecomastia	Decreased spontaneous erections
Loss of axillary and pubic hair	Hot flashes
Small or shrinking testes	Fatigue, decreased motivation
Infertility related to low sperm counts	Depression or dysthymia
Height, BMD, and muscle loss	Poor concentration and memory
Anemia, mild (normochromic, normocytic)	Sleep disturbance or increased sleepiness
Increased BMI and body fat percentage	

BMD: bone mineral density; BMI: body mass index.
Source: Reference 7.

Hypogonadism

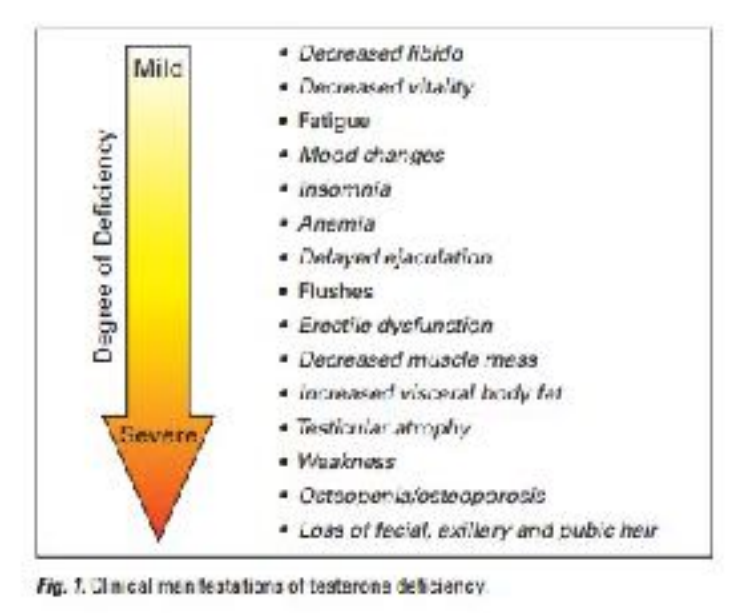


Fig. 1. Clinical manifestations of testerone deficiency

Diagnosis of AD

- Clinical signs and symptoms often nonspecific
- Aging Male Symptom Scale consists of 17 questions
- Allows one to quantify degree of improvement in symptoms after therapy
- Confirmatory biochemical testing
- Lower limit 300ng/dL
- T levels peak in morning so test in morning
- Must confirm low T levels with a repeat test

Aging Male Symptom Scale

Symptoms	Before				After			
	0	1	2	3	0	1	2	3
Decline in your feeling of general well-being	2	3	8		2	5	6	
Joint pain and muscular ache	3	4	3	3	3	5	5	
Excessive sweating	7	4	2		8	5		
Sleep problems		4	5	4		6	5	2
Increased need for sleep, often feeling tired		3	7	3	2	5	6	
Irritability	2	7	4		2	9	2	
Nervousness	8	5	2		6	7		
Anxiety	3	4	4	2	4	6	3	
Physical exhaustion/lacking vitality		1	6	6		4	8	1
Decrease in muscular strength		2	5	6		3	8	2
Depressive mood	2	5	4	2	5	4	4	
Feeling that you have passed your peak		6	5	2		6	6	1
Feeling burnt out, having hit rock bottom		2	6	3		7	6	
Decreased in beard growth		5	6	2		7	5	1
Decrease in ability/frequency to perform sexually			4	9			9	4
Decrease in the number of morning erections			8	5		2	10	1
Decrease in sexual desire/libido			3	10			8	5

0, none; 1, mild; 2, moderate; 3, severe; Fisher's exact test, $p = 1.0$; McNemar test, $p = 0.1021$.

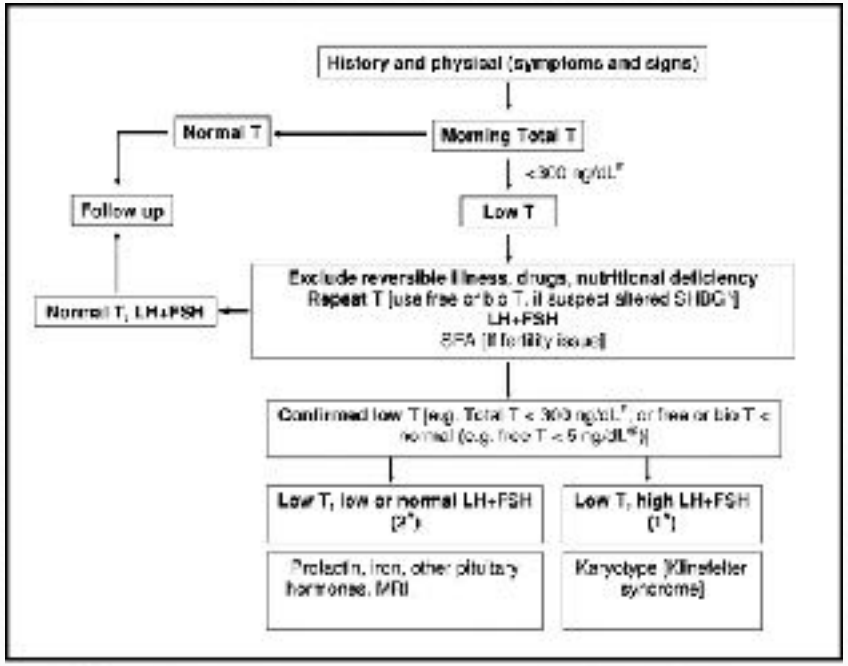
Diagnosis

- Serum total testosterone represents both protein bound and unbound T
- Bioavailable T refers to albumin bound T and unbound T
- Free T or bioavailable T should be measured when total T levels are at the lower limit of normal range or when altered SHBG levels suspected
- Assess gonadotropins and prolactin during confirmatory testing to exclude secondary hypogonadism
- MRI brain indicated in abnormality of the HPG axis

SHBG

Decrease SHBG	Increase SHBG
Androgens	Estrogens
Obesity	Pregnancy (Estrogens)
Insulin resistance	Weight loss
Metabolic syndrome	Alcoholic cirrhosis
Type 2 diabetes mellitus	Hepatitis-B and hepatitis-C infection
Gestational diabetes mellitus	Hemochromatosis
Polycystic ovary syndrome	Hyperthyroidism
Non-alcoholic fatty liver disease	Growth hormone deficiency
Acromegaly	Acute intermittent porphyria
Cushing's syndrome	First generation anticonvulsants
Congenital adrenal hyperplasia	
Hyperprolactinemia	
Tumor necrosis factor alpha	
Interleukin-1 beta	

Work Up Algorithm



Modified from Bhasin et al.


ALWAYS GRAB YOUR
DAY BY THE BALLS

Treatments

- To treat or not to treat!

Indications for Treatment of AD

- Goal of treatment is to restore physiologic T levels while alleviating symptomatic AD
- Lifestyle modifications paramount
- Given to AD men demonstrating a decline in muscle mass and strength, reduction in BMD, and decrease in sexual function
- TRT preparations: oral, buccal, transdermal, IM injections, and sub Q implantation

Oral preparation

- Associated with hepatotoxicity
- Considered obsolete and no longer recommended
- Testosterone undecanoate (not available in U.S)
- Absorption is via lymphatics and must be taken with at least 20 mg of fat
- Short half-life (4 hours) and requires multiple dosing (2-3 times daily)
- Has advantages of flexible dosing, self-administration, and immediate decrease in concentrations after cessation of therapy

Transbuccal preparation

- Absorption through oral mucosa bypassing liver metabolism (sustained release tab)
- Softening and molding of tab to the shape of gum work to apply the system
- Tablet must be removed after 12 hours to avoid local irritation
- Testosterone buccal

Transdermal preparations

- Deliver consistent serum T levels into circulation during treatment
- To be used daily
- Patches associated with local skin reactions and decrease compliance rates
- Comes in scrotal and non scrotal patches
- Rapidly absorbed into stratum corneum forming a reservoir and serves as rate-controlling membrane
- Transference potential exists (can reduce by washing excess gel after mandatory residence time of 2-4 hours; clothes also form barrier to transference

Injectable preparations

- Absorbed directly into bloodstream
- Cypionate and enanthate esters available
- IM every 1-2 weeks
- Supraphysiologic levels within 24 hours followed by gradual decline to AD levels following 10-14 days
- Wide fluctuation in T concentrations associated with frequent side effects of polycythemia, dose adaptation, temporary interruption of therapy, and/or phlebotomy
- Long-acting injectable preparation leads to gradual release into circulation mitigating fluctuation of T levels (not available in U.S)

Subcutaneous Implant preparations

- T pellet is the only long-acting formulation approved for the treatment of male AD in the U.S.
- Inserted into subcutaneous tissue under local anesthesia
- Can lead to infection or pellet extrusion
- Serum T reach supraphysiologic levels at 1 month with gradual decline the following 3-6 months
- Can increase patient compliance

Monitoring during therapy

Table 2. Baseline and Follow-Up in TRT

Level	Baseline	Follow-up	Notes
Testosterone	Two morning testosterone levels needed	3-6 mo after initiation, then annually	If testosterone is >700 ng/dL or <350 ng/dL, the dose and frequency of TRT should be adjusted
Hematocrit	Do not initiate TRT if HCT >50%	3-6 mo after initiation, then annually	Discontinue if HCT >54%
PSA[a]	Do not initiate TRT if PSA ≥4 ng/mL or PSA ≥3 ng/mL in high risk patients	3-6 mo after initiation, then annually	Referral to urologist may be necessary if abnormal PSA related parameters are detected
FSH and LH	To distinguish between primary and secondary origin	N/A	N/A

[a] In accordance with age and race of patients using evidence-based guidelines for prostate cancer screening.
FSH: follicle-stimulating hormone; HCT: hematocrit; LH: luteinizing hormone; N/A: not applicable; PSA: prostate-specific antigen; TRT: testosterone replacement therapy.
Source: Reference 4.

Contraindications of TRT

- **Very high risk** of serious adverse outcomes

- Metastatic prostate cancer
- Breast cancer

- **Moderate to high risk** of adverse outcomes

-Unevaluated prostate nodule or induration

- Hematocrit > 50%
- Unevaluated sleep apnea
- Poorly controlled CHF
- Severe LUTS from BPH

Side Effects of TRT

- **Erythrocytosis- most common side effect of TRT (injections > topical therapy)**

-Testosterone stimulates erythropoiesis (poorly understood- ? improvement of iron bioavailability)

-ADT and AD- risk factors for anemia

-Men with CKD- AD associated with reduced responsiveness to erythropoiesis-stimulating agents

- Increased blood viscosity can aggravate vascular disease in the coronary, cerebrovascular, or peripheral vascular circulation (more in elderly with pre-existing conditions)
- If seen- dose reduction, withholding therapy, therapeutic phlebotomy, or blood donation

Sleep Apnea

- TRT associated with development of sleep apnea
- Seen in those on higher dose TRT and risk factors for sleep apnea
- No affect of TRT on anatomy of airways
- More of a central mechanism of altered breathing patterns

Dermatologic reactions

- More common with transdermal patches (up to 66%) than gel preps
- IM injections can cause local pain, ecchymosis, erythema, swelling, hematoma, abscess, or furuncles
- Can see acne, oily skin, changes in body hair, and flushing

Fluid Retention

- Usually uncommon and generally mild
- Caution with initiating TRT in men with CHF or renal insufficiency

Gynecomastia

- Painful breast enlargement
- Very rare
- Caused by increased estradiol levels from aromatization
- Managed by dose adjustment

TRT and BPH

- TRT can lead to increased prostate volume during first 6 mo of treatment (growth of prostate androgen dependent)
- No worsening LUTS on TRT
- Severe LUTS (IPSS>20) is a relative contraindication to TRT
- Consider evaluation and treatment before initiation of therapy
- Paramount importance to monitor urinary symptoms while on TRT

Testicular Hypofunction

- Size and consistency often diminish on TRT
- Exogenous T leads to excess negative feedback on the HPG axis
- Suppresses endogenous T production and spermatogenesis
- Recovery after TRT cessation usually occurs in 12-15 months (normal spermatogenesis not always observed)
- Caution when using TRT in men who still desire fertility
- Can use pretreatment sperm cryopreservation or concomitant administration of hCG (to preserve spermatogenesis)

Testosterone Therapy for ED

- Prevalence of AD in men with ED ranges from 23%-47%
- ED an important independent risk factor for CVD
- T in the CNS can stimulate release of excitatory neurotransmitters such as dopamine, oxytocin, and nitric oxide
- Peripherally T modulates components of erectile function: structure, function, and innervation of smooth muscle cells, endothelial function of penile vessels, and fibroelastic properties of the corpus cavernosum
- Combination therapy with TRT and PDE-5 inh highly debated topic
- Addition of TRT only beneficial in AD men with T levels < 300 ng/dL)

Testosterone Therapy for ED

- In young men with symptomatic AD, TRT should be first line treatment (can add PDE-5 inh if necessary)
- In elderly men with ED, PDE-5 inh should be first line therapy with optimization of comorbidities
- With nonresponders, TRT only used after biochemical confirmation of AD
- When erection is restored by PDE-5 inh, no further benefit of erectile function with TRT

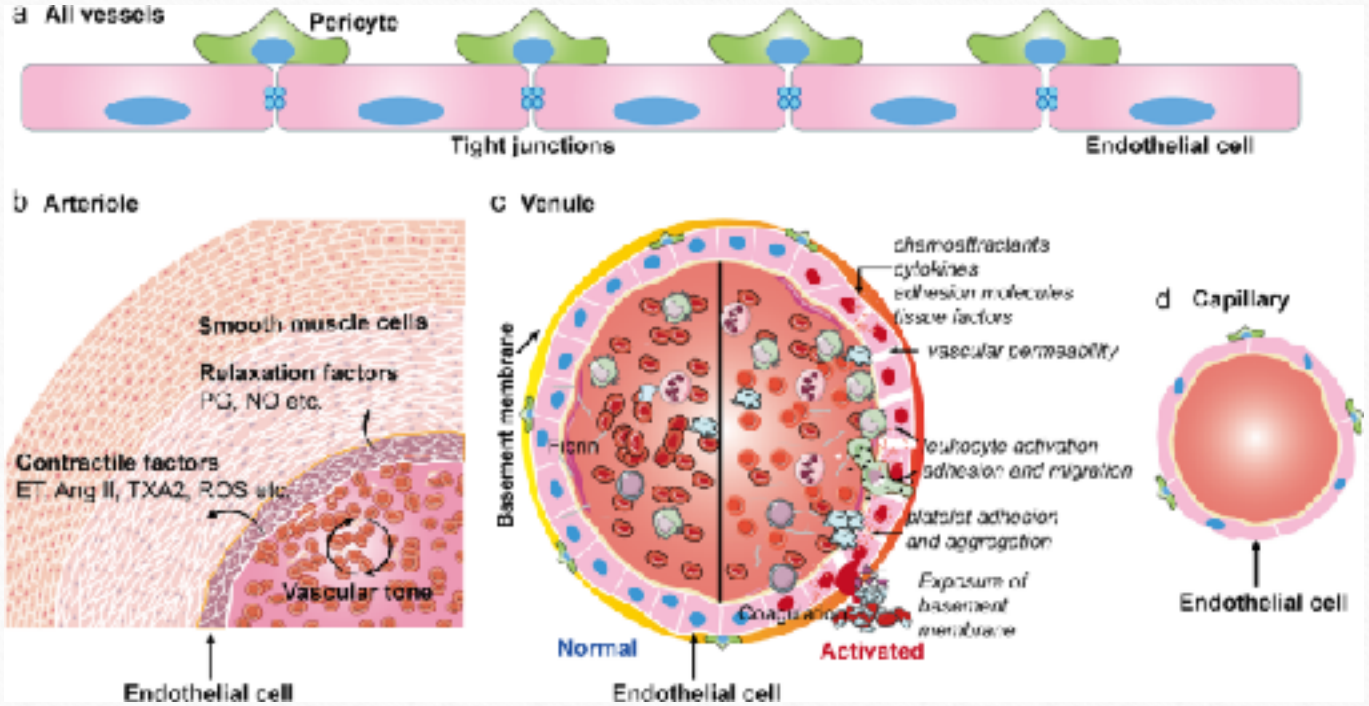
Prostate Cancer

- TRT **did not** show an increase in the incidence of prostate cancer or the risk for prostate biopsy compared to placebo groups
- TRT used as a strategy for sexual function rehabilitation following prostate cancer treatment (no increase in biochemical recurrence)
- Before starting TRT do baseline PSA and DRE
- If abnormal then needs evaluated
- Must follow PSA levels while on TRT

Cardiovascular Disease and Testosterone

- CVD leading cause of death in developed countries
- Men at greater risk than premenopausal women (potential influence of sex hormones)
- ADT associated with increased risk of CV events in patients with prostate cancer
- ADT influence on CVD- increased body weight, decreased insulin sensitivity, altered lipid profile, and increased fat mass
- Low endogenous levels of T associated with CAD (anti-inflammatory)

Endothelial Cell System



Cerebral Vascular Disease

- Low levels of total T and bioavailable T predictive of increased incidence of TIA and cerebral vascular accidents
- Low T concentration associated with increased carotid intimal-medial thickness
- Gender specific with predilection for men

Controversies of TRT

- The effects of exogenous testosterone have been reported to be beneficial. TRT in men with hypogonadism and CAD has been reported to increase time to 1mm ST-segment depression with stress testing (Webb, Adamson, de Zeigler, & Collins, 1999)
- A double-blinded randomized placebo-controlled trial by English, Seeds, Jones, Diver, and Channer (2000), reported reduction in exercise-induced myocardial ischemia with no significant changes in lipid or coagulation profile with TRT.
- A retrospective Veterans Affairs study by Shores, Smith, Forsberg, Anawalt, and Matsumoto (2012) concluded that those treated with testosterone had a lower mortality rate compared with those who were not (10.3% vs. 20.7%, $p < .0001$).

Controversies of TRT

- In a randomized, double-blinded, placebo-controlled parallel trial of 76 men with heart failure, men treated with TRT (5 mg Androderm) had an improvement in exercise capacity and symptoms from baseline compared with placebo (p = .006; Malkin et al., 2006).
- Meta-analysis studied 51 comparative, randomized and nonrandomized trials and reported no significant effect on cardiovascular outcomes, including myocardial infarction, coronary revascularization procedures, or arrhythmias. However, they did note that it was associated with increase in hemoglobin and hematocrit and a small decrease in high-density lipoprotein (Fernández-Balsells et al., 2010).
- Haddad et al. (2007) analyzed six placebo-controlled randomized trials of 308 men undergoing treatment with placebo or TRT. Adverse cardiac events included death, myocardial infarction, angina, arrhythmia, revascularization, and stroke (Haddad et al., 2007; Oskui et al., 2013). They reported no significant difference in rates of events between TRT and placebo-treated groups, with OR 1.82 (.78-4.23).

Controversies of TRT

- While these early studies seem to indicate that TRT does not cause adverse cardiac events, there are several criticisms. The quality of the evidence included in these meta-analyses was variable. There was marked heterogeneity in terms of what constituted cardiovascular events in the studies. Additionally, the duration of the trials was often short, and therefore lacks long-term insight into the safety of the treatment (Vigen et al., 2013).

Controversies of TRT

- Contrary to the previous studies, more recent studies seem to suggest there is an increase in adverse cardiovascular events associated with TRT.
- Basaria et al. (2010), Testosterone in Older Men with Mobility Limitations (TOM trial), was a placebo-controlled randomized trial that enrolled older men with lower levels of testosterone to evaluate the effects of testosterone administration on lower extremity strength and physical function.
- 209 men evaluating safety of 100 mg T gel patch
- trial was stopped early because 23 patients in the testosterone group suffered more than one adverse cardiovascular event in comparison with the 7 in the placebo group. The adverse events reported include acute coronary syndrome, chest pain, syncope, myocardial infarction, angioplasty, coronary artery bypass graft, atrial fibrillation, and stroke (after 6 mo treatment)
- Limitations of small pop size and mean age 74; majority of subjects had chronic diseases (diabetes, hyperlipidemia, HTN and heart disease)
- **Currently** the only randomized controlled trial evaluating the cardiovascular risks associated with TRT

Controversies of TRT

- Vigen et al. (2013) studied cardiovascular events with TRT in a national cohort of veterans with hypogonadism who underwent coronary angiography
- Men > 60 and 80% had CAD
- assessed the association between TRT and all-cause mortality, myocardial infraction, and stroke
- 8,709 participants; absolute risk increase of 5.8% ($p < .05$) of adverse cardiovascular events in the TRT group compared with placebo
- Limitations- small size, retrospective, no randomization, variability in T measuring levels
- Unsure why some men with Low T weren't treated and if T was prescribed appropriately
- Raises the issue of whether the men treated with testosterone were more symptomatic and therefore more likely to have an underlying cardiovascular condition.
- Largest issue is the **generalizability** of the study. Most of the men were elderly and had documented CAD and therefore were already at a high risk for cardiovascular events.

Controversies of TRT

- Xu, Freeman, Cowling, and Schoolin (2013) et al.
- Meta-analysis of placebo-controlled randomized trials included a larger number of participants (2994), mostly elderly men, compared with the previous meta-analyses.
- concluded that there was a statistically significant increase in cardiovascular-related events in men with TRT lasting 12 or more weeks, with OR 1.54 ($p < .05$; Xu et al., 2013).
- Interestingly, they identified that the risk of adverse events with testosterone therapy was higher in studies not funded by the pharmaceutical industry compared with those that were.

Controversies of TRT

- cohort study by Finkle et al. (2014) examined the risk of myocardial infarction following the initiation of testosterone therapy in 55,593 young and old men
- significant increased risk of myocardial infarction following TRT in older men (>65 years) with a relative risk increase of 2.19 (1.27-3.77) and in younger men (<65 years) with prediagnosed heart disease, with relative risk 2.9 ($p < .05$), within the 90 days following initiation of TRT.
- no increased risk in men less than 65 without heart disease.
- limitation of this study was that serum testosterone was not collected, making it difficult to determine whether or not patients were eugonadal while on the therapy. Additionally, the control group in this study consisted of patients who were prescribed phophodiesterase inhibitors (vasodilatory affects which may be cardioprotective) for erectile dysfunction.

Pitfalls of current studies

- Neither study measured levels of estrogen (can increase CV disease)
- Neither study measured Hematocrit levels (increased thrombosis risks)
- Since not all patients were followed up- unsure if supraphysiologic T (can induce oxidative damage and endothelial dysfunction
- DHT not measured and is a potent atherosclerotic agent

Mental Well Being

Is Working From Home Beneficial?

- **Impacts of Working From Home During COVID-19 Pandemic on Physical and Mental Well-Being of Office Workstation Users**
- Yijing Xiao, Burcin Becerik-Gerber, DDes, Gale Lucas, PhD, and Shawn C. Roll, PhD; J Occup Environ Med. 2021 Mar; 63(3): 181–190.

- workers reported a decline in overall physical and mental health status and an increased number of new physical and mental health issues
- Significant predictors of decreased physical and mental health status included decreased physical activity, increased junk food intake, lack of communication with coworkers, and having a toddler at home.

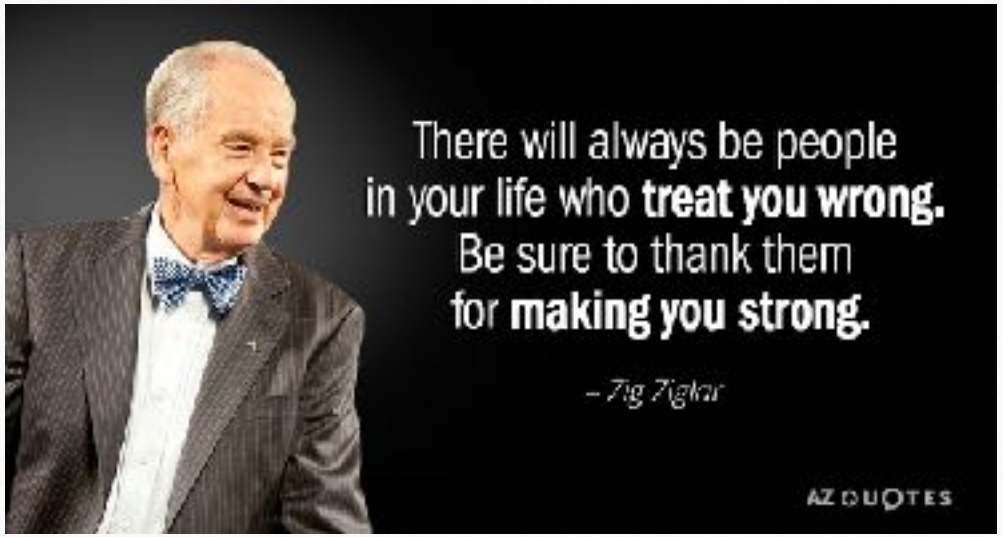
Is Working From Home Beneficial?

- 2/3 of respondents reported having one or more new physical health issues, and nearly 3/4 of respondents experienced at least one new mental health issue
- Female respondents and respondents with annual income of less than 100k reported health issues compared to male respondents and respondents with higher incomes.
- Respondents who lived with at least one teenager, had higher satisfaction over indoor environmental quality factors at home, had a designated workspace, and had a good workstation set up, all had lower chance of experiencing new physical and mental health issues.

Conclusions

- Prostate cancer screening with psa beneficial
- Multiple screening tests available for prostate cancer
- Aging has dramatic affects on T production and quality of life
- Comorbidities important deciders prior to initiating TRT
- Multiple controversies over TRT
- Mental health extremely important for longevity and preventing “burn out”
- Know when to incorporate the Urologist in practice patterns

Thank You!


There will always be people
in your life who **treat you wrong.**
Be sure to thank them
for **making you strong.**
– Zig Ziglar
AZ QUOTES


IF YOU CAN **DREAM** IT,
THEN YOU CAN **ACHIEVE**
IT. YOU WILL GET ALL YOU
WANT IN **LIFE** IF YOU **HELP**
ENOUGH OTHER **PEOPLE**
GET WHAT THEY **WANT.**
ZIG ZIGLAR