



# The Inseparable Link Between Testosterone and the Prostate

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# THE INSEPARABLE LINK BETWEEN TESTOSTERONE AND THE PROSTATE

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# TESTOSTERONE FACTS



# Testosterone Fast Facts

T is a steroid hormone and cannot be stored in the cells that produce it; instead, testosterone is released from the cells following production

T is produced by direct nervous stimulation of the hypothalamus by the CNS or by reduced feedback inhibition on the hypothalamus by testosterone.

T has anti-catabolic effects through inhibition of cortisol signaling by blocking the glucocorticoid receptor

Anti-catabolic effects aid in recovery



# Testosterone Fast Facts

T has a half life of 12 minutes - Lin BJ et al. Urology. 1994 Jun;43(6):834-7.

T increase is pulsatile driven and by negative feedback from other steroid hormones

T Levels are highest in the morning and fluctuates during the day

- Pataky MW et al., Mayo Clin Proc. 2021

# HOW IS TESTOSTERONE PRODUCED

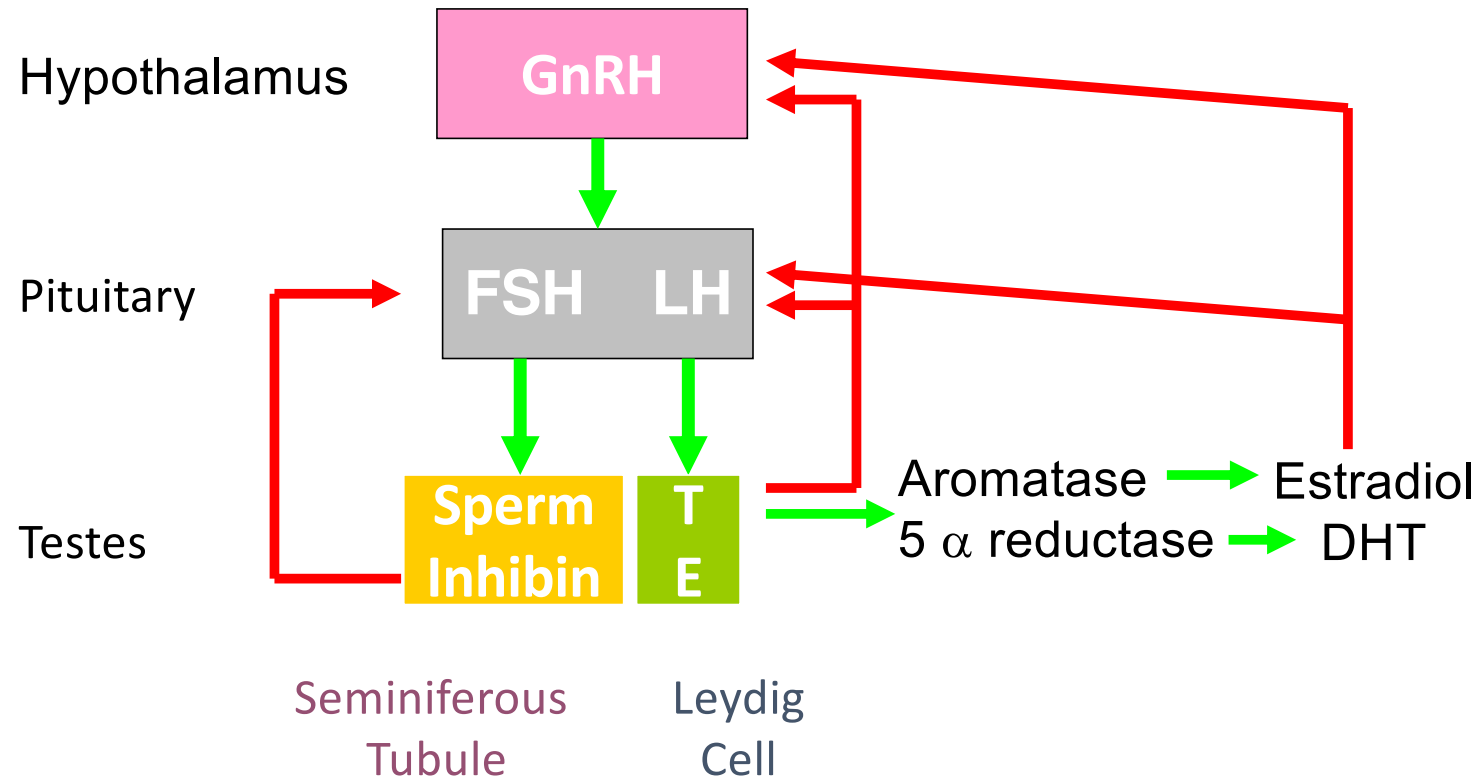
# Detail Pathway of T Production

- ➡ Specialized neurons produce GnRH in the hypothalamus
  - ➡ GnRH (via the hypothalamic-hypophyseal portal vein) anterior lobe of pituitary gland to release LH and FSH
  - ➡ (via circulation) stimulate Leydig cells in men (chorionic gonadotropin also stimulate Leydig cells)
  - ➡ G-proteins and, in turn, adenylate cyclase increase cAMP
  - ➡ protein kinase A (PKA)
  - ➡ steroidogenic acute regulatory (StAR) protein.
- [FYI - protein kinase C (PKC) signal pathway can strongly modulate Leydig cell steroidogenesis]

- Asiedu et al. Aging Male 2017



# Normal Male HPT



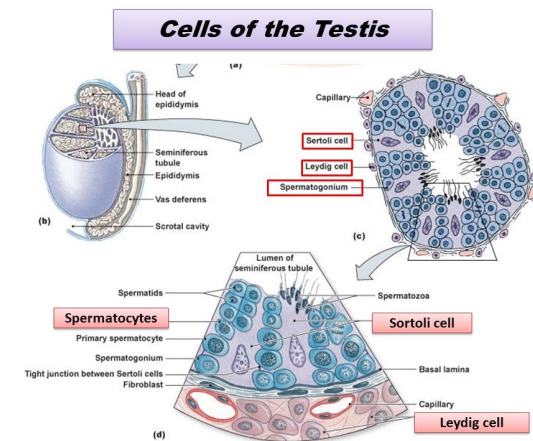


# Sites for Testosterone Production

## Leydig cell

- Affected by obesity
- Stress through excess glucocorticoids
- Zn deficiency

- Zirkin BR et al Biol Reprod. 2018 Jul 1;99(1):101-111.



# KEY STRUCTURES IN T PRODUCTION & TRANSPORT

# Key structures in the T Chain

- Healthy functioning HPG axis and feedback systems
- Involves “proper behavior” of key enzymes
- Management of transporting proteins, mainly SHBG
- Plenty, healthy and proper functioning Leydig cells
- Plenty, healthy and proper functioning AR's

- Asiedu et al. Aging Male 2017



# Transport of Testosterone

- Testosterone is hydrophobic and has to bind to proteins for transport in the blood and storage (in the blood).
- Sex Hormone-Binding Globulin (SHBG) binds to approximately 44–60% of total serum testosterone.
- The remaining testosterone is either loosely bound to albumin and other binding proteins or free
- 0.2–2% of total testosterone is in the free form
- SHBG reduces the movement of testosterone from the blood into other bio-compartments; whereas, albumin does not appear to interfere with this movement

–Selva DM et al., Journal of Clinical Investigation. 2007 Dec;117(12):3979–3987.

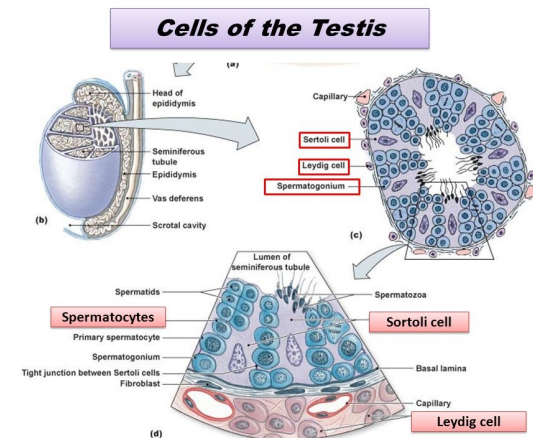
# Free Testosterone

- Free testosterone (FT) is the fraction of the total testosterone (T) that is readily available to the cells and is dependent on the levels of sex hormone binding globulin (SHBG) and albumin
- SHBG bound testosterone remains in the circulation with no binding function in this form.
- Higher total testosterone and lower SHBG levels can increase FT.
- The European Male Aging Study (EMAS) , 3000 men, Low FT Sx's associated w decreased sexual thoughts, weak morning erections, and erectile dysfunction. <230 ng/dL or serum TT between 230 to 317 ng/dl *and* free testosterone level <7 ng/mL (220 pmol/L).

# Sites for Testosterone Production in Men

## Leydig cell

- Affected by obesity
- Stress through excess glucocorticoids
- Zn deficiency





# Androgen Receptors (AR's)

AR's found in the prostate, adrenal gland, skeletal muscle, liver and in the central nervous system.

Testosterone also has a weak bonding ability to estrogen and progesterone receptors, where DHT has a specific affinity to AR

The androgen receptor is most closely related to the progesterone receptor, and progestins in higher dosages can block the androgen receptor.

DHT binds to AR two times more potently than T





# SHBG

- SHBG is produced in the liver where it regulates bioavailability of sex steroids , T & E.
- SHBG is decreased by androgens, advancing age, and hypothyroidism.
- SHBG concentrations are lower in obese/overweight men because of an inhibitory effect of higher insulin concentrations on SHBG production
- High levels of SHBG are associated with decreased bone mineral density and increased fracture risk in older men
- liver fat, but not visceral fat or total body fat, was found to be an independent predictor of SHBG plasma level. - A. Peter, *et al* .Diabetes 59 (2010)



# SHBG

Increase concentrations

- Ageing
- Hyperthyroidism
- Hyperoestrogenaemia
- Liver disease
- HIV
- Use of anticonvulsants

Anorexia (return to normal levels after weight gain, serves as a reliable index for nutritional status in eating disorders)

- Yonah Krakowsky et al. Serum Concentrations of Sex Hormone-binding Globulin Vary Widely in Younger and Older Men: Clinical Data from a Men's Health Practice. European Urology Focus, 2017, 1-7.



# SHBG

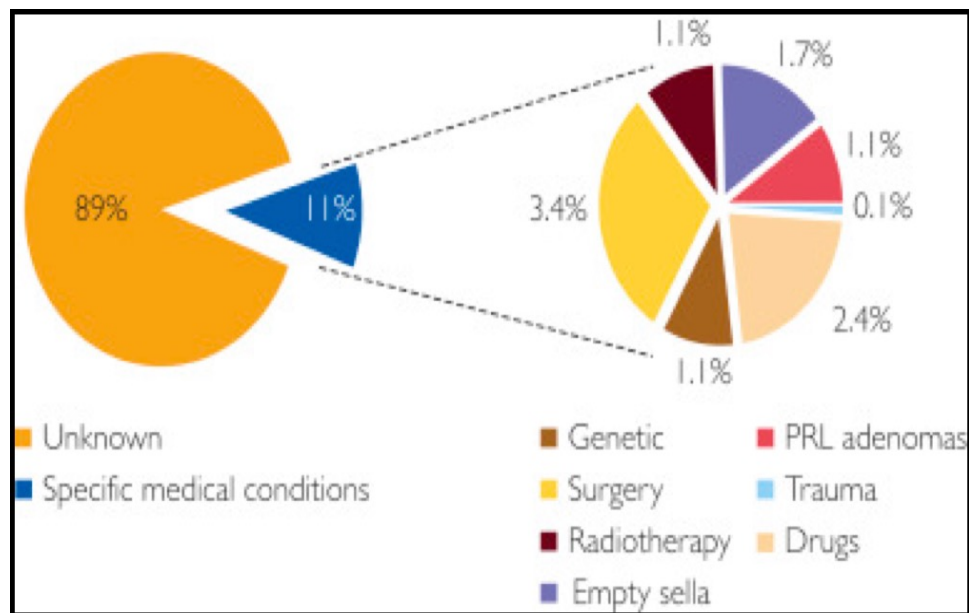
## Decreased concentrations

- Obesity
- Insulin resistance and diabetes
- Hypothyroidism
- Growth-hormone excess
- Glucocorticoids
- Androgens
- Progestins
- Nephrotic syndrome

- L. Niskanen, *et al.* Changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance in abdominally obese men with the metabolic syndrome, *Diabetes Obes. Metab.*, 6 (2004), pp. 208-215

# MORBIDITY AND MORTALITY IN LOW T

# Up to 89% of hypogonadism does not fit into Classical Schema.



# Increase Mortality with Low T in Men

Severe LOH has been related to an overall 5.5-fold higher risk of all-cause mortality [2-fold higher in those with testosterone  $\leq 8$  nmol/l (2.3 ng/ml), irrespective of symptoms, and 3-fold higher in those with three sexual symptoms, irrespective of testosterone concentrations]. – Pye et al. *J. Clin Endocrinol. Metabol.*, 99 (2014)

Epidemiologic studies and meta-analyses have demonstrated higher all-cause mortality and cardiovascular mortality in men with low testosterone concentrations. - Araujo et al; *J of Clinical Endocrinology and Metabolism*; 2011



# Cardiovascular Health & TRT

- Low T is associated with increased BP, dyslipidemia, atherosclerosis, arrhythmia, thrombosis, endothelial dysfunction - J.B. Ruige et al. J. Clin. Endocrinol. Metabol., 98 (2013), pp. 4300–4310
- TRT increases risk of CV disease and MI by 30% in men receiving TRT - Basaria et al, *N Engl J Med* 2010.
- TRT does not increase risk of MI, stroke, CV events relative to placebo - Ali Z, American College of Cardiology 2015 Scientific Sessions, March 14, 2015, San Diego, CA



# Cardiovascular Health & TRT

- RCT - > 5000 men, placebo controlled
- men with established CVD or multiple cardiac risk factors were included
- TRT was noninferior to placebo with respect to the occurrence of major adverse cardiac events during a mean 22-month follow-up, and the overall incidence of adverse events was low.
  - Lincoff AM et. al, TRAVERSE Study Investigators. Cardiovascular Safety of Testosterone-Replacement Therapy. N Engl J Med. 2023 Jul 13;389(2):107-117.

# RATIOS WITH OTHER HORMONES



# Estradiol/Testosterone

- Testosterone is converted to estradiol by aromatase (enzyme)
- As men age the ratio of estradiol to testosterone increases
- Elevated estradiol/testosterone increases the risk of BPH and prostate cancer
- It is not only the decline in testosterone but also the increase in estradiol that cause the symptoms of Andropause

– Roberts et al. *Prostate* 2004

# Estrogen in Men

- Blood estradiol in 501 men with chronic heart failure
- Those in the lowest estradiol quintile (serum estradiol levels under 12.90 pg/mL) had a 317% increased death rate compared to the balanced group.
- The men in the *balanced* quintile—with the fewest deaths—had serum estradiol levels between 21.80 and 30.11 pg/mL (Ewa et al 2009).

Labcorp (7.6 – 42.6 pg/ml)

# PROSTATE FACTS



# Prostate Facts

A normal size is 20 grams; 3cm in length, 4cm wide, and 2 cm depth

Location is inferior to bladder, posterior to the pubic symphysis, anterior to the rectum, superior to the perineal membrane

Histologically divided in 3 zones – anterior, posterior and transitional

largest accessory sex gland in men

70% is glandular tissue, 30% is smooth muscle

- Berry SJ, et al. J Urol, 1984, 132:474-479

# Top 10 Diagnosed Diseases in Men Age $\geq 50$ Years

Rank	Disease	1-year prevalence (%) (n = 963,452 person-years)
1	Coronary Artery Disease/Hyperlipidemia	51.3
2	Hypertension	45.2
3	Diabetes Mellitus Type 2	17.5
4	Enlarged Prostate	13.5
5	Osteoarthritis	13.3
6	Arrhythmias	8.8
7	Cataract	8.6
8	Gastroesophageal reflux disease	8.4
9	Bursitis	8.0
10	Prostate Cancer	7.8





# The Big Three

- Benign Prostatic Hyperplasia
- Prostatitis
- Prostate Cancer



# BENIGN PROSTATIC HYPERPLASIA (BPH)

# Facts about BPH

Affects 50% of men over 50 yo, then up 80% by 80yo

BPH is not considered a clinical condition until LUTS is developed

Definition: Proliferation of cell (hyperplasia) in Stromal and epithelial cells of the transitional zone

Men with BPH are not an increased risk of prostate cancer.

Urinary obstruction can cause bladder dysfunction - detrusor over activity or under activity

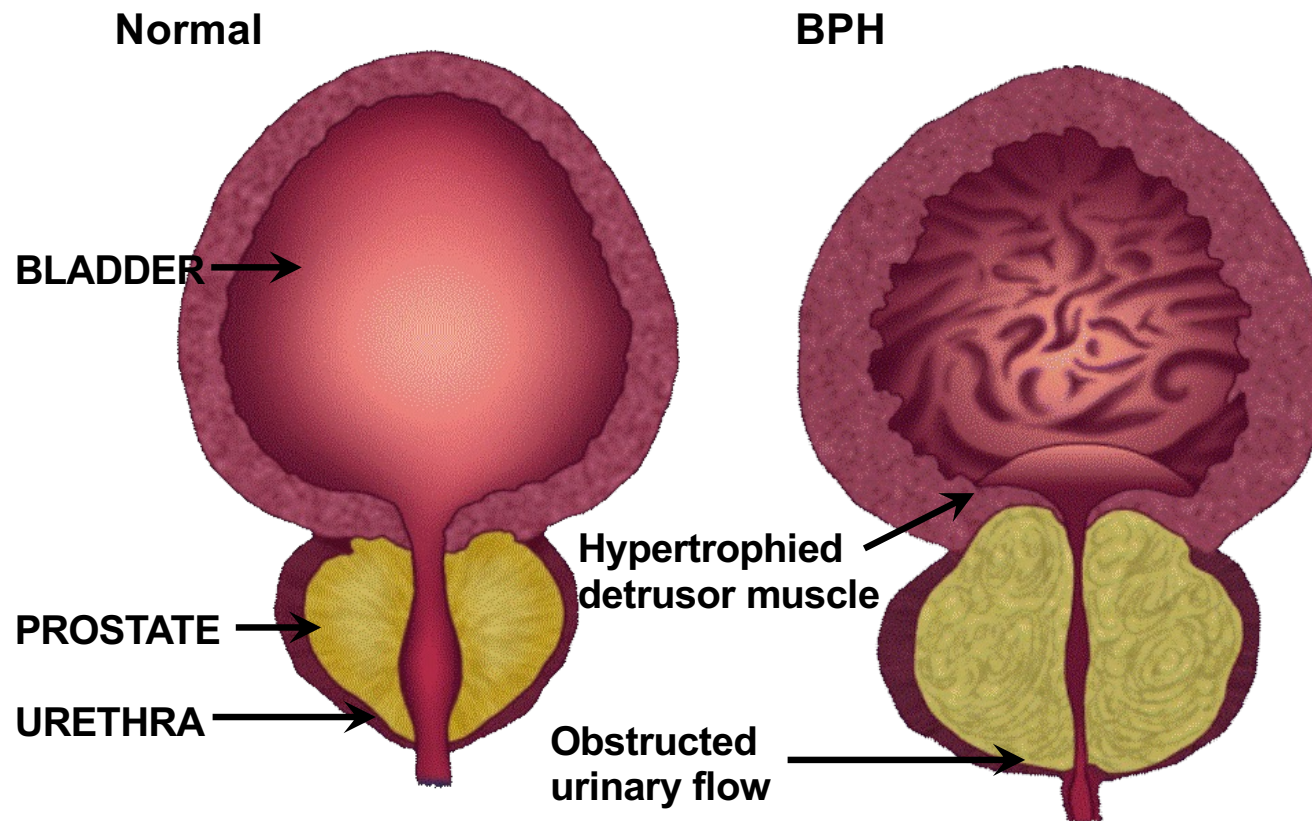
# Facts about BPH

IPSS is an excellent questionnaire to measure severity of LUTS

Men from SouthEast Asia have smaller prostates than men from Western countries.

BPH is ass w low Androgens and high Estrogen - De Nunzio et al . Eur.  
Urol.,2012

# Anatomy of BPH



# BPH SYMPTOMS

## Obstructive and Irritative

- Impairment of size/force of stream
- Hesitancy
- Intermittency
- Terminal dribbling
- Incomplete emptying
- Nocturia
- Frequency
- Urgency
- Dysuria



# Risk factors for BPH

Men w LUTS have higher HgA1C - Rohrmann et al. Int. j. Obes. 2005

↑Obesity = ↑prostate volume - Parsons et al. J of Uro. 2013

↑Waist to Hip ratio = ↑prostate volume - Kristal et al. J. of Uro. 2007

↑CRP assoc w ↑BPH - Rohrmann et al. Prostate 2005

Bacterial and viral strains found in BPH biopsy  
specimens - Chughtai et al. Curr. Urol. 2011



# Risk factors for BPH

- Age, > 50 yo, increases about 0.6ml a year,  
Increase volume not necessarily associated with LUTS but it does inc the risk of LUTS
- Metabolic syndrome ( HTN, Hyperlipidemia, glucose intolerance, central obesity, and insulin resistance) - 3 or more components assoc w LUTS- Gacci et al. BJU , 2015
- Prostate growth is 47% in men with T2D, 17% in men with HTN and 36% in obese men, 31% in men with low HDL and 28% in men w high fasting glucose - Hammarsten et al., Prostate Cancer Prostate Dis. 1998

# Hormones and BPH / LUTS

- DihydroTestosterone (DHT) is significantly increased in BPH patients. - [Stanzcyck et al 2003](#)
- Serum androgen levels decrease during aging, the levels of  $17\beta$ -estradiol ( $E_2$ ) remain constant increasing the ratio  $E_2/T$ . This altered relationship is clearly associated with the development of the disease BPH/LUTS.
  - Roberts et al., Prostate, 2004

# Hormones and BPH / LUTS

Two types of Estrogen receptors, ER- $\alpha$  and ER- $\beta$ , activation of ER- $\alpha$  in the prostate is associated with

E2 levels in the stromal cells of BPH patients increase during aging, and hyperplasia and inflammation. - [Nicholson and Ricke, 2011](#)

this seems to be associated with a high expression of aromatase, the enzyme that converts androgens into estrogens.

- [Ho et al., J Endocrinol. 2008](#)

# IPSS (International Prostate Symptom Score)

- Objective measurement to grade symptoms
- Useful to quantify severity, help to choose appropriate treatment & monitoring response
- Mild = 0-7, Moderate = 8-19, Severe 20-35

# PROSTATE CANCER



# The Big Three

- Benign Prostatic Hyperplasia
- Prostatitis
- Prostate Cancer





# Prostate Cancer Screening

Continues to note that damages may occur during this screening period.

2018 - reported that there is adequate evidence from randomized clinical trials documenting that PSA-based screening in men aged 55–69 years might prevent approximately 1.3 deaths from PCa over approximately 13 years per 1,000 men screened.





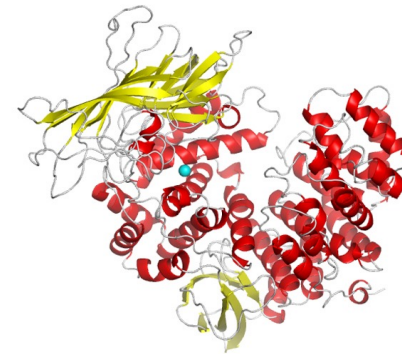
# PSA

- Cancer
- BPH
- Prostatitis
- Infarct, retention



# PSA Facts

- Produced by the glandular epithelium of the prostate
- Trace amounts in salivary, pancreatic and breast tissue
- Found in semen, urine and blood
- Serine protease that liquefies semen to improve sperm mobility
- Found in 3 forms in serum:
  - Bound to  $\alpha$ -1-Antichymotrypsin
  - Bound to  $\alpha$ -2-Macroglobulin
  - Free PSA



- Balk SP et al. Biology of prostate-specific antigen. J Clin Oncol. 2003 Jan 15;21(2):383-91.

# PSA: Sensitivity/Specificity

- Sensitivity: 67.5-80%

(20-30% tumors will be missed if PSA<4.0 ng/ml used)

## Ways to Improve Sensitivity:

- a.) age-adjusted PSA
- b.) PSA velocity

- Specificity: 60-70% (if PSA>4.0 ng/ml)

(only ¼ prostate biopsies reveal CaP)

## Ways to Improve Specificity:

- a.) Age adjustment b.) Free-to-total PSA c.) PSA density

# PSA is NOT Perfect

- Poor sensitivity (35–70%), specificity (60–90%) for prostate cancer
- Sensitivity of biopsy in screened is 60-80% at best
- The traditional PSA cut-off of 4.0 is no longer an absolute indication for biopsy
- Other factors that affect PSA:
  - Infection/Inflammation/Instrumentation
  - Urinary retention
  - Ejaculation/Vigorous massage
  - Advanced age/Benign enlargement

# Improving Specificity of PSA

- Repeat PSA before reacting
- PSA Density
  - $\geq 0.15 \text{ ng/mL/cm}^3$  associated with CaP
- PSA velocity
  - A rate of change  $> 0.75 \text{ ng/mL/yr}$  ( $4 < \text{PSA} < 10$ )
  - A rate of change  $> 0.35 \text{ ng/mL/yr}$  ( $\text{PSA} < 2.5$ )
  - Rates  $> 2 \text{ ng/mL/year}$  have been associated with a quicker time to death from recurrent disease
- Percent free PSA
  - $< 10\%$  more likely prostate cancer
  - $> 25\%$  more likely BPH
- Age-Specific Thresholds

- Merriel, S.W.D. et. Al. Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients. *BMC Med* **20**, 54 (2022).



# Prostate Cancer

- The most common type of cancer in men and second most frequent cause of cancer-related death in men
- One in 6 men will develop prostate cancer (PC) during his lifetime.
- An estimated 217,730 men diagnosed and, 32,050 deaths in the United States in 2010

- Siegel RL, Miller KD, Fuchs HE, Jemal A (2021) Cancer statistics, 2021. CA Cancer J Clin 71:7–33



# Prostate Cancer Recurrence

- After prostatectomy or radiation therapy, 1/3 of PC patients will develop recurrent disease, marked by a rising PSA on serial tests. Men with recurrent PC are at greater increased risk of metastases and premature death. Although hormonal therapy may extend survival in some cases, there is no curative treatment.

- Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, and Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 281:1591-7. 1999.



# Prostate Cancer Screening

## USPSTF

2012 - issued a grade "D" recommendation against prostate-specific antigen (PSA) screening for men of all ages

2013 - new recommendation is now grade "C," suggesting that there is a benefit to the use of PSA but that the test should be used selectively based on the professional judgment and patient preferences

# History of Testosterone Association with Prostate Cancer

- Dr. Charles B. Huggins, urologist at the University of Chicago, circa 1940 , observed that the dogs' prostates shrunk after castration and cancerous-appearing areas also demonstrated prostate shrinkage.
- As an experiment, Huggins et al. removed the testicles or applied estrogen to a group of men who had metastatic prostate cancer to their bones. (PSA test did not exist until late 1980's)
- Alkaline phosphatase dropped substantially within days of lowering testosterone or E treatment in 8 men with PCr metz – and injecting testosterone to 3 men with prostate cancer caused acid phosphatase to rise.
- Conclusions: testosterone levels caused prostate cancer to shrink, and that raising testosterone levels caused it to grow. - Huggins and Hodges; Cancer Res, 1 (1941)

# Low T = Increase risk of PrCa

High incidence rate of aggressive CaP ( $p = 0.028$ ) among men with low T defined as  $<7.6\text{nmol/l}$  ( $220\text{ng/d}$ ).

- Lane et al. Urology 2008

Beyond analyzing Gleason grade, high-risk disease including was associated with low T at prostatectomy.

- Xylinas et al. BJU Int 2011

673 men undergoing prostatectomy, had their morning T with surgical pathology outcomes and observed a significant risk of advanced disease that included seminal vesicle invasion in severely hypogonadal men, defined as testosterone  $<3.4\text{nmol/l}$  ( $100\text{ng/dl}$ ).



# The Saturation Model of Testosterone

The saturation model accounts for the key observation that prostate tissue is sensitive to changes in serum testosterone at low concentrations, but becomes indifferent to these changes at higher concentrations. - Morgentaler & Traish; Eur Urol 2009

Exposure to increasing concentrations of androgen causes prostate tissue growth, but this growth rate plateaus when the concentration reaches a limit. - Morgentaler, Urol Clin North Am 2007

There exists a threshold (saturation point) beyond which there is no further ability to induce androgen-driven changes in prostate tissue growth. -Khera et al. Eur Urol 2014

# Testosterone Therapy after PrCa

149,354 men including 1181 men who received TRT after a diagnosis with PrCa. Overall, TRT was not associated with overall or cancer-specific mortality- Kaplan et al. J Sex Med 2011

103 men treated with TRT after prostatectomy. There was an overall increase in serum PSA, but no evidence of increased cancer recurrence over 36 months - Pastuszak et al. J Urol 2013

Study evaluated prostate cancer progression and biochemical recurrence in :radiation therapy, radical prostatectomy, or cryotherapy, or AS regimen - No significant progression  
- Ory et al. J. Urol 2016

# Where are we now

18 experts from multiple disciplines in 2015 convention

There was unanimous agreement on several key points:

- T deficiency was a serious global problem; the evidence failed to support increased risk of PCa or CV risk; total T was a useful but unreliable test to determine androgen status; and the possibility that T therapy is cardioprotective should be investigated, particularly in men with metabolic conditions such as diabetes and obesity.

- Siltari A et al., Testosterone replacement therapy is not associated with increased prostate cancer incidence, prostate cancer-specific, or cardiovascular disease-specific mortality in Finnish men. *Acta Oncol.* 2023 Dec;62(12):1898-1904





THANK YOU







**Friday 1:30pm – 2:30pm**

## **The Inseparable Link Between Testosterone and the Prostate**

Please scan this QR code on you mobile  
or tablet device to access the session feedback survey



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