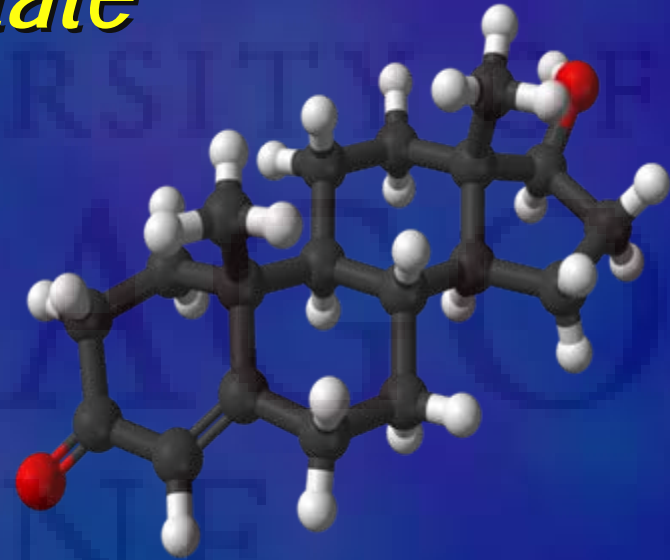


# *Male Hypogonadism and testosterone therapy in patient with prostate Cancer*

***Milad Abusag MD***

First year Fellow

10/3/2013



# *HPI*

- 65 year old male with PMH of Lt side cryptorchidism (underwent Lt side Orchiectomy in early life), GERD, OSA (not on CPAP), Obesity and Prostate cancer.
- Prostate cancer was Dx two years ago (**organ confined >>> no extra prostatic extension, no LN involvement**) and underwent total prostatectomy.
- He didn't receive any radiation therapy or aromatase inhibitor.
- ❖ After the surgery >>>
- ✓ Erectile dysfunction

## HPI continue

- ❖ No morning erection but still have sexual desire.
- ❖ No headache, no blurry vision, VF defect or double vision. no N/V, no weakness
- ❖ Viagra and Bimix penile injection (papaverine plus phentolamine ) were tried and without benefit.
- ❖ Testosterone level on 3/2013 was 250 and repeated few weeks prior to this visit >> 196 (total T) and 7.6 (free T)

- **Past Medical History:** GERD, OSA, Obesity, Lt side Cryptorchidism (underwent Orchiectomy in early life **simple w prosthesis**) and Prostate cancer
- **Past Surgical History:** prostatectomy and Lt side orchiectomy
- **Social History:** quit smoking about 15 years ago , no alcohol or use illicit drugs. Has 4 children

### **Current Medications:**

- a. PRN Colace
- b. Tramadol PRN for chronic back pain.
- c. penile injection (with Bimix)

# ROS

- **Constitutional:** No fever, no chills, **reported mild fatigue.**
- **HENT:** No blurred vision, No sore throat, no VF problem
- **Neck:** No neck swelling, difficulty swallowing,
- **Cardio/pulm:** No CP, SOB or palpitation, no orthopnea or PND. No cough or wheezing.
- **GI:** No N/V/D, no constipation, no abdominal pain, no melena or hematochezia
- **GU: + ve ED,** but Denied any dysuria, hematuria, flank pain, or discharge. Sexual desire preserved
- **Skin:** No h/o rash, no hair loss,
- **MSK:** No joint pain/swelling, muscle pain, reported mild back pain.
- **Neuro:** no numbness, no tingling, no weakness, CN intact
- **Psych:** No depression,

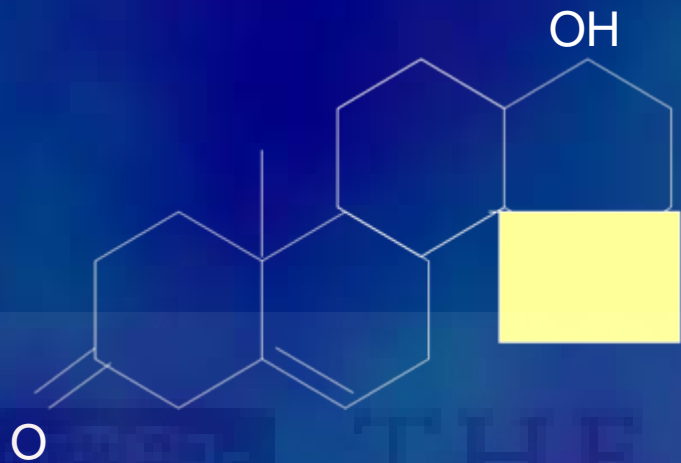
# On Examination

- **Vitals:** BP 127/78 | Pulse 63 | Ht 175.3 cm (5' 9") | Wt 99.383 kg (219 lb 1.6 oz) | BMI 32.36 kg/m<sup>2</sup>
- **General:** awake alert, anxious, obese man
- **HEENT:** normocephalic non traumatic
- **Neck:** supple, no LN enlargement, no thyromegaly, no thyroid tenderness, no JVD.
- **CVS/Pulm:** clear equal air entry no added sounds, S1 + S2, no murmur, no heave.
- **Abd:** soft lax no tenderness, no organomegaly, audible bowel sounds.
- **GU:** Lt side testicular prosthesis, Rt testes soft (**I didn't measure size**), no mass, non tender, normal pubic hair.
- **Skin:** warm, no rash, no darkening
- **Neuro:** CN intact, sensation normal , muscle power normal
- **Psych:** normal mood, and affect

## **Lab results**

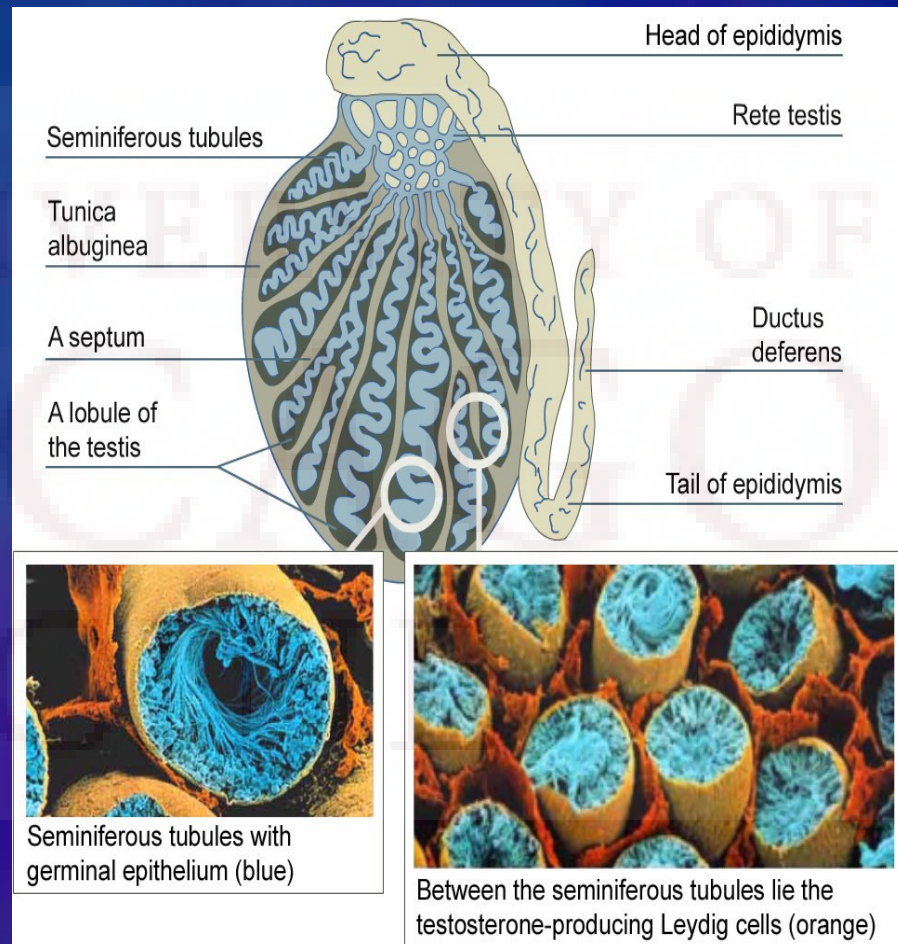
<b>Hb/Hct</b>	<b>13/7/40.7</b>
<b>BG</b>	<b>92</b>
<b>BUN/Cr</b>	<b>21/0.9</b>
<b>PSA</b>	<b>Less than 0.05</b>
<b>Total T</b>	<b>196 ng/dl</b>
<b>Free T</b>	<b>7.6 pg/ml</b>
<b>PRL</b>	<b>6.99</b>
<b>LH</b>	<b>8 (reference 2 – 6.8)</b>
<b>FSH</b>	<b>10.4 (reference 1.2 – 8)</b>
<b>FT4</b>	<b>1.24</b>
<b>TSH</b>	<b>3.43</b>



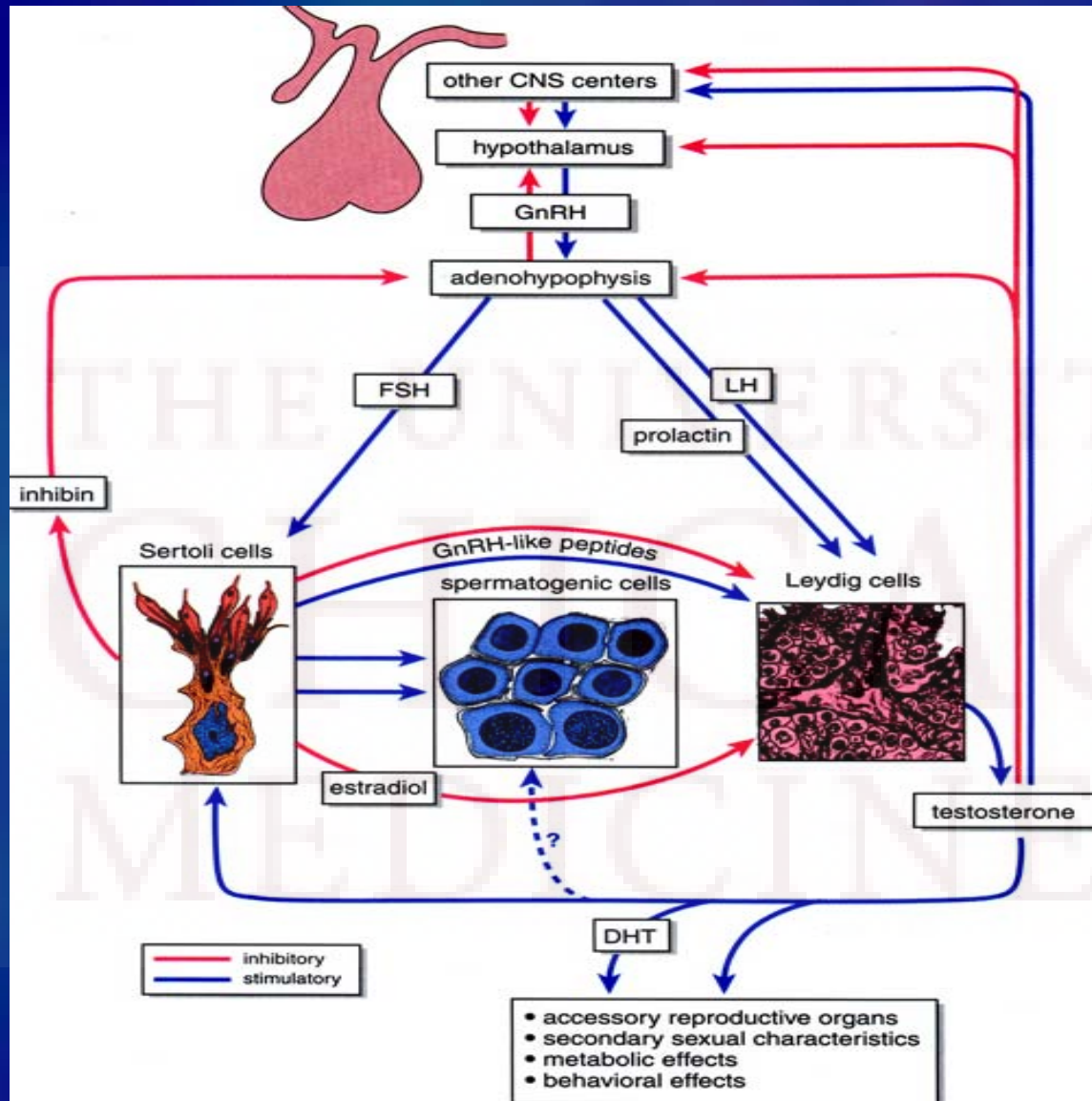


# Testosterone

- Testosterone is the most important hormone produced by the testis
- Between 5 and 7mg of testosterone are produced by the Leydig cells daily in adult men







Testosterone

5  $\alpha$  Reductase.

Aromatase

Dihydrotestosterone

Estradiol

THE UNIVERSITY OF CHICAGO  
MEDICINE

# Definition of male hypogonadism

- ✓ **Clinical syndrome resulting from failure of the testes to produce adequate amounts of androgen and/or sperm.**
- ✓ **Need clinical symptoms coupled with low testosterone level**

Bhasin et al. The endocrine society's clinical practice Guideline. JCEM 2010

- ✓ **Prevalence in men age 60-69years, cross sectional and longitudinal studies find**
  - 20% have low total Testosterone
  - 35% have low Free Testosterone

# Clinical features of Testosterone deficiency

## Emotional

- ❖ Depression
- ❖ Reduce sense of well-being
- ❖ Poor concentration



## Reproductive system

- ✓ Subfertility
- ✓ Subnormal Genital mass
- ✓ Loss of pubic hair
- ✓ Sexual dysfunction.
- ✓ Breast discomfort, Gynecomastia

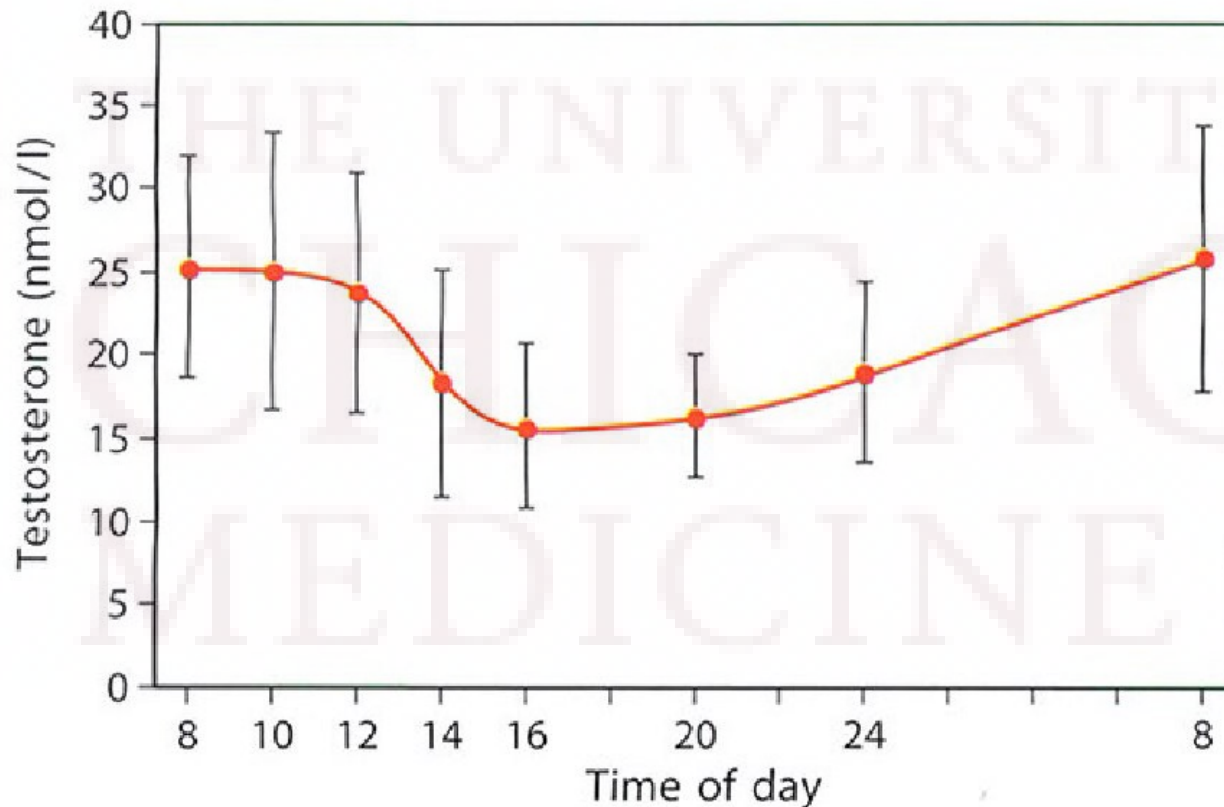
## General body effect

- ❖ Decrease muscle mass
- ❖ Decrease bone mass
- ❖ Abdominal Obesity
- ❖ Loss of Libido
- ❖ Hot Flashes
- ❖ Decrease Body hair

# Challenging in measurement of serum testosterone

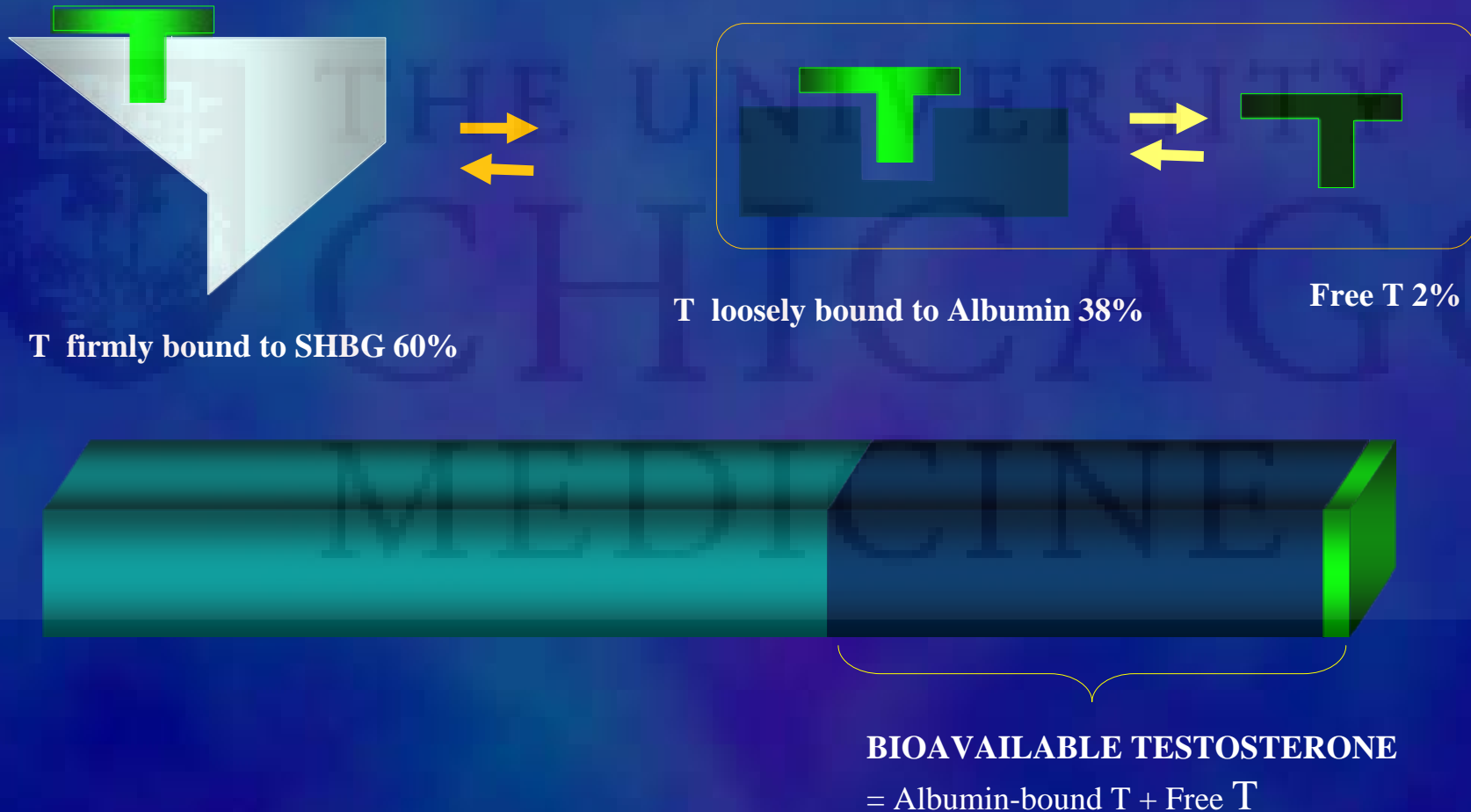
- **Testosterone vary significantly due to**
  - I. Circadian Rhythm**
  - II. Assay variation**
  - III. Illness**
  - IV. Change in Binding Ptn (SHBG)**

# Circadian rhythm of testosterone



Nieschlag E & Behre HM. Andrology, Male reproductive health and dysfunction (2nd Edition). Springer, Heidelberg; 2002

# *Binding of testosterone*





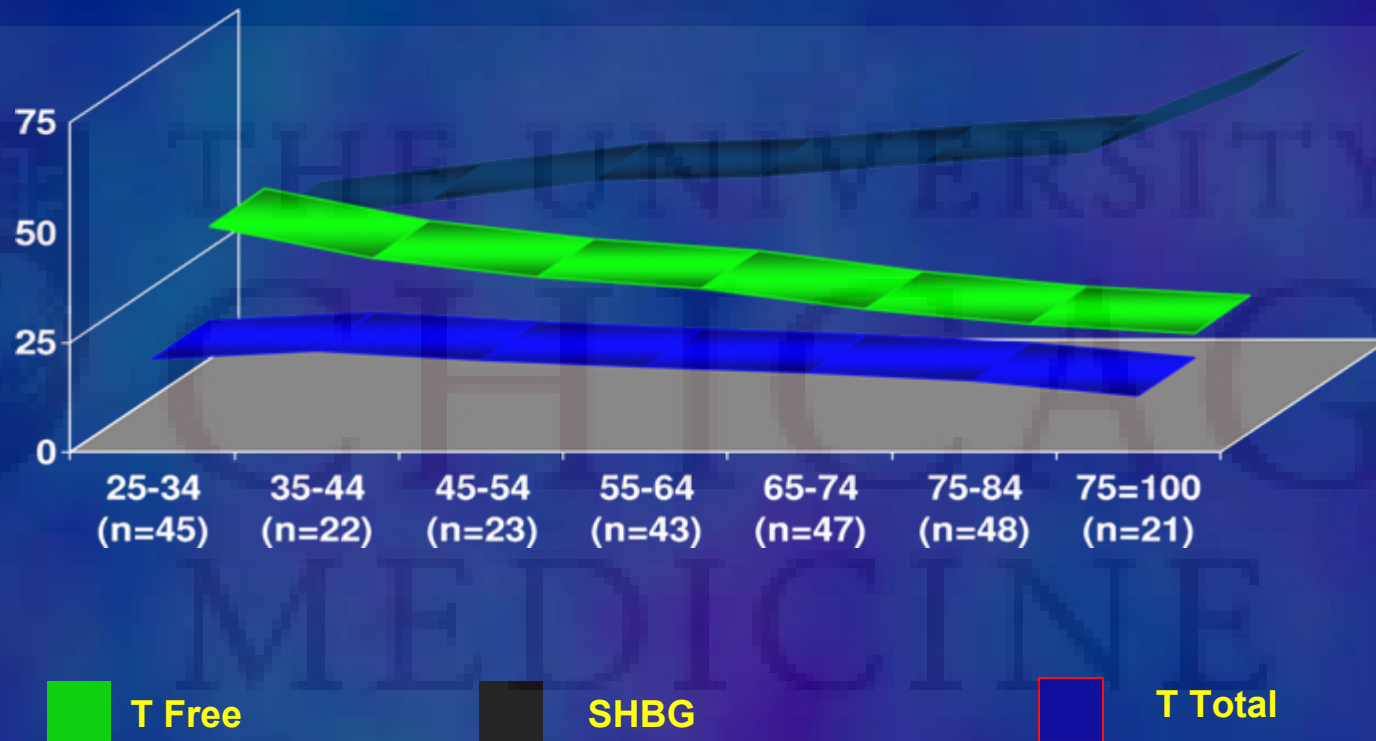
# Decrease SHBG

- Moderate to severe obesity
- Nephrotic syndrome
- DM
- Use of glucocorticoid
- Acromegaly
- Hypothyroidism

# Increase SHBG

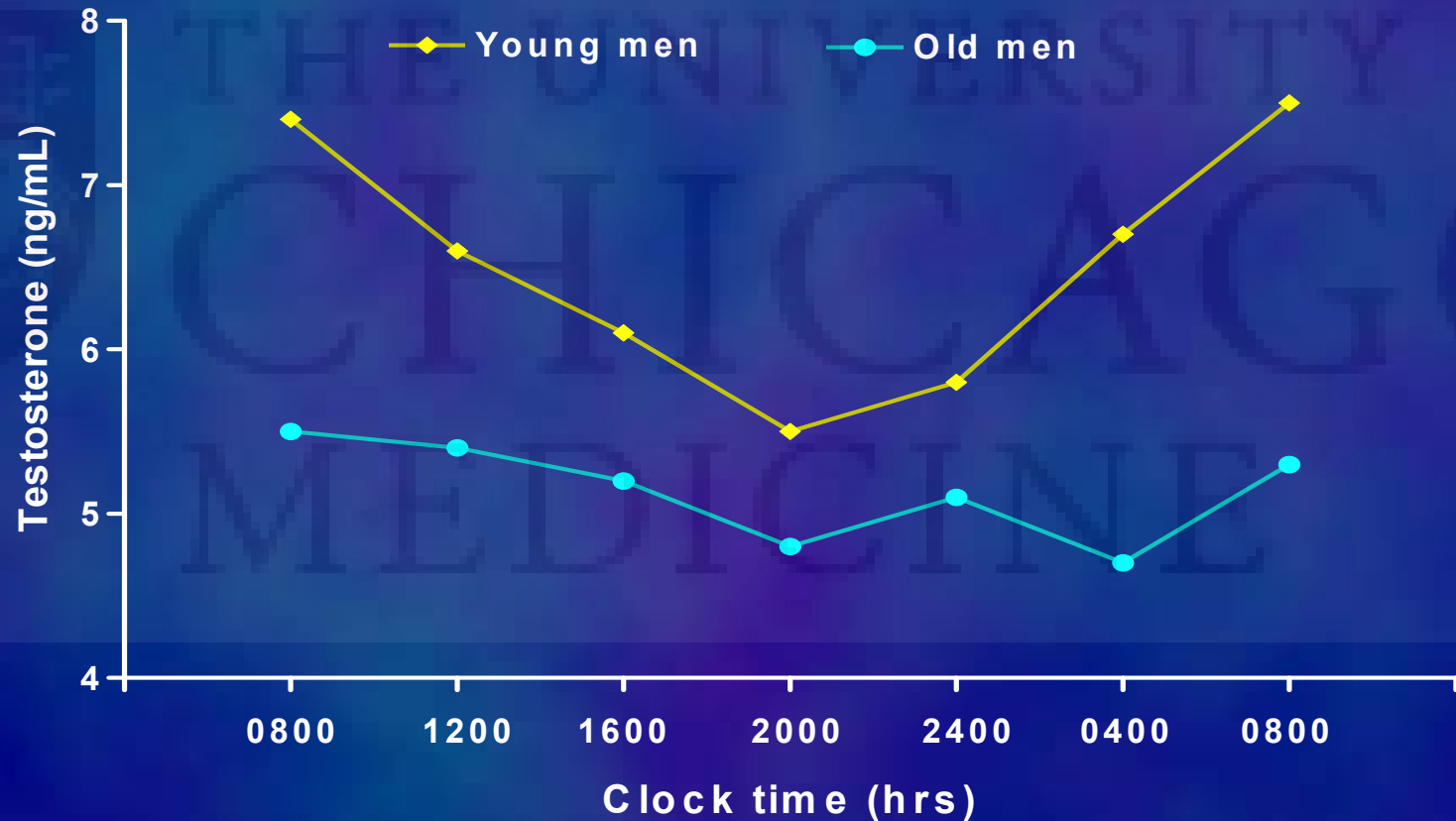
- Aging
- Hepatic cirrhosis
- Use of estrogen
- Hyperthyroidism
- HIV infection.
- Use of anticonvulsants.

# Advanced age and Testosterone level



Nieschlag E et al. *Eur Urology* 2005;48:1-4. Vermeulen A et al. *J Clin Endocrinol Metab* 1996;81:1821-1826

# Testosterone Secretion: Comparison of Young and Elderly Men



# *Approach to Low Serum Testosterone*

Verify low testosterone near 8 am <sup>1,2</sup>

Check LH/FSH<sup>3</sup>

Low or normal range LH/FSH

Elevated LH/FSH

Secondary Hypogonadism

Primary Hypogonadism

Evaluate for Gonadotroph  
Suppression or Deficiency  
(Hypothalamic/Pituitary Process)

Evaluate for Testicular Disorder

# My Clinical Qs

- Safety of testosterone therapy in pt with h/o prostate Cancer
- Prevalence of Hypogonadism in pt with ED.
- Improvement of Hypogonadism by treatment of OSA.

# Safety of testosterone therapy in pt with h/o prostate Cancer

## Effects of testosterone treatments on prostate volume and serum prostate specific antigen levels in male Hypogonadism.

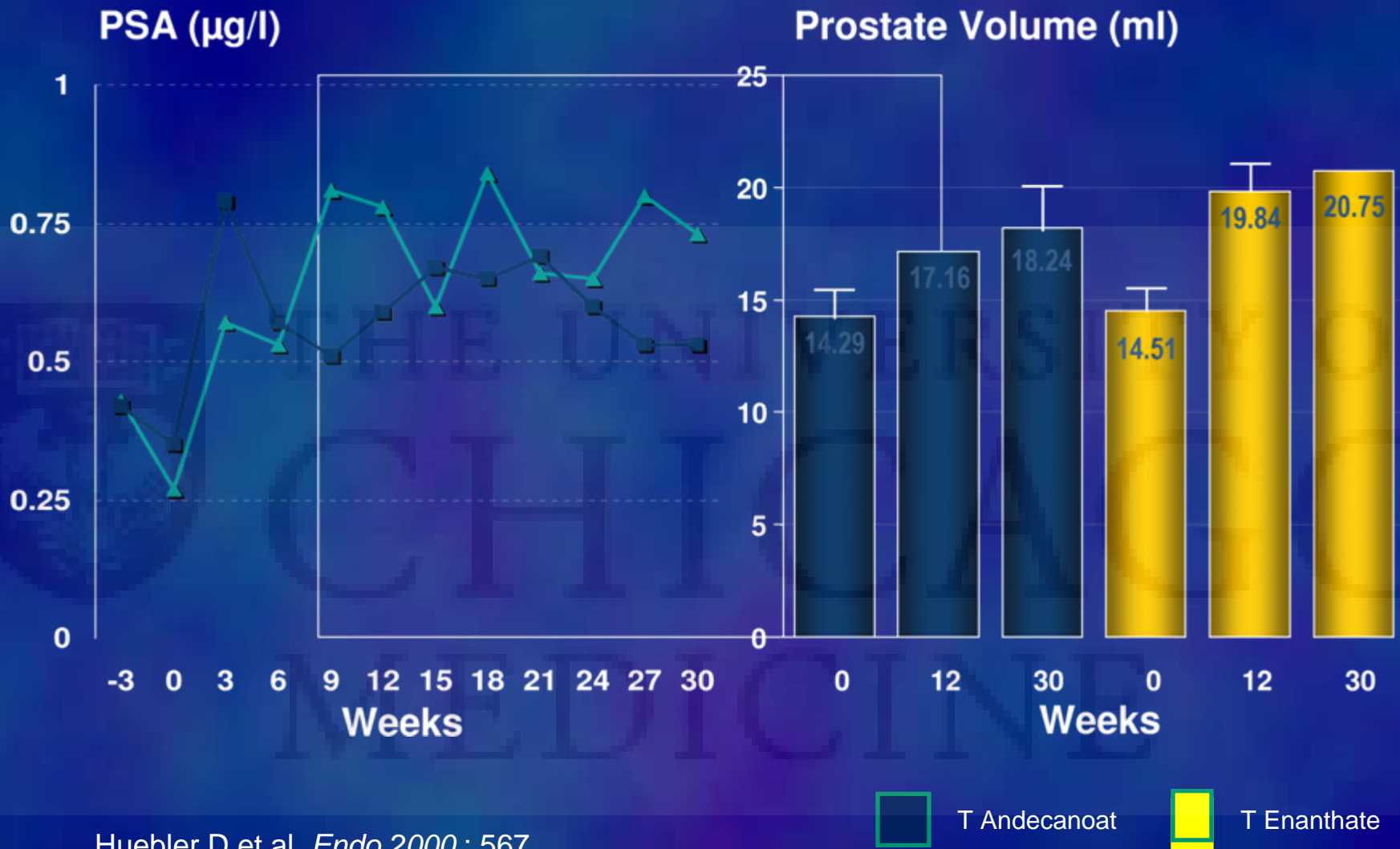
Ozata M, Bulur M, Beyhan Z, Sengül A, Saglam M, Turan M, Corakci A, Ali Gundogan M.

### Source

Department of Endocrinology, Gülhane School of Medicine, Etlik-Ankara, Turkey.

Endocr J. 1997 Oct;44(5):719-24.

- ✓ Determined serum PSA, prostate size and testicular size levels before and 3 months after treatment in 13 patients with idiopathic hypogonadotropic hypogonadism (IHH)
- ✓ PSA levels, Right and left testicular volumes and the prostate volumes were increased after 3 months of testosterone treatment.
- ✓ In this group PSA levels were correlated with prostate volume before treatment but not after therapy.



Huebler D et al. *Endo* 2000 : 567.

**Guidelines:** 40 years of age or older with baseline PSA greater than 0.6 ng/ml, perform digital rectal examination + check PSA level before start TT, at 3-6 months after and then according to prostate cancer screening guidelines.



## Testosterone replacement therapy after primary treatment for prostate cancer.

Agarwal PK, Oefelein MG.

Department of Urology, Cleveland clinic, J Urol. 2005 Feb;173(2):533-6

- ✓ Ten hypogonadal patients previously treated with radical prostatectomy for organ confined prostate cancer. They presented with low serum total testosterone (TT) and symptoms of hypogonadism after radical prostatectomy.
- ✓ Patients had baseline serum determinations of prostate specific antigen (PSA) and TT, and were started on testosterone supplementation.
- ✓ They were assessed periodically for changes in **PSA and TT, and for symptomatic improvement** using the hormone domain of the Extended Prostate Inventory Composite Health Related Quality of Life questionnaire.

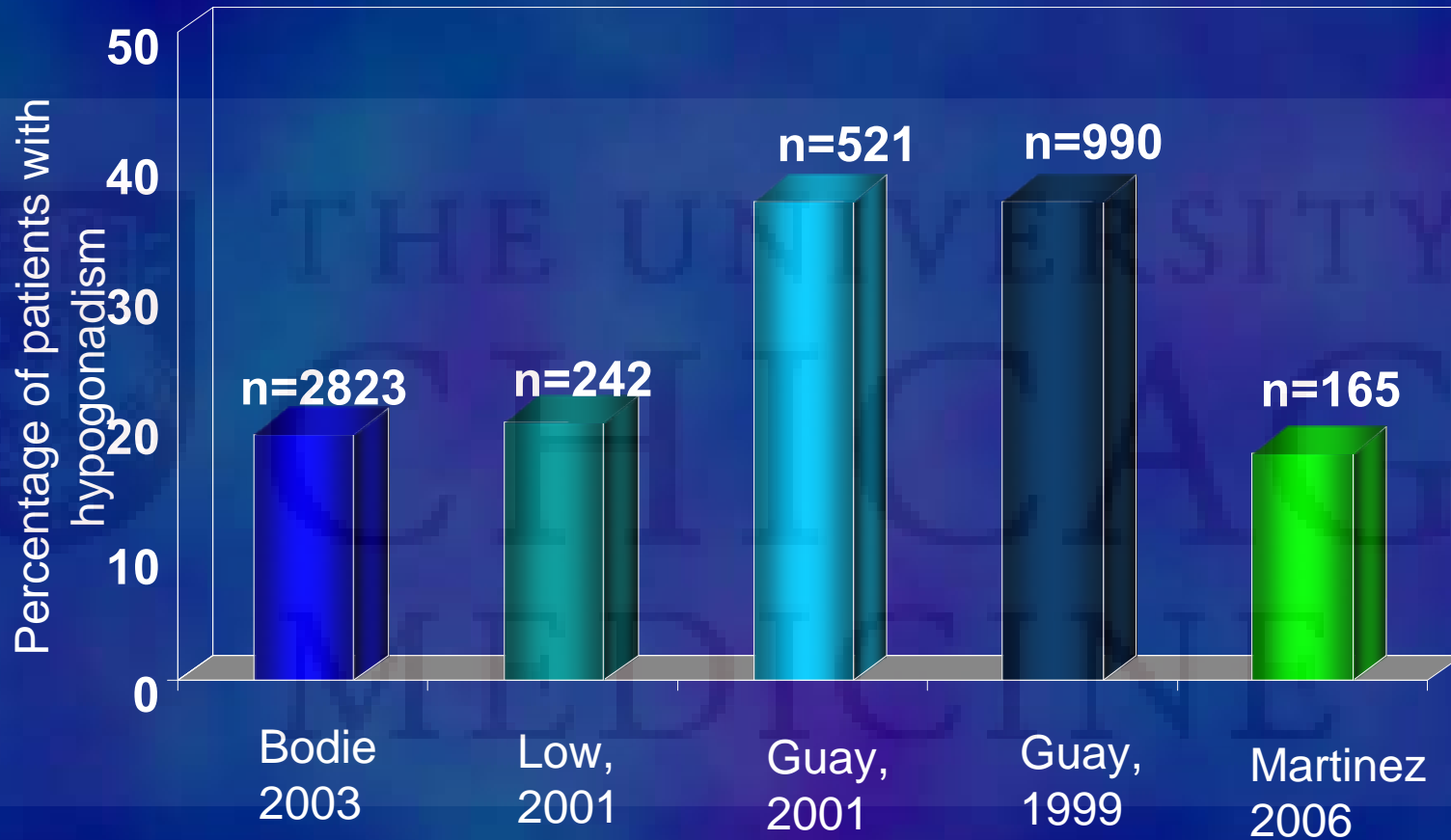
## Result

- ✓ At a median followup of 19 months **no patient** had detectable (greater than 0.1 ng/ml) PSA.
- ✓ TT increased significantly after starting TRT from a mean +/- SD of 197 +/- 67 to 591 +/- 180 ng/dl ( $p = 0.0002$ ).

## Conclusion

- ✓ At a **median of 19 months of TRT** hypogonadal patients with a history of prostate cancer had **no PSA recurrence and had statistically significant improvements in TT** and hypogonadal symptoms.
- ✓ In highly select patients after prostatectomy, TRT can be administered carefully and with benefit to hypogonadal patients with prostate cancer.

# Prevalence of Hypogonadism in ED



Bodie J et al. *J Urol* 2003; 169:2262-2264

Low WY et al. *J Sex Med* 2004;1, Suppl. 1:111.

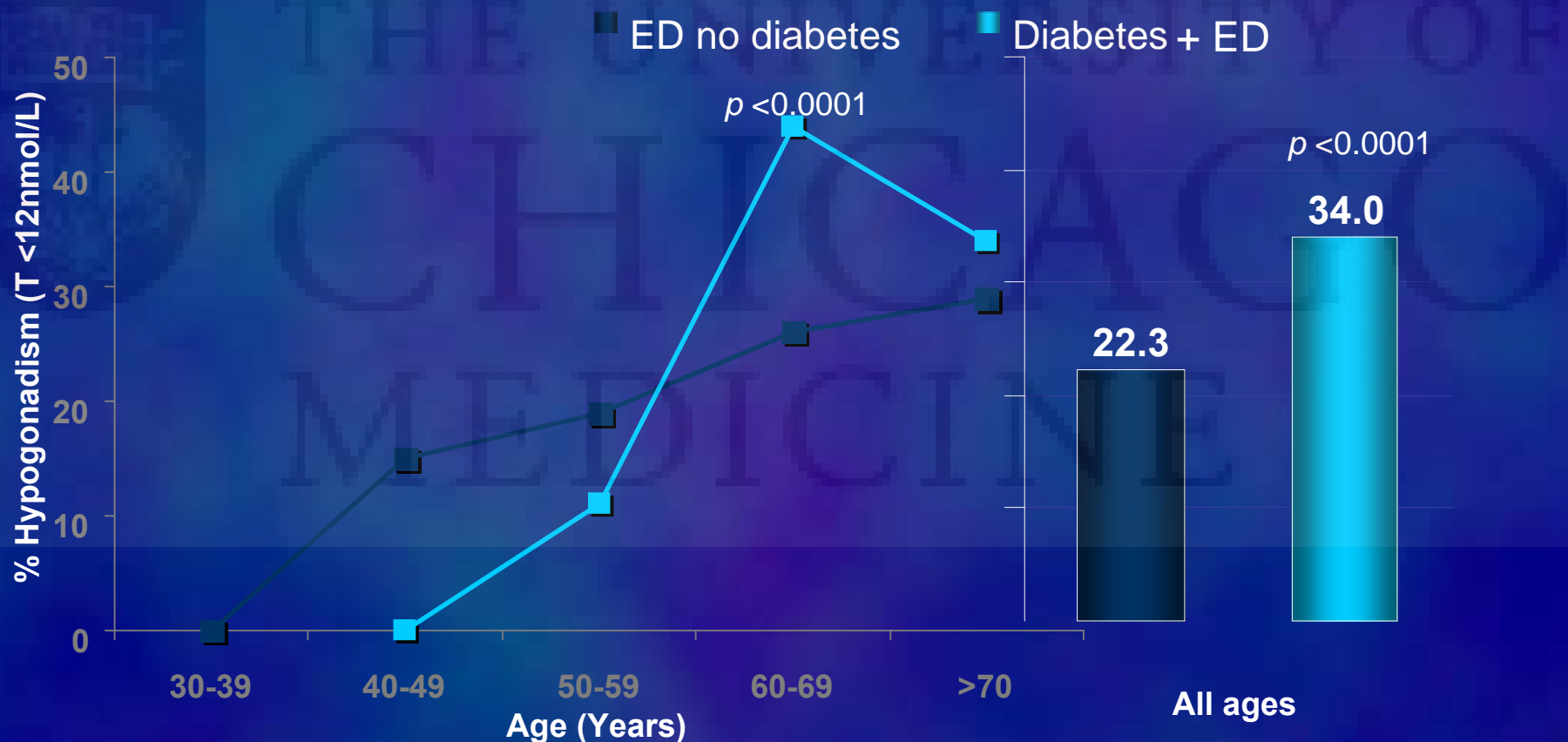
Guay AT et al. *J Androl* 2001;22(5):793-797.

Guay AT et al. *Endocr Pract* 1999;5(6): 314-321

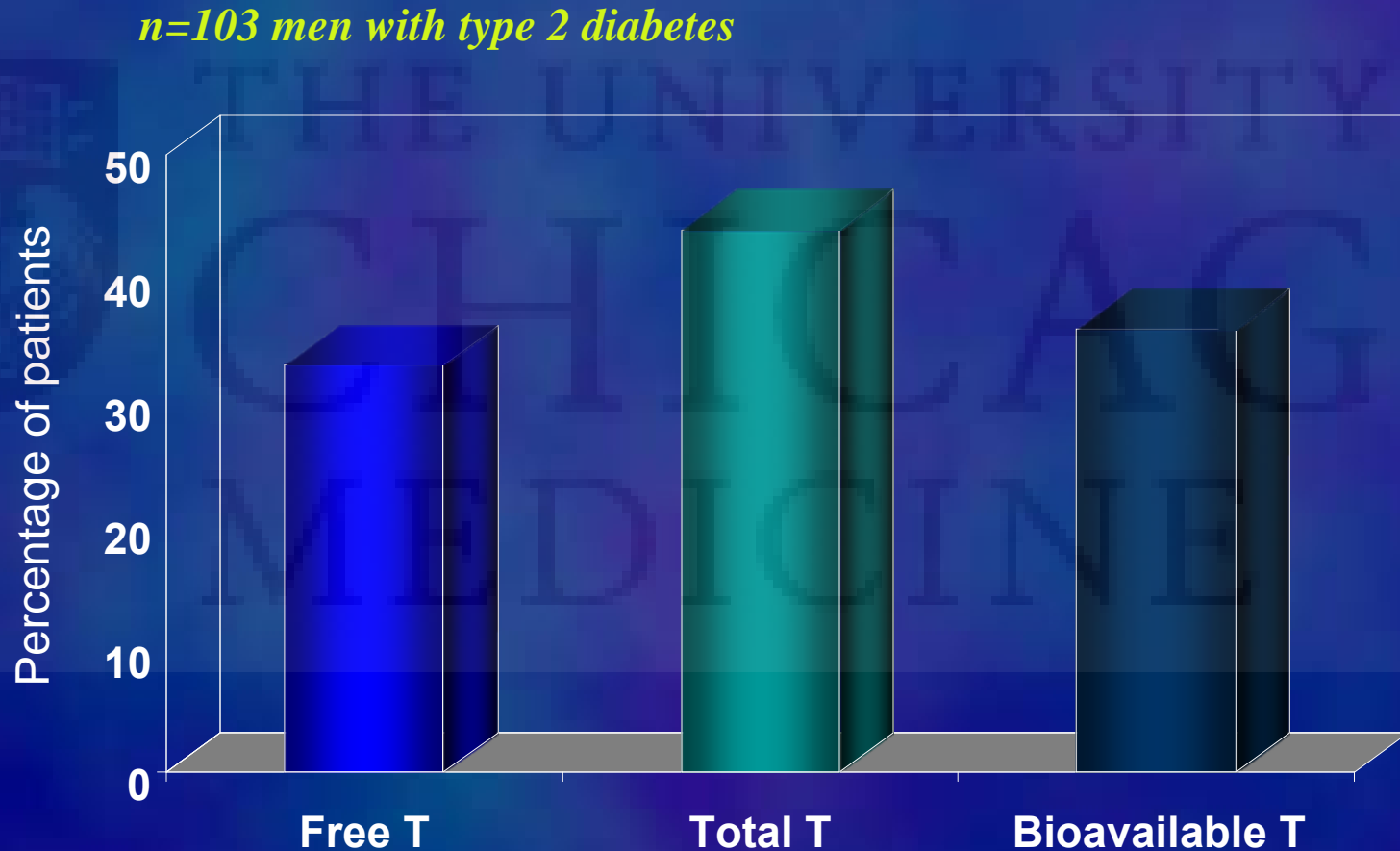
Martinez-Jabaloyas JM et al. *BJU Int* 2006;97:1278-1283

# Hypogonadism in diabetic vs non diabetic men with ED

*n=1027 men with ED with and without type 2 diabetes mellitus*



# Prevalence of Hypogonadism in patients with DM



# Improvement of Hypogonadism by treatment of OSA

**Sexual functions of men with obstructive sleep apnoea syndrome and hypogonadism may improve upon testosterone administration: a pilot study.**

Zhuravlev VN, Frank MA, Gomzhin AI. 2009 Jun;41(3):193-5. doi: 10.1111/j.1439-0272.2008.00914.x.

Ural State Medical Academy, Yekaterinburg, Russian Federation.

72 patients with obstructive sleep apnea syndrome

32 had erectile dysfunction (ED)

hypogonadism in 24 cases

8 have normal Testosterone

Treated with CPAP and FDE inhibitor (6 improved)

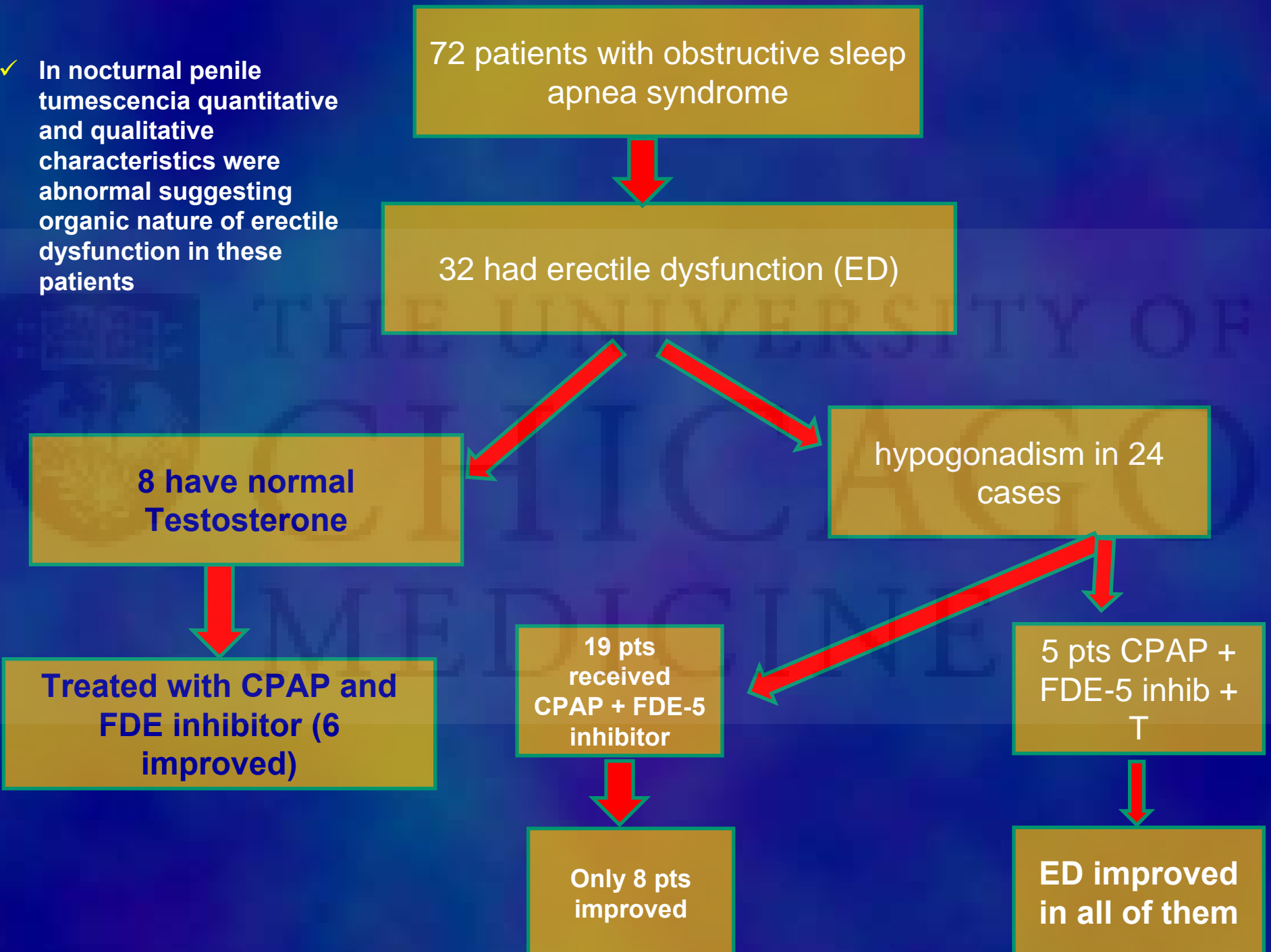
19 pts received CPAP + FDE-5 inhibitor

Only 8 pts improved

5 pts CPAP + FDE-5 inhib + T

ED improved in all of them

✓ In nocturnal penile tumescencia quantitative and qualitative characteristics were abnormal suggesting organic nature of erectile dysfunction in these patients



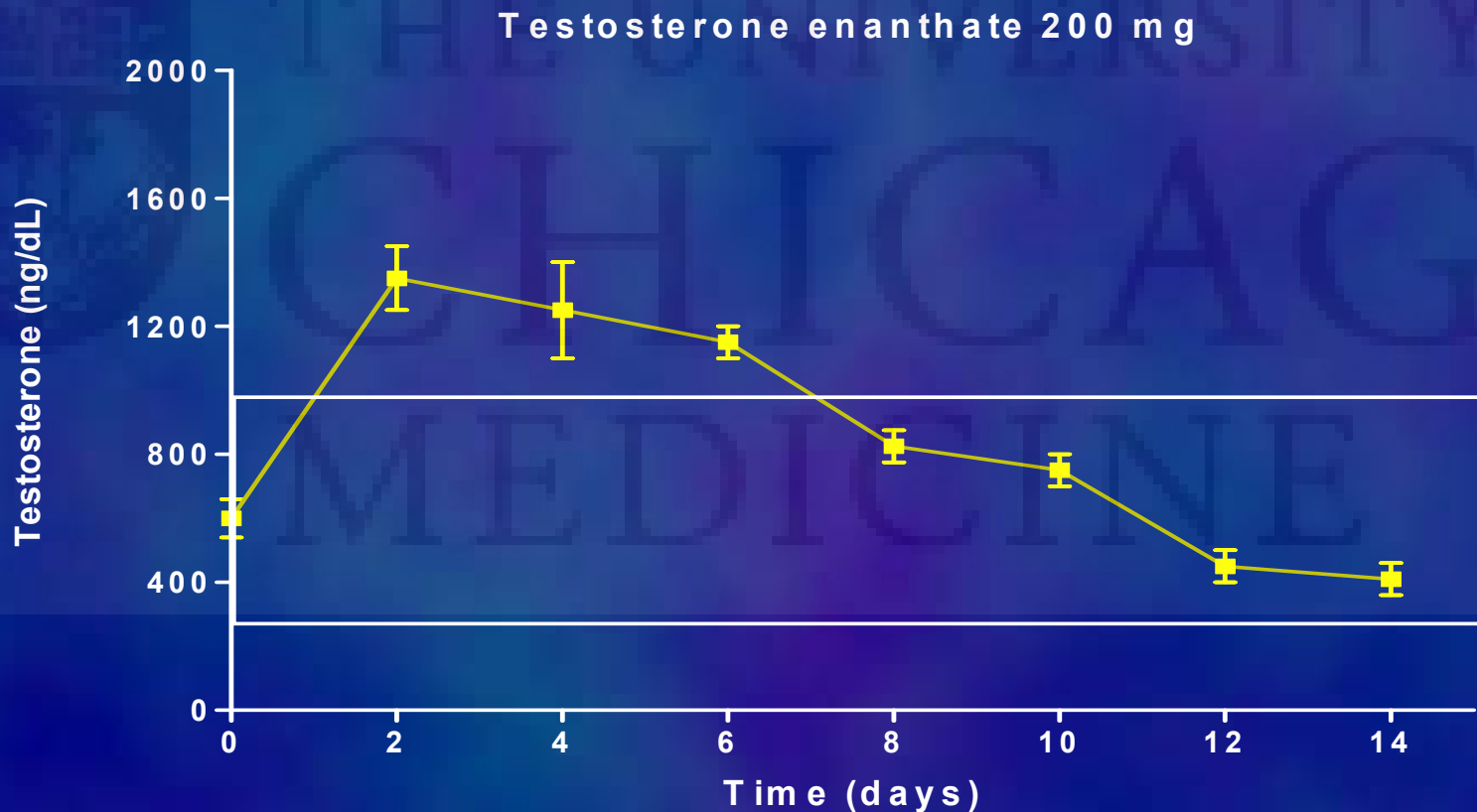


# Available Testosterone in USA

<b>IM injection</b>	<b>Enanthate</b> 100 mg q/wk, 200 mg q/2wks, 300 mg q/3wks <b>Undecanoate:</b> Q 2-3 months inj
<b>Transdermal</b>	<b>Adnroderm:</b> 5mg/day (2.5 mg BID) <b>Testoderm:</b> scrotal patch (1 patch/day)
<b>Gel</b>	5-10 gm/day
<b>Buccal tablet</b>	30 mg buccal mucosa BID
<b>SQ pellets</b>	<b>Testopel:</b> 57 mg/pellet; 6-12 pellets (450-900 mg) Q 306 months.

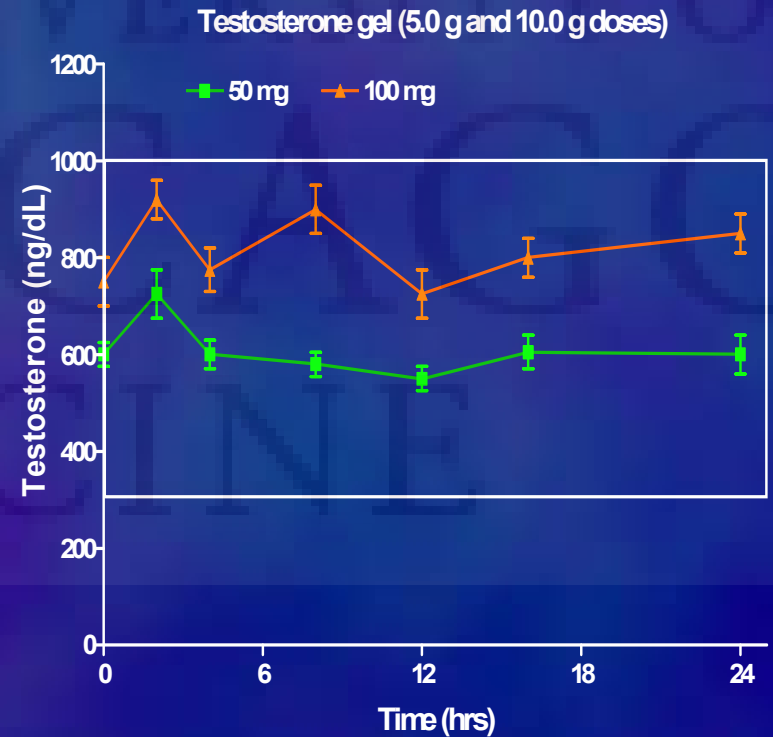
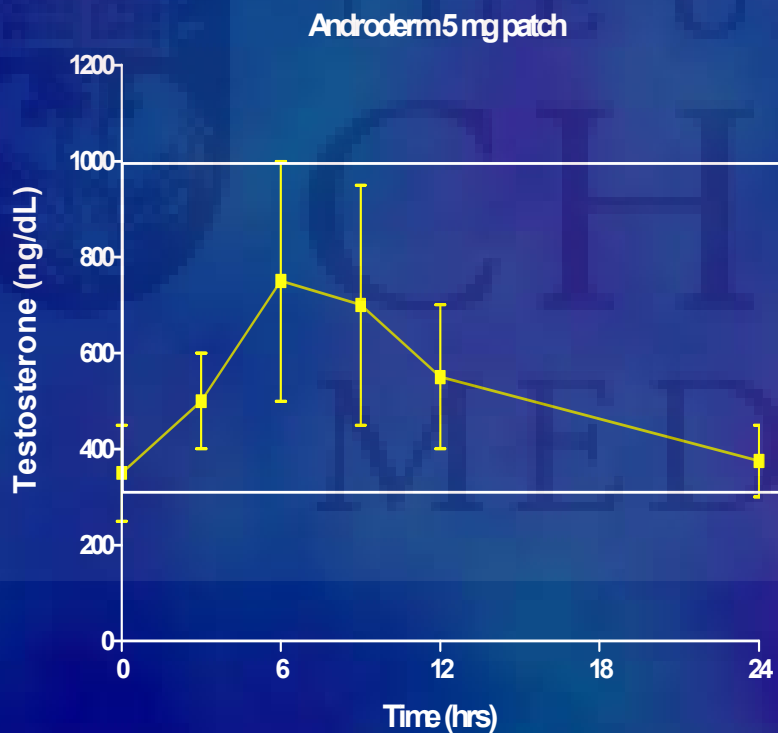
# Intramuscular Testosterone

Serum testosterone levels after a single 200 mg IM dose of testosterone enanthate.



# Transdermal Testosterone

Serum testosterone levels after single applications of a 5 mg Androderm patch and 5.0 g and 10.0 g testosterone gel doses.



## Back to our patient

- BMD done and was normal.
- He was started on T gel and will follow him periodically with PSA

# *Summary*

- Repeat confirmatory level should always be performed at a reliable reference laboratory
- On occasion, total testosterone levels may be low but bioavailable and/or free testosterone levels may be normal
- Initial evaluation should also include serum prolactin, TSH, free T4
- There is no conclusive evidence that testosterone therapy increases the risk of developing prostate cancer nor is there any evidence to suggest that it can convert subclinical or indolent prostate cancer into a clinically significant one.
- Screening for hypogonadism in men with ED is necessary to identify cases of **severe hypogonadism** and some cases of mild to moderate hypogonadism, who may benefit from testosterone treatment.
- 40 years of age or older with baseline PSA greater than 0.6 ng/ml, perform digital rectal examination + check PSA level before start TT, at 3-6 months after and then according to prostate cancer screening guidelines.

# References

1. Harrison's principle of internal medicine
2. Greenspan's Basic & clinical Endocrinology 9<sup>th</sup> Edition
3. Barlow DH. Causes of sexual dysfunction: the role of anxiety and cognitive interference. *J Consult Clin Psychol.* 1986;54:140-148.
4. Carlin BW. Impotence and diabetes. *Metabolism.* 1988;37(2 Suppl 1):19-21.
5. Up to date male hypogonadism
6. Murray FT, Geisser M, Murphy TC. Evaluation and treatment of erectile dysfunction. *Am J Med Sci.* 1995;309:99-109.
7. Rosen RC, Leiblum SR, eds. *Erectile Disorders: Assessment and Treatment.* New York: Guilford Press, 1992.
8. Rowland DL, Greenleaf WJ, Dorfman LJ, Davidson JM. Aging and sexual function in men. *Arch Sex Behav.*



# Thank you

Milad Abusag MD  
First year fellow