

Should Testosterone Levels Influence Decision to Biopsy?

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Disclosures

- **Consultant- Abbvie, Boston Scientific, Coloplast, Endo**

Decision to Biopsy?

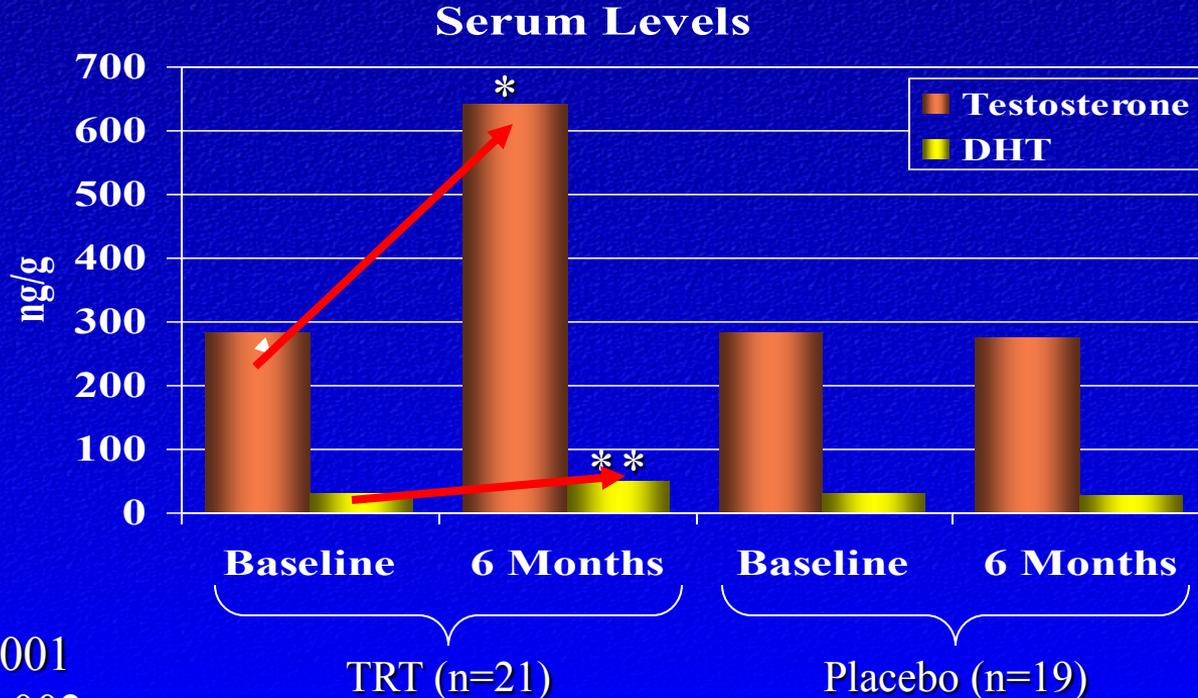
- Patients with elevated PSA?
- Active surveillance patients?
- Repeat biopsy in high risk patients?

What value does testosterone offer to men prior to radical prostatectomy or on active surveillance?

Effects of TTh on Prostate Tissue of Aging Men with Low Serum T

- R, DB, PC trial of 44 men (44-78 years)
- Inclusion criteria:
 - T < 300 ng/dl
 - Symptoms of hypogonadism
- Randomly assigned to receive 150 mg TE or placebo q 2 weeks X 6 months
- 12-core TRUS prostate biopsies were performed at baseline and 6 months

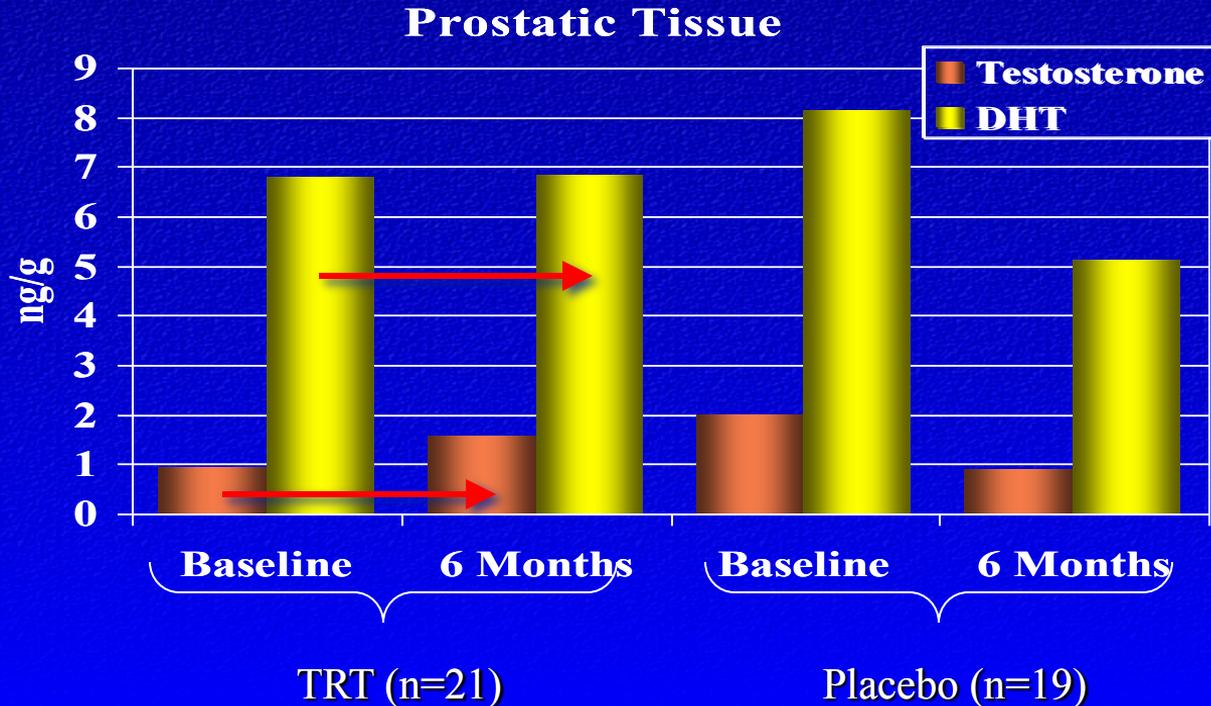
Effects of TTh on Prostate Tissue of Aging Men with Low Serum T



* $p < .001$

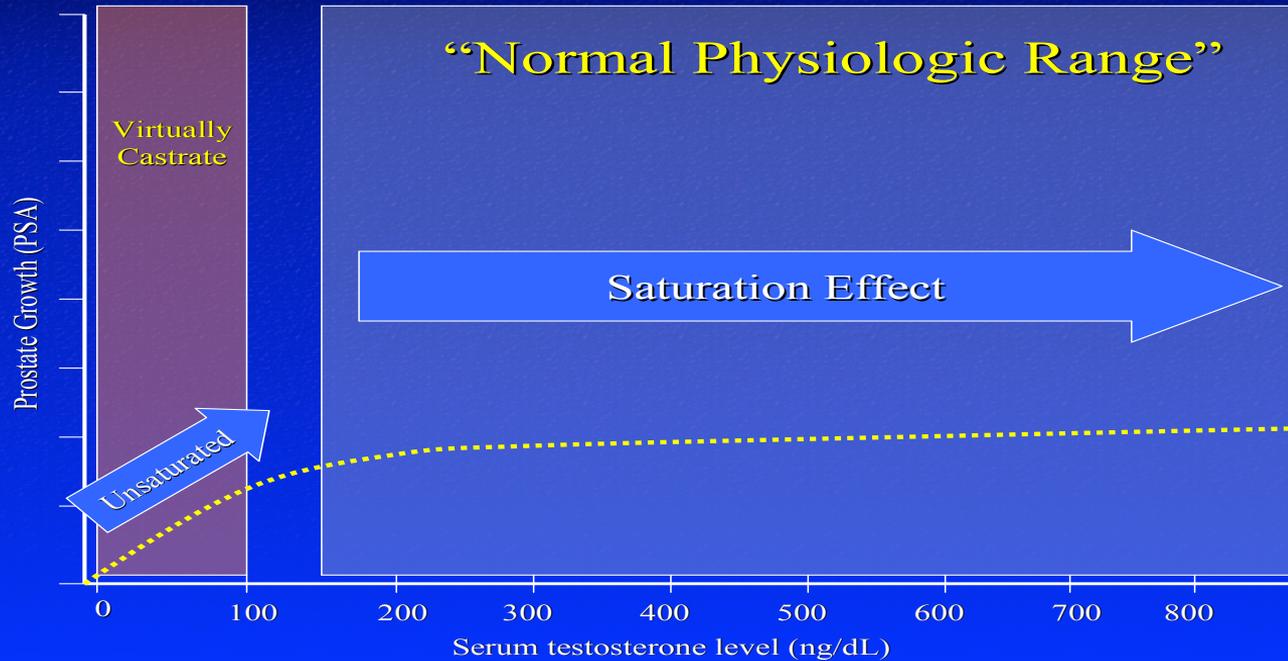
** $p < .002$

Effects of TTh on Prostate Tissue of Aging Men with Low Serum T



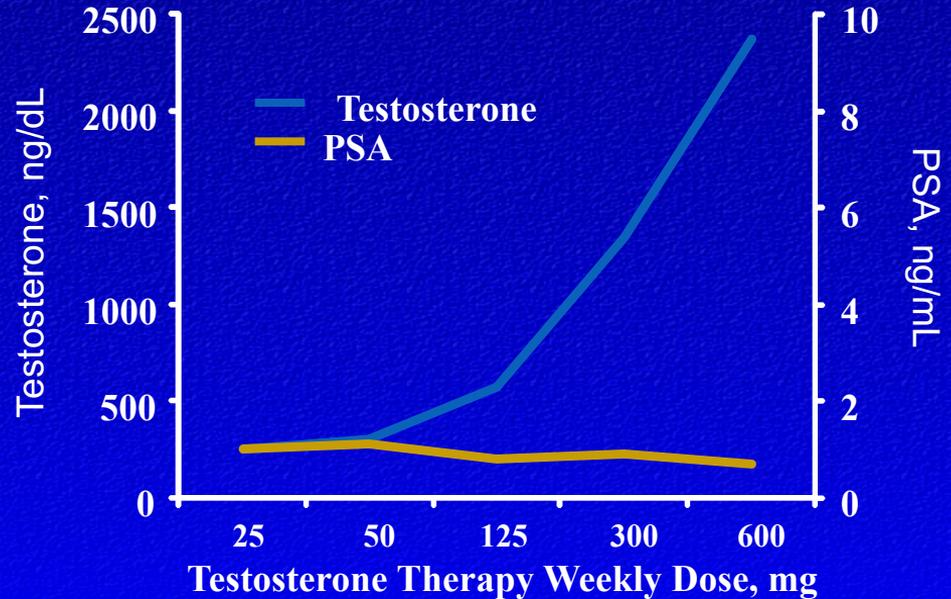
Prostate Saturation Model

Saturation Model of Physiologic Testosterone Replacement

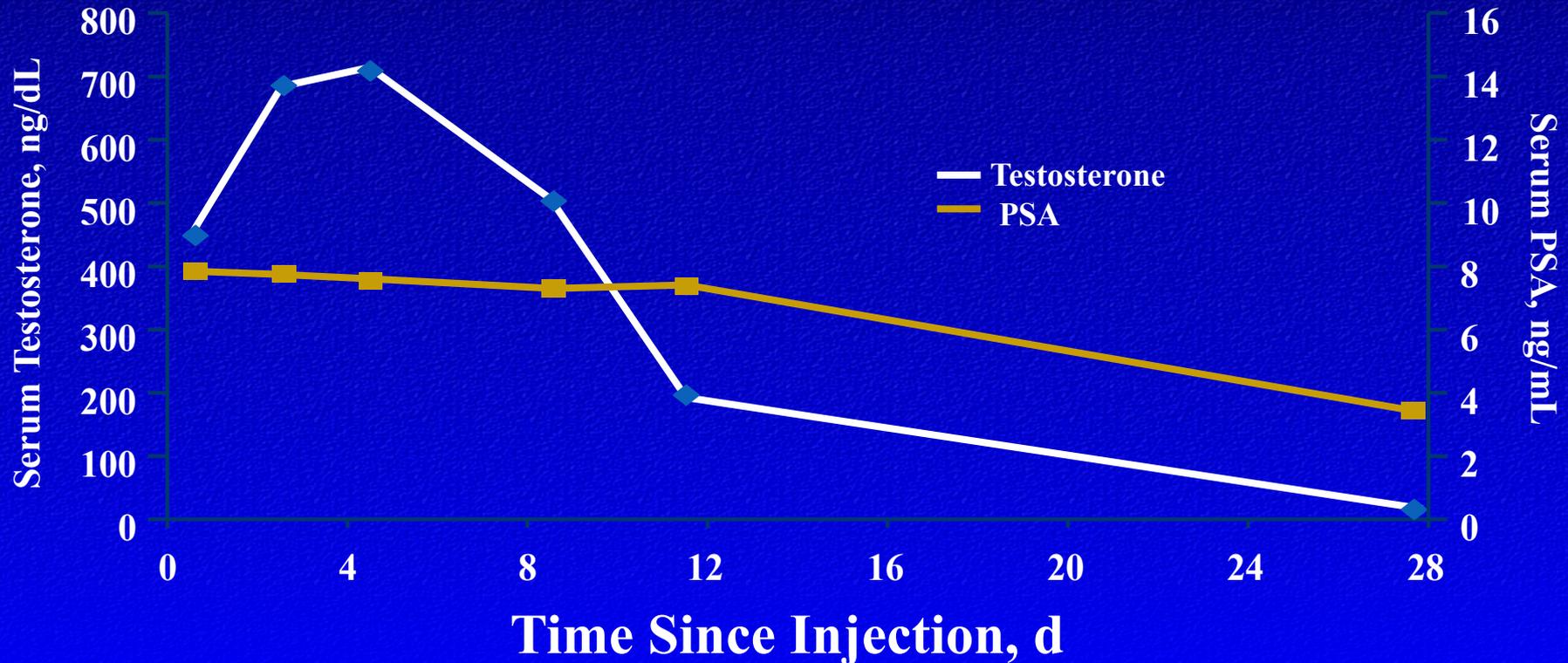


PSA at Supraphysiologic Levels of Testosterone

- Testosterone 600 mg or placebo weekly for 10 weeks
- PSA did not change significantly from baseline despite supraphysiologic testosterone levels (>2500 ng/dL)



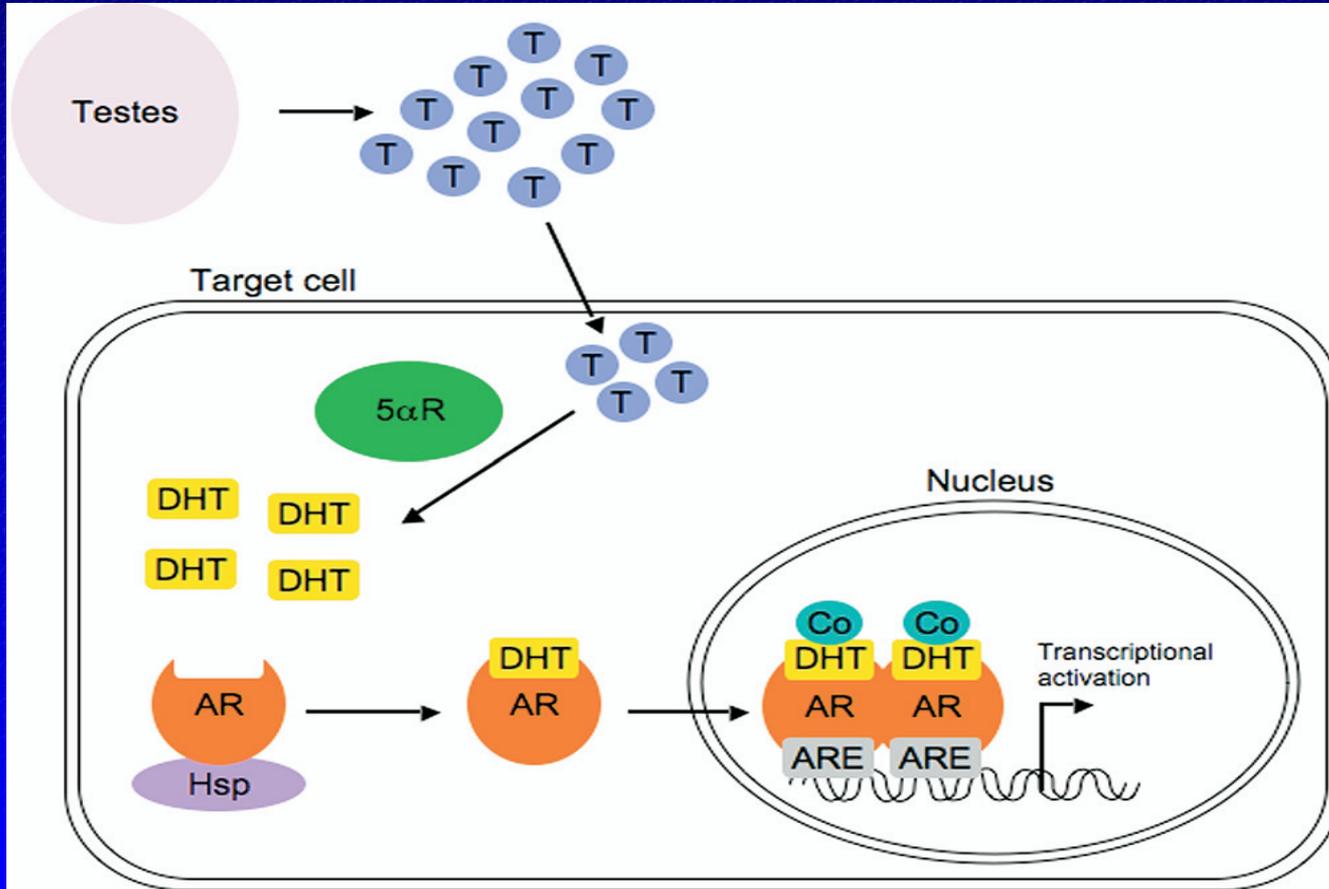
Serum PSA and Testosterone Flare



Data from Tomera K et al. *J Urol*. 2001;165(5):1585-1589.

Reproduced from Morgentaler A, Traish AM. *Eur Urol*. 2009;55(2):310-320

Molecular Basis for Saturation



AR becomes maximally bound to androgen (saturated) at ~8 nmol/L (250 ng/dl)

Morgentaler A, Traish AM Eur Urol 2009; 55: 310

Changes in Prostate Specific Antigen in Hypogonadal Men After 12 Months of Testosterone Replacement Therapy: Support for the Prostate Saturation Theory

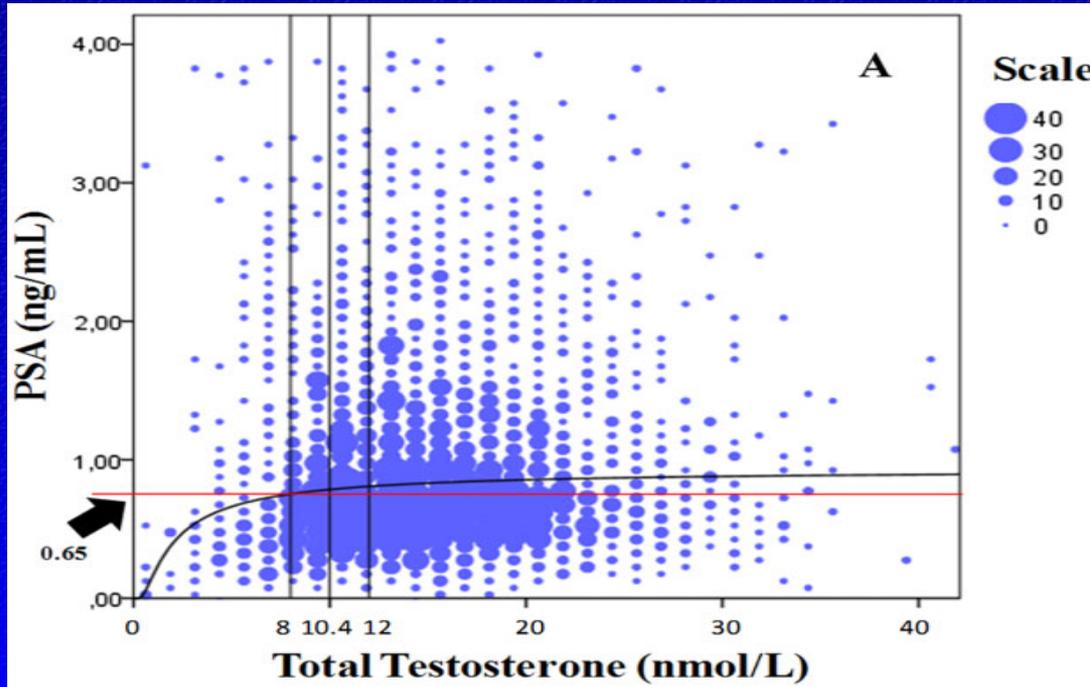
Mohit Khera,^{*,†} Rajib K. Bhattacharya,[‡] Gary Blick,[§] Harvey Kushner,^{||} Dat Nguyen^{||} and Martin M. Miner[¶]

From the Scott Department of Urology, Baylor College of Medicine, Houston, Texas (MK); University of Kansas Medical Center, Kansas City, Kansas (RKB); Ortho Medical LLC, Norwalk, Connecticut (GB); Auxilium Pharmaceuticals, Malvern, Pennsylvania (HK, DN); and Miram Hospital Men's Health Center, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island (MMM)

- 451 hypogonadal men started on TTh for 12 months
- Divided into 2 groups
 - Group A: Testosterone < 250ng/dl
 - Group B: Testosterone > 250ng/dl
- **ONLY in group A (Testosterone < 250ng/dl):**
 - PSA correlates with testosterone and free testosterone

PSA AND SATURATION

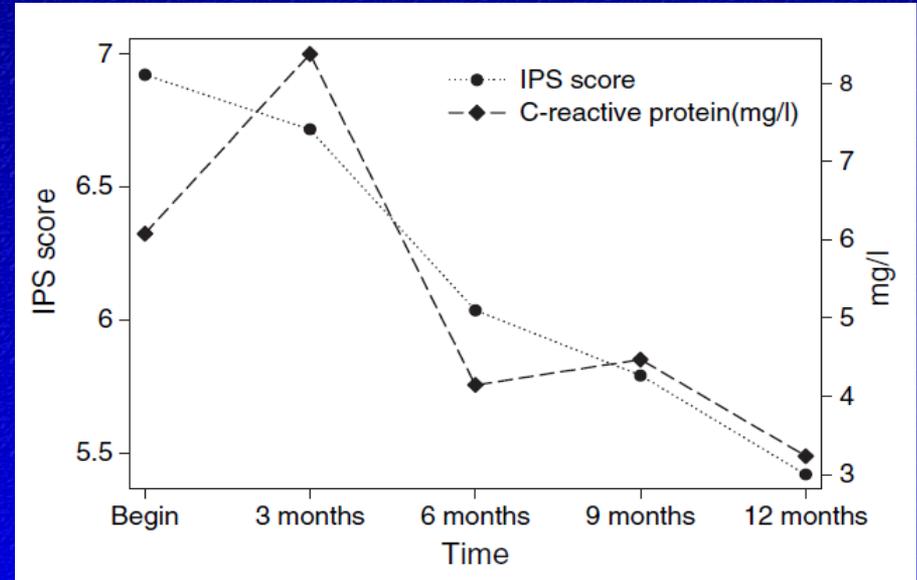
Rastrelli et al, J Sex Med 2013



- 2967 men
- Seen for sexual dysfunction
- All with PSA < 4.0
- Saturation point
~ 8 nmol/L (230 ng/dl)

Testosterone and LUTS

- 95 hypogonadal men treated with long-acting IM testosterone undecanoate every 3 months for 12 months
- Results
 - No significant change in prostate volume
 - Significant improvement in PVR
 - Significant improvement in IPSS
 - Significant improvement in CRP



Testosterone and Detection of Prostate Cancer

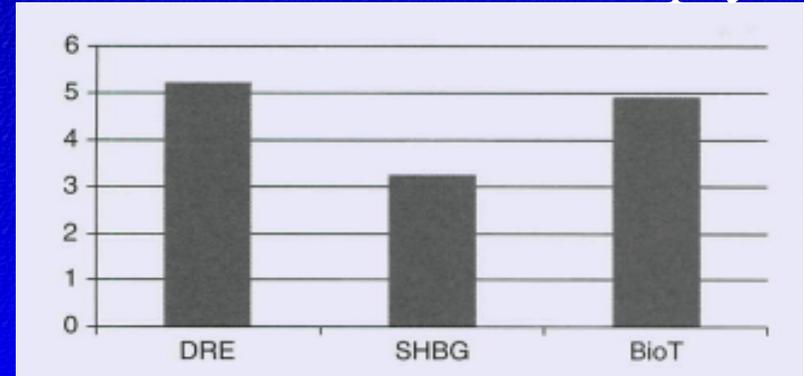
Higher sex hormone-binding globulin and lower bioavailable testosterone are related to prostate cancer detection on prostate biopsy

EDUARDO GARCÍA-CRUZ^{1,5}, ALBERT CARRIÓN PUIG¹,
ALEJANDRO GARCÍA-LARROSA², ANDREA SALLENT¹,
ROBERTO CASTANEDA-ARGAIZ¹, MARTA PIQUERAS¹, MARÍA JOSE RIBAL¹,
ASIER LEIBAR-TAMAYO^{3,5}, JAVIER ROMERO-OTERO^{4,5} & ANTONIO ALCARAZ¹

¹Urology Department, Hospital Clínic Barcelona, Barcelona, Spain, ²Hospital de Viladecans, Barcelona, Spain, ³Hospital Galdakao, Bilbao, Spain, ⁴Hospital 12 de Octubre, Madrid, Spain, and ⁵Red Española de Investigación en Salud del Hombre (REISHO)

- 279 men underwent 10 core prostate biopsy
- Age, prostate volume, DRE status, PSA, PSA density, testosterone, SHBG were all assessed to

Odds Ratio of Finding Prostate Cancer on Biopsy



Low testosterone level predicts prostate cancer in re-biopsy in patients with high grade prostatic intraepithelial neoplasia

Eduard García-Cruz, Marta Piqueras, Maria José Ribal, Jorge Huguet, Rodrigo Serapiao, Lluís Peri, Laura Izquierdo and Antonio Alcaraz
Urology Department, Hospital Clínic de Barcelona, Barcelona, Spain
 Accepted for publication 9 November 2011

- 82 men with HGPIN undergoing prostate biopsy
- Hormone profile (T, SHBG) and PSA and prostate volume were similar in 45 men

TABLE 2 Comparative analysis between patients with a positive and those with a negative rebiopsy

	Positive rebiopsy, n = 10	Negative rebiopsy, n = 35	P
Mean (SD) age, years	68 (8)	76 (7)	0.192
Mean (SD) PSA level, ng/dL	10.9 (7.0)	9.5 (7.1)	0.630
Mean (SD) PSA density, ng/dL*g	0.37 (0.23)	0.39 (43)	0.950
Mean (SD) prostate volume, mL	50 (22)	54 (24)	0.690
Normal DRE (%)	10/10 (100)	27/30 (90)	0.298
Multifocality (%)	5/8 (62.5)	19/29 (65.5)	0.874
Mean (SD) testosterone level, ng/dL	490 (150)	488 (176)	0.981
Mean (SD) free calculated testosterone level, ng/dL	6.9 (1.2)	9.3 (3.2)	0.041
Mean (SD) bioavailable testosterone level, ng/dL	162 (28)	217 (74)	0.04
Mean (SD) SHBG level, nmol/L	58 (19)	39 (16)	0.020

Serum testosterone improves the accuracy of Prostate Health Index for the detection of prostate cancer



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^a Department of Urology, University Hospital Charité, Berlin, Germany

^b Department of Urology, Sana Hospital, Offenbach, Germany

^c Berlin Institute for Urologic Research, Berlin, Germany

- Aim: To assess if serum testosterone can improve the diagnostic validity of PHI test
- 193 men scheduled for biopsy had PHI and testosterone panel
 - PCa= 99, No PCa= 94
- Compared with the non-malignant controls, PCa patients had significantly higher PSA concentrations and PHI values, but lower % fPSA values and lower

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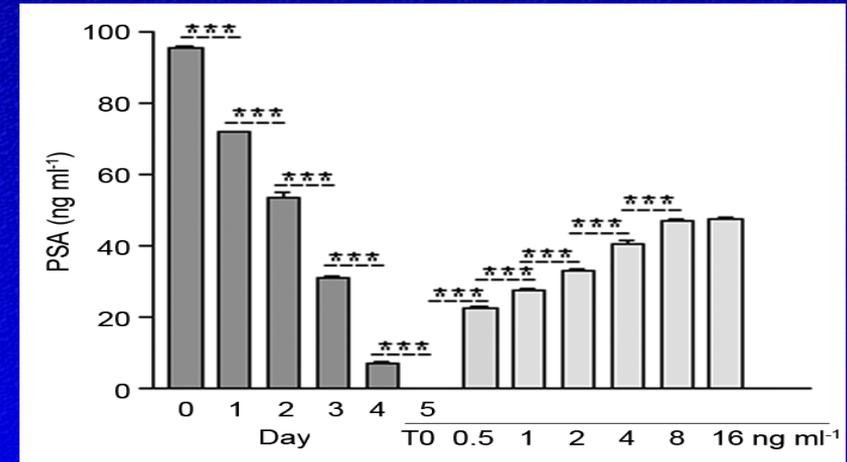
^c Berlin Institute for Urologic Research, Berlin, Germany

- PHI showed the largest area under the ROC curve (AUC = 0.73) that was increased further by the inclusion of bioT or tT in a binary logistic regression model
- The AUC of PHI in patients with tT concentrations of <8 nmol/L (230ng/dl) was significantly larger than that in patients with higher tT values (0.86 vs. 0.70; P= 0.024)
- **Conclusion: The PHI-based discrimination between PCa patients and non-malignant controls could be improved by the simultaneous determination of testosterone. Patients with testosterone concentrations of <8 nmol/L(230ng/dl) have the greatest benefit.**

Combined tests of prostate specific antigen and testosterone will improve diagnosis and monitoring the progression of prostate cancer

Weitao Song, Vikram Soni, Mohit Kherra

- 24 wells of 15,000 LNCaP cells
- RPMI-1640 medium changed every day
- Different amounts of testosterone added to LNCaP cells and



Testosterone as a Marker for Prostate Cancer Severity

Low Testosterone Associated with Increased Risk of Prostate Cancer

- Isom-Batz, et al. J Urol. 2005; 173: 1935-1937
 - Lower testosterone correlated with higher:
 - Pathological stage
 - Clinical stage
- Teloken, et al. J Urol. 2005; 174: 2178-2180
 - Lower testosterone correlated with:
 - Increased positive surgical margins
 - 39% in low TT vs 14.6% in normal TT
- Schatzl, et al. J Urol. 2003; 169: 1312-1315
 - Lower testosterone correlated with:
 - Higher tumor density

Low T Increases Prostate Cancer Risk

References	Number of Pts	Study Type	Endogenous TTh Level	CaP Outcomes
Morgentaler et al.[29]	77	Retrospective	T <300 ng/dl or free T <1.6 ng/dl	CaP incidence of 14% (11/77)
Mearini et al.[31]	206	Prospective	≤2.4ng/ml ≤0.5ng/ml	14.2% of patients had clinically locally advanced or metastatic CAP, and 57.1% have a pathological locally advanced CaP
Shin et al.[32]	568	Prospective	<3.85ng/ml	CaP incidence 38.0% (vs. 29.5% high testosterone)
Karamanolakis et al. [39]	718	Prospective	<3.0 ng/ml	CaP incidence 30% (29/97)
Morgentaler et al. [30]	345	Retrospective	<250ng/dl	CaP incidence 21% (vs. 12% in men with T>250ng/dl)
Hoffman et al.[33]	117	Retrospective	T<300ng/dl or free T<1.5ng/dl	CaP incidence 43% (vs. 22%)
Garcia-Cruz et al.[34]	137	Prospective	<346 ng/dl	Tumor burden 53% (vs. 32% in men with T >346 ng/dl); tumor bilaterality 50% (vs. 25.5% in men with T >346)
Isom-Batz et al.[35]	326	Retrospective	<385ng/dl	Associated with advanced pathological stage (OR 2.3, 95% CI 1.1-5.0; p = 0.03)
Lane et al.[36]	455	Prospective	<220ng/dl	Higher frequency of Gleason 4-5 disease (OR 2.4, 95% CI 1.01-5.7; p = 0.48)
Botto et al.[40]	431	Prospective	<3ng/ml	Higher frequency of Gleason 4 disease (47% vs. 28%)
Salonia et al.[37]	673	Prospective	Total T <1ng/ml	Higher incidence of seminal vesicle invasion (OR 3.11)
Teloken et al.[38]	64	Retrospective	<2.7ng/ml	Increased positive surgical margins (p = 0.026)

Testosterone as a Predictor of Cancer Progression or Recurrence

Lower Pre-operative Testosterone Levels Increase the Risk for Prostate Cancer Recurrence

- 272 patients with localized prostate cancer were treated with radical prostatectomy
- Preoperative testosterone measured in all patients
 - <300 ng/dl: 49 patients
 - >300 ng/dl: 223 patients
- Independent and significant predictors of PSA recurrence were:
 - Gleason score (p=0.006),
 - Surgical margin status (p=0.0001),
 - PSA (p=0.0001)
 - Preoperative testosterone level (p=0.021)

Low free testosterone levels predict disease reclassification in men with prostate cancer undergoing active surveillance

Ignacio F. San Francisco, Pablo A. Rojas, William C. DeWolf* and Abraham Morgentaler*

- 154 men were followed with AS for prostate cancer
- 54 (35%) progressed to active treatment
- Men who progressed had significantly lower free testosterone levels than those who remained on AS (0.75 vs 1.02 ng/dL, $P = 0.03$)
- Free testosterone levels <0.45 ng/dL were associated with a **seven-fold** increase in the risk of disease progression (OR 4.3, 95% CI 1.25-14.73)
- **Multivariate analysis** demonstrated that free



Conclusion

- **PSA values correlate with T values at lower levels of serum testosterone (Prostate Saturation Model)**
- **Low serum testosterone can be a marker for occult prostate cancer, prostate cancer progression and recurrence, and severity of prostate cancer**
- **Clinicians should take into account a patient's testosterone level when unsure**



Thank You

Texas Medical Center, Houston