Bari,
7-10 novembre 2013

Simposio:
Terapie endocrino- metaboliche e rischio oncologico

Androgeni

L.Foppiani
S.C. Medicina Interna, Ospedali Galliera, Genova

12°Congresso Nazionale AME

6th Joint Meeting with AACE

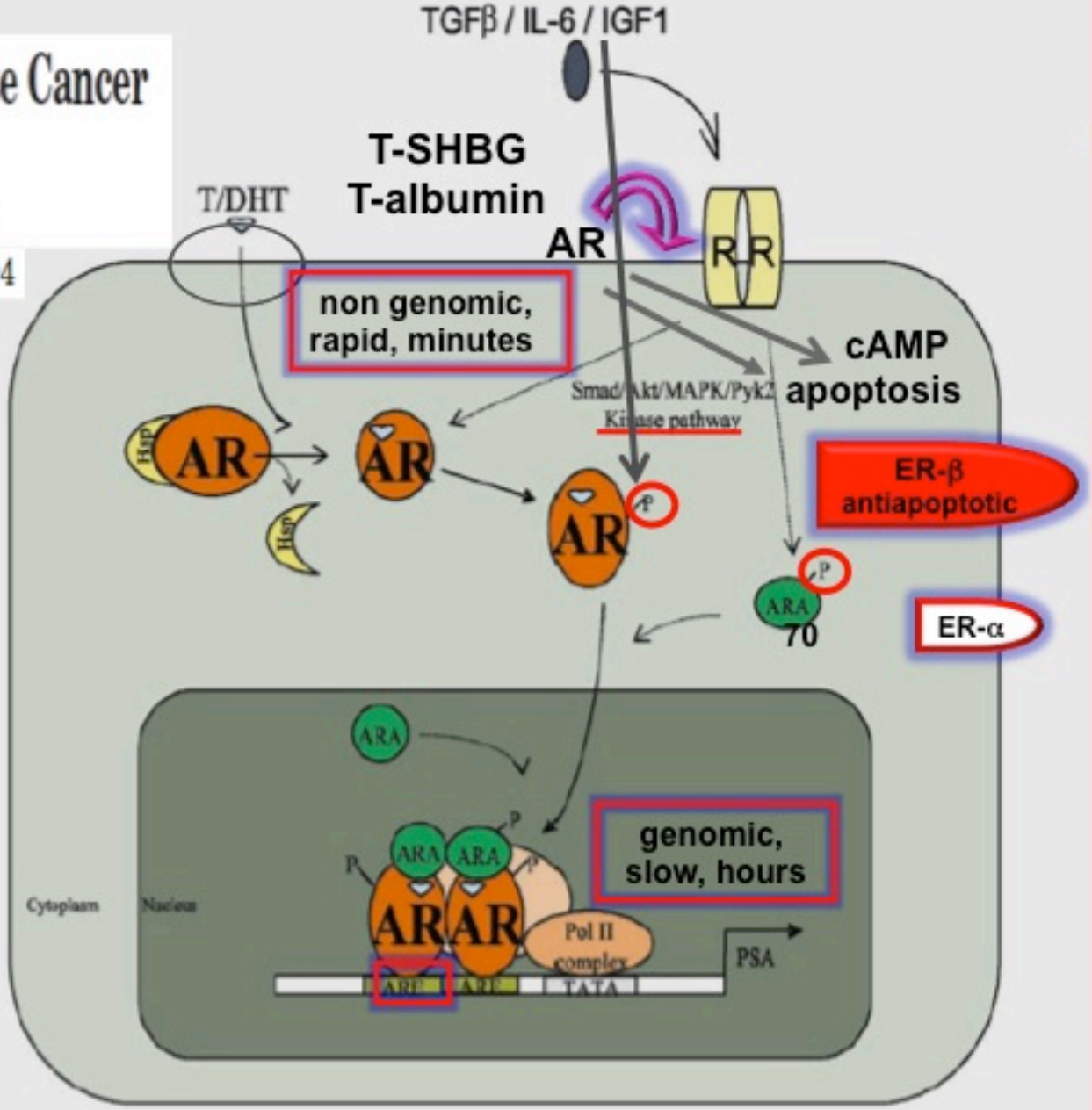
Bari 7-10 Novembre 2013

Androgen Receptor in Prostate Cancer

CYNTHIA A. HEINLEIN AND CHAWNSHANG CHANG

Endocrine Reviews 25(2):276–308 2004

FIG. 1. Androgen-AR action in the prostate. Testosterone (T) and DHT bind to AR and promote the association of AR coregulators (ARAs). AR then translocates to the nucleus and binds to AREs in the promoter regions of target genes to induce cell proliferation and apoptosis. Other signal transduction pathways, such as those involving TGFβ, IL-6, and IGF-I, can also enhance AR activity via phosphorylation of AR and/or ARAs. Hsp, Heat shock protein; R, membrane receptor; P, protein phosphorylation.



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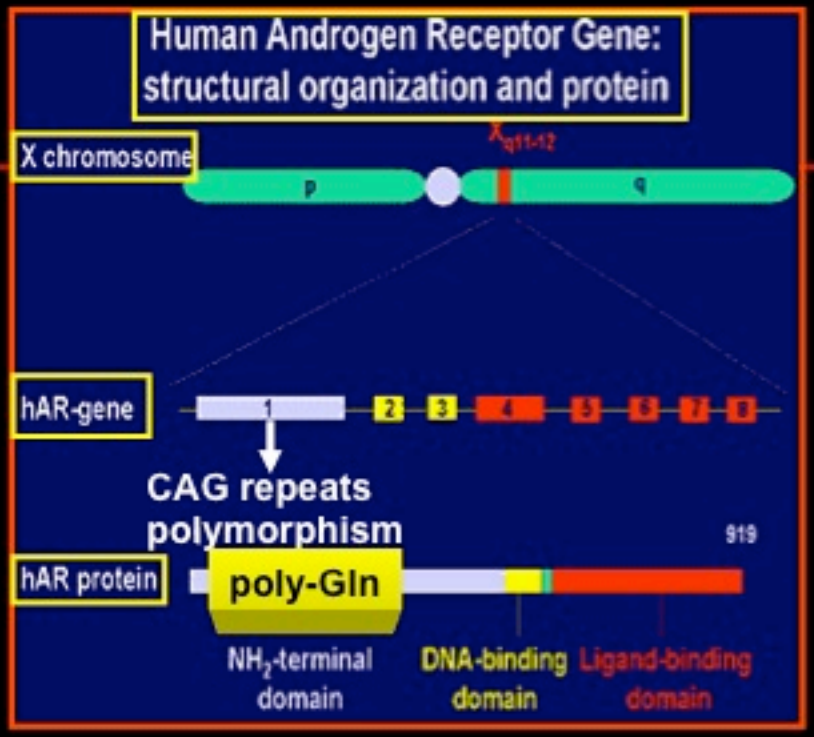
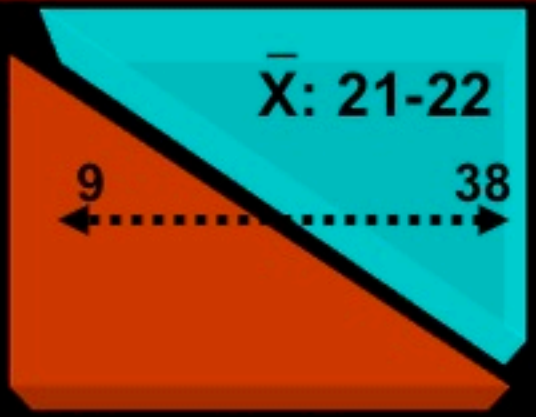
Human Androgen Receptor Gene: structural organization and protein

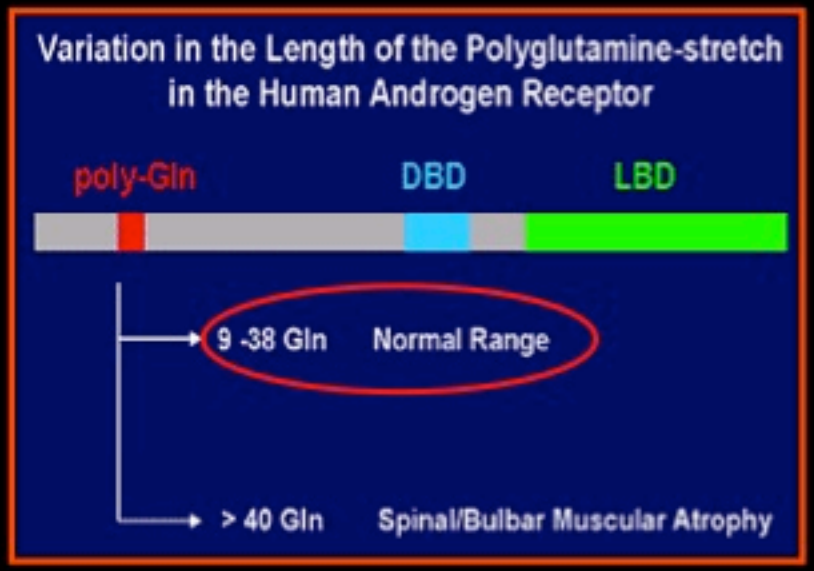


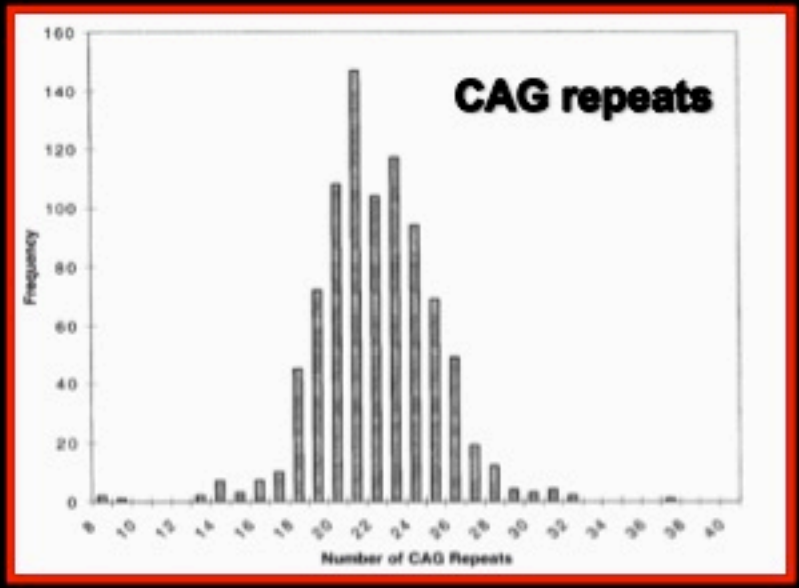
CAG repeats AR



aumento attività transcrizionale

Variation in the Length of the Polyglutamine-stretch in the Human Androgen Receptor





The CAG repeat within the androgen receptor gene and its relationship to prostate cancer

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 3320–3323, April 1997

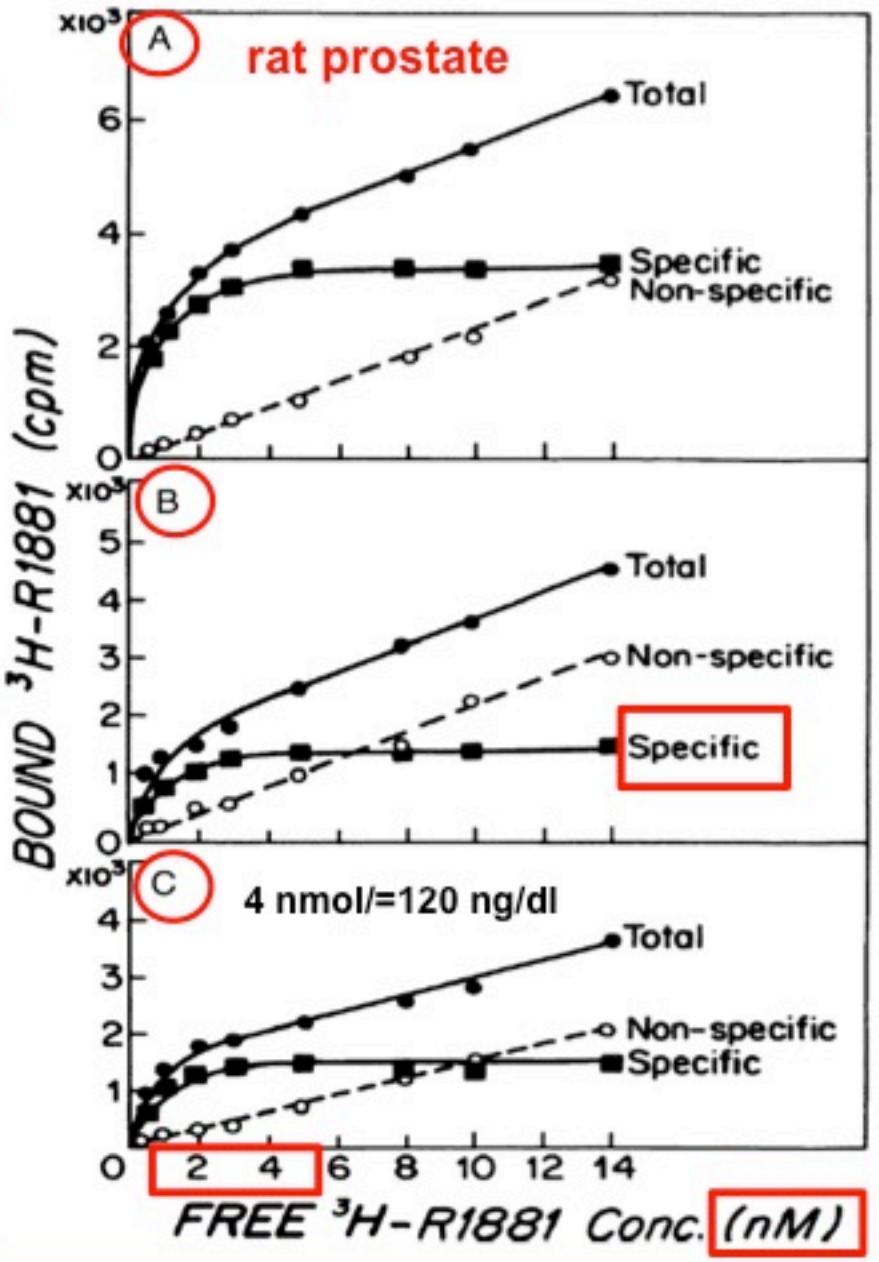
EDWARD GIOVANNUCCI*†, MEIR J. STAMPFER*‡, KRISHNA KRITHIVAS§, MYLES BROWN¶, ADAM BRUFSKY§¶, JAMES TALCOTT§, CHARLES H. HENNEKENS‡‖, AND PHILIP W. KANTOFF§

Category	N°	OR (six decrement in CAG repeat)	95% IC	p
Total	587	1.28	1.01-1.61	0.04
High grade	210	1.59	1.14-2.22	0.007
Advanced state	180	1.75	1.23-2.50	0.002
Metastatic	56	2.44	1.32-4.55	0.004
Fatal	43	2.08	1.05-4.00	0.04

OR of prostate cancer for a CAG microsatellite repeat lenght decrement of six repeats in AR

Figure 1. Binding of synthetic androgen [3H]R1881 to androgen receptor in Noble rat ventral (*A*), dorsolateral (*B*) and anterior (*C*) prostate. Note that specific androgen binding to AR reaches maximum at low androgen concentrations (2 to 3 nM, roughly 60 to 90 ng/dl) in all 3 prostate lobes without further binding over wide range of increasing concentrations of [3H]R1881. Choice of [3H]R1881 as ligand for AR binding assay is due to its high affinity for AR and low affinity for nonspecific plasma proteins, including sex hormone binding globulin. *Conc.*, con-

Ho et al. J Androl 1985




TESTOSTERONE
GASOLINE


PROSTATA

?

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Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men

European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study

Kay-Tee Khaw, Mitch Dowsett, Elizabeth Folkerd, Sheila Bingham, Nicholas Wareham, Robert Luben, Ailsa Welch and Nicholas Day

Circulation 2007;116;2694-2701

Table 3. Distribution of Cases and Controls Among Men 42 to 78 Years of Age and OR* of Mortality Due to All Causes, Cardiovascular Disease, and Cancer by Quartile Group of Serum Testosterone in EPIC-Norfolk 1993 to 2003

n=11606 men

OR: 0.75 OR: 0.62 OR: 0.59

	Quartile Groups of Testosterone				
	1 <12.5 nmol/L	2 12.5–15.6 nmol/L	3 15.7–19.6 nmol/L	4 >19.6 nmol/L	*P* for Trend
Cancer mortality: cases/controls, n	88/335	73/379	71/384	71/391	0.04

Table 4. ORs* of Mortality Due to All Causes, Cardiovascular Disease, and Cancer Associated With Serum Testosterone Increase of 6 nmol/L in Men 42 to 78 Years of Age in EPIC-Norfolk 1993 to 2003, Adjusted for Age and Covariates

		Age Adjusted		Age and Covariate† Adjusted	
	Cases/Controls, n	OR (95% CI)	*P*	OR (95% CI)	*P*
Cancer mortality	249/1489	0.81 (0.69–0.94)	<0.01	0.81 (0.65–1.01)	0.06

*ORs are shown per 6-nmol/L increase in serum testosterone (~1 SD) with logistic regression. All ORs are adjusted for age and date of visit.

Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline

Shalender Bhasin, Glenn R. Cunningham, Frances J. Hayes, Alvin M. Matsumoto, Peter J. Snyder, Ronald S. Swerdloff, and Victor M. Montori

tion, sense of well-being, muscle mass and strength, and bone mineral density. We recommend against starting testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule or induration or prostate-specific antigen greater than 4 ng/ml or greater than 3 ng/ml in men at high risk for prostate cancer such as African-Americans or men with first-degree relatives with prostate cancer without further urological evaluation, hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms with International Prostate Symptom Score above 19, or uncontrolled or poorly controlled heart failure. When testosterone therapy is instituted, we suggest aiming at achieving testosterone levels during treatment in the mid-normal range with any of the approved formulations, chosen on the basis of the patient's preference, consideration of pharmacokinetics, treatment burden, and cost. Men receiving testosterone therapy should be monitored using a standardized plan. (*J Clin Endocrinol Metab* 95: 2536–2559, 2010)

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Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis

J Clin Endocrinol Metab 95: 2560–2575, 2010)

M. Mercè Fernández-Balsells, Mohammad Hassan Murad, Melanie Lane, Juliana F. Lampropulos, Felipe Albuquerque, Rebecca J. Mullan, Neera Agrwal, Mohamed B. Elamin, Juan F. Gallegos-Orozco, Amy T. Wang, Patricia J. Erwin, Shalender Bhasin, and Victor M. Montori

Objective: The aim of this study was to conduct a systematic review and meta-analyses of testosterone trials to evaluate the adverse effects of testosterone treatment in men.

Data Sources: We searched MEDLINE, EMBASE, and Cochrane CENTRAL from 2003 through August 2008. Review of reference lists and contact with experts further identified candidate studies.

Study Selection: Eligible studies were comparative, randomized, and nonrandomized and reported the effects of testosterone on outcomes of interest (death, cardiovascular events and risk factors, prostate outcomes, and erythrocytosis). Reviewers, working independently and in duplicate, determined study eligibility.

51 studies

Data Extraction: Reviewers working independently and in duplicate determined the methodological quality of studies and collected descriptive, quality, and outcome data.

Data Synthesis: The methodological quality of the 51 included studies varied from low to medium, and follow-up duration ranged from 3 months to 3 yr. Testosterone treatment was associated with a significant increase in hemoglobin [weighted mean difference (WMD), 0.80 g/dl; 95% confidence interval (CI), 0.45 to 1.14] and hematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01), and a decrease in high-density lipoprotein cholesterol (WMD, −0.49 mg/dl; 95% CI, −0.85 to −0.13). There was no significant effect on mortality, prostate, or cardiovascular outcomes.

FIG. 2. Results of the random effects meta-analyses of testosterone on patient-important outcomes.

Androgens and prostate cancer risk

Sara Wirén MD
Pär Stattin* MD, PhD

Best Practice & Research Clinical Endocrinology & Metabolism
Vol. 22, No. 4, pp. 601–613, 2008

Endogenous Sex Hormones and Prostate Cancer: A Collaborative Analysis of 18 Prospective Studies

Endogenous Hormones and Prostate Cancer Collaborative Group

J Natl Cancer Inst 2008;100:170–183

n= 3886 pz con Ca prostata
n= 6438 controlli

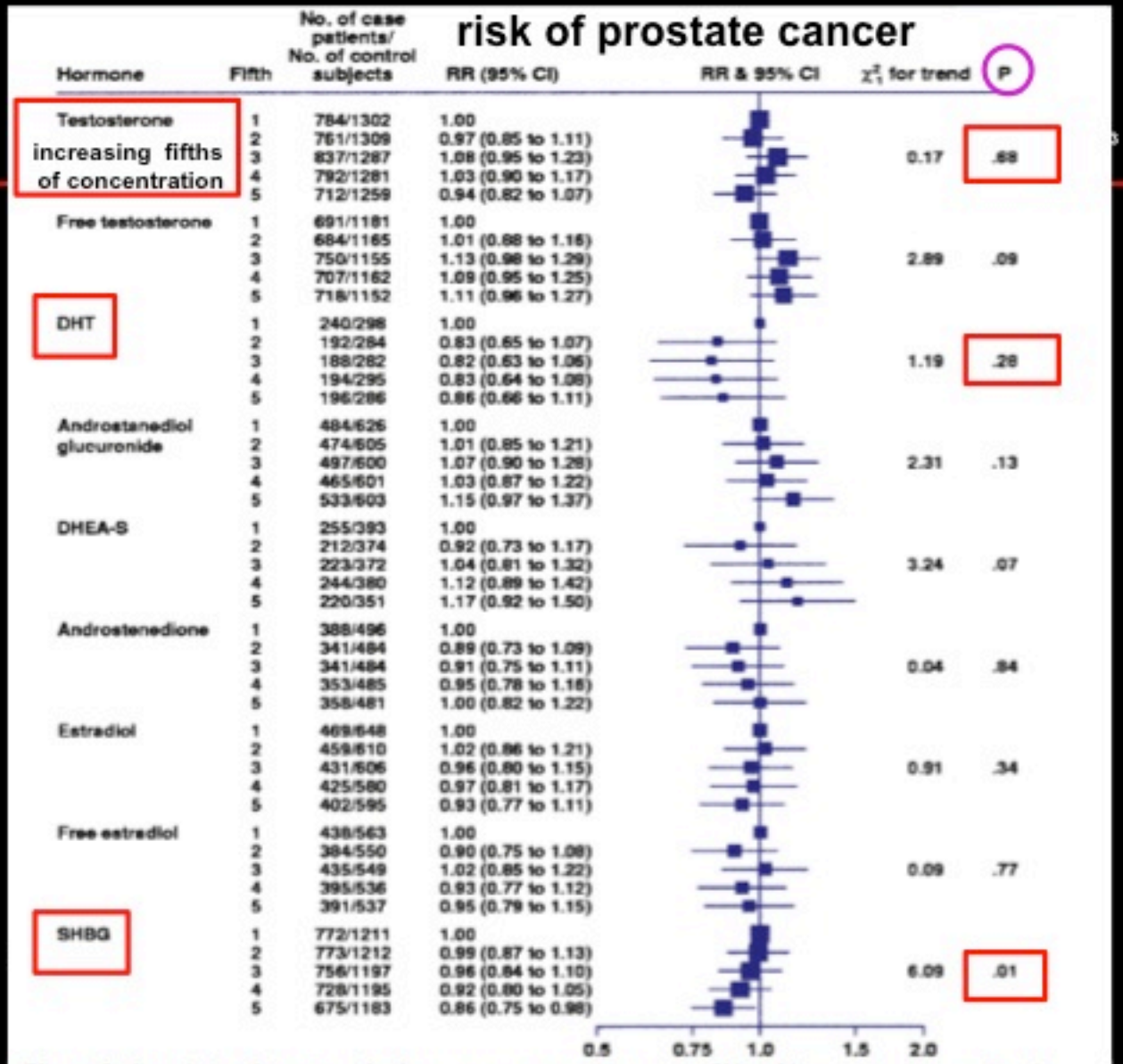

Figure 1. Associations between risk of prostate cancer and increasing fifths of hormone concentrations in the Endogenous Sex Hormones and Prostate Cancer Collaborative Analysis of 18 prospective studies, including 3886 men with incident prostate cancer and 6438 control subjects.[36] The position of each square indicates the magnitude of the relative risk, and the area of the square is proportional to the amount of statistical information available. The length of the horizontal line through the square indicates the 95% confidence interval (CI). RR, relative risk; DHT, dihydrotestosterone; DHEA-S, dehydroepiandrosterone sulphate; SHBG, sex hormone binding globulin. Reprinted from Roddam et al (2008, *Journal of the National Cancer Institute* **100**: 170–183) with permission.

Serum Testosterone and Dihydrotestosterone and Prostate Cancer Risk in the Placebo Arm of the Reduction by Dutasteride of Prostate Cancer Events Trial

EUROPEAN UROLOGY 62 (2012) 757–764

Roberto L. Muller[a,b,*], *Leah Gerber*[a,b], *Daniel M. Moreira*[c], *Gerald Andriole*[d], *Ramiro Castro-Santamaria*[e], *Stephen J. Freedland*[a,b,f]

Design, setting, and participants: Of 8122 men in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, 4073 men (50.1%) received placebo. Key entry criteria were PSA 2.5–10 ng/ml and one prior negative biopsy.

Results and limitations: Of 4073 men, 3255 (79.9%) had at least one biopsy after randomization and were analyzed. Androgen levels tested continuously or by quintiles were generally unrelated to PCa detection or grade. PCa detection was similar among men with low compared with normal baseline testosterone levels (25.5% and 25.1%; $p = 0.831$). In secondary analysis, higher testosterone levels at baseline were associated with higher PCa detection (odds ratio: 1.23; 95% confidence interval, 1.06–1.43; $p = 0.006$) only if men had low baseline testosterone (<10 nmol/l). For men with normal baseline testosterone (≥10 nmol/l), higher testosterone levels at baseline were unrelated to PCa risk ($p = 0.33$). No association was found for DHT and PCa (all $p > 0.85$).

Conclusions: Baseline serum testosterone and DHT levels were unrelated to PCa detection or grade. Our findings of the lowest testosterone levels being associated with the lowest PCa risk with no further changes with higher testosterone support a saturation model but must be confirmed in future studies using an a priori defined hypothesis.

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PREVALENCE OF PROSTATE CANCER AMONG HYPOGONADAL MEN WITH PROSTATE-SPECIFIC ANTIGEN LEVELS OF 4.0 ng/mL OR LESS

ABRAHAM MORGENTALER AND ERNANI LUIS RHODEN

1:7

ABSTRACT

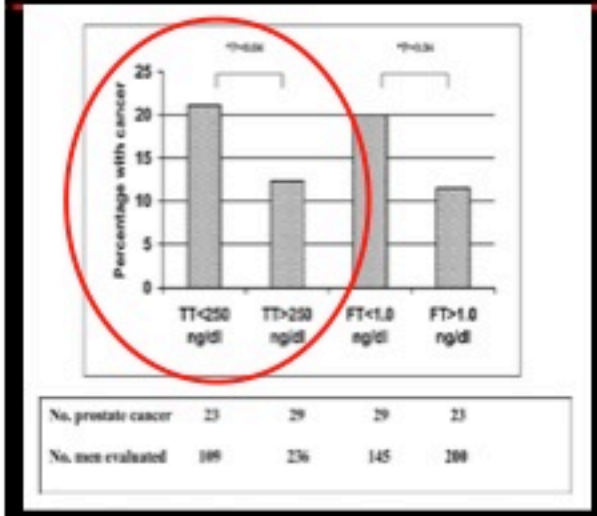
Objectives. To determine the prevalence of prostate cancer in hypogonadal men with a prostate-specific antigen (PSA) level of 4.0 ng/mL or less.

Methods. A total of 345 consecutive hypogonadal men with a PSA level of 4.0 ng/mL or less underwent evaluation with digital rectal examination and prostate biopsy before initiating a program of testosterone replacement therapy. All men had low serum levels of total or free testosterone, defined as less than 300 and 1.5 ng/dL, respectively. mean age of 58.9 years.

Results. Cancer was identified in 15.1%. The cancer detection rate was 5.6%, 17.5%, 26.4%, and 36.4% for a PSA level of 1.0 or less, 1.1 to 2.0, 2.1 to 3.0, and 3.1 to 4.0 ng/mL, respectively ($P < 0.05$). Cancer was detected in 26 (30.2%) of 86 men with a PSA level of 2.0 to 4.0 ng/mL. Cancer was detected in 21% of men with a testosterone level of 250 ng/dL or less compared with 12% of men with a testosterone level greater than 250 ng/dL ($P = 0.04$). Men with free testosterone levels of 1.0 ng/dL or less had a cancer rate of 20% compared with 12% for men with greater values ($P = 0.04$). The odds ratio of cancer detection for men in the lowest tertile compared with the highest tertile was 2.15 (95% confidence interval 1.01 to 4.55) for total testosterone and 2.26 (95% confidence interval 1.07 to 4.78) for free testosterone.

Conclusions. Prostate cancer was present in more than 1 of 7 hypogonadal men with PSA of 4.0 ng/mL or less. An increased risk of prostate cancer was associated with more severe reductions in testosterone.

UROLOGY 68: 1263–1267, 2006.



- tumor vessel density
- AR density

Associations of serum testosterone with microvessel density, androgen receptor density and androgen receptor gene polymorphism in prostate cancer. Schatzl et al. J Urol 169: 1312-5, 2003.

Pre-operative serum testosterone levels as an indipendent predictor of treatment failure following radical prostatectomy. Yamamoto et al. Eur Urol 52: 696-701, 2007.

Preoperative Serum Testosterone Level as an Independent Predictor of Treatment Failure following Radical Prostatectomy

EUROPEAN UROLOGY 52 (2007) 696–701

Shinya Yamamoto[a,*], *Junji Yonese*[a], *Satoru Kawakami*[a], *Yuhei Ohkubo*[a], *Manabu Tatokoro*[a], *Yoshinobu Komai*[a], *Hideki Takeshita*[a], *Yuichi Ishikawa*[b], *Iwao Fukui*[a]

Methods: Of 304 patients diagnosed with clinically localized pCA who had been treated with RP alone, 272 patients whose preoperative TS level had been measured were eligible for this analysis. Postoperative TS

Results: Of the 272 patients 49 had low (<300 ng/dl) and 223 had normal preoperative TS level. In a stepwise multivariate analysis, preoperative TS ($p = 0.021$) was an independent and significant predictor of PSA failure along with RP Gleason score ($p = 0.006$), surgical margin status ($p = 0.0001$), and PSA ($p = 0.0001$). Five-year PSA failure–free survival rate of the patients with preoperative low TS (67.8%) was significantly worse than that with normal TS (84.9%) ($p = 0.035$). Serum TS levels increased significantly after RP ($p < 0.0001$). The increment of TS level in preoperative low TS group was significantly greater than that in preoperative normal TS group ($p = 0.0003$).

Conclusions: The current results demonstrated that preoperative TS level is an independent and significant predictor of PSA failure after RP in patients with clinically localized pCA.

TRT AND HYPOGONADISM

- 406 M ipogonadici (età: 56-60 aa) randomizzati per ricevere placebo, T gel, T patch per 90 giorni → ↑ PSA 17% (1.2 ng/ml → 1.4 ng/ml) nei trattati NS vs placebo (Steidle et al. JCEM 2003)
- 163 M ipogonadici (età media: 51 aa) trattati con T gel per 42 mesi → ↑ PSA 30% (0.85 ng/ml → 1.11 ng/ml) (Wang et al. JCEM 2004)
- 371 M ipogonadici (età media: 58.5 aa) trattati con T gel per 1 anno → ↑ PSA 30% (1.26 ng/ml → 1.64 ng/ml) (Dean et al. Rev Urol 2005)
- 58 M ipogonadici (età media: 58.3 aa) trattati con T (i.m. o gel) per 1 anno → ↑ PSA 17% (1.83 ng/ml → 2.14 ng/ml) ma nel 43% PSA= e nel 20% PSA ↓ (Roden et al. Int J Impot Res 2006)

TRT (19 randomized trials, follow-up up to 3 yrs) → 5 pCa/461 pts treated (prevalence 1.1% ~ to general population; OR: 1.09, 95% CI: 0.48-2.49)

Testosterone replacement therapy for late onset hypogonadism: what is the risk of inducing prostate cancer?

DC Gould and RS Kirby

Prostate Cancer and Prostatic Diseases (2006) 9, 14–18

Table 1 Studies of testosterone therapy in which the identification of prostate cancer was reported [— indicates not placebo controlled]

Study Author	*Duration months*	*Increase in PSA ng/ml/no. pts*		*Prostate cancer no. ca/no. pts*		*Route of Administration*
		Placebo	*Testosterone*	*Placebo*	*Testosterone*	
Tenover[28]	3	—	0.6/13	—	0/13	i.m.
Hajjar *et al.*[29]	24	0.25/15	0.5/26	0/27	0/45	i.m.
Dobs *et al.*[30]	24	—	0/33	—	2/33	i.m.
	24	—	0.5	—	1/33	Patch
Sih *et al.*[31]	12	0.5/15	0.9/17	0/15	0/17	i.m.
Guay *et al.*[32]	3	—	0.2/16	—		Patch
		—	0.63/25	—	3 overall	i.m.
		—	1.0/49	—		clomiphene
Svetec *et al.*[33]	12.8	—	0.29/49	—	0/48	i.m.
Kenny *et al.*[34]	12	0.3/33	0.6/34	0/33	0/34	Patch
Wang *et al.*[35]	6	—	0/76	—	0/76	Patch
		—	1.1/73	—	0/73	Gel (50 mg)
		—	1.2/78	—	1/78	Gel (100 mg)
Gooren[36]	120	—	NA	—	0/33	Oral
Gerstenbluth *et al.*[37]	58 (all > 36)	—	0.65/23	—	0/23	i.m.
Snyder *et al.*[38]	36		NA	0/54	1/54	Patch
Snyder *et al.*[39]	36	—	NA	—	0/18	Scr. patch
Wang *et al.*[40]	42	—	0.26/123	—	3/123	Gel
Schubert *et al.*[41]	37.5	—	NA	—	0/40	Nebido
Feneley *et al.*[42]	⩽15 years	—	NA	—	10/1500	Oral implants mesterolone
Rhoden *et al.*[43]	12	—	0.25(PIN–)	—	1/20(PIN+)	i.m.
		—	0.33(PIN+)		0/55(PIN–)	Gel

PSA E TESTOSTERONE-REPLACEMENT THERAPY (TRT) (J.Gore & J.Rajfer, Rev Urol 2004)

- Nell'ipogonadismo il volume prostatico è ridotto vs controlli sani e si normalizza con la TRT ai controlli age-matched
- Nell'ipogonadismo il PSA è ridotto vs controlli sani
- L'aumento del PSA negli ipogonadici in TRT è ~0.3 ng/ml/anno e raggiunge ~ 0.4 ng/ml/anno nell'anziano
- Necessità di monitoraggio clinico e del PSA se aumento >1.4 ng/ml any time o >0.4 ng/ml/anno
- I pazienti in terapia con finasteride hanno una riduzione di circa 2 volte del PSA

If the PSA rises

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Table 5. Changes in Prostate-Specific Antigen (PSA) Levels and Prostate Biopsy.

A number of approaches exist regarding when to consider prostate biopsy or urologic referral for men with normal PSA levels at base line. These include the following:

- Perform biopsy or refer to urologist if PSA rises above 4.0 ng/ml (several clinical trials).
- Perform biopsy or refer to urologist if PSA rises above 4.0 ng/ml or if it increases either by more than 1.5 ng/ml/yr or by more than 0.75 ng/ml/yr over 2 yr (Endocrine Society[60]).
- Perform biopsy or refer to urologist if PSA rises above 4.0 ng/ml, or if it rises either by more than 1.0 ng/ml in the first 6 mo of treatment or by more than 0.4 ng/ml/yr thereafter (Bhasin et al.[61]).
- Perform biopsy before initiation of testosterone-replacement therapy. Repeat biopsy for PSA increase of 1.0 ng/ml in any year. If PSA rises by 0.7–0.9 ng/ml, repeat PSA measurement in 3–6 mo and perform biopsy for any further increase (Morgentaler et al.[50]).

Risks of Testosterone-Replacement Therapy and Recommendations for Monitoring

N Engl J Med 2004;350:482-92.

Ernani Luis Rhoden, M.D., and Abraham Morgentaler, M.D.

TRT-HYPOGONADISM-PSA

Khera M et al. Curr Urol Rep 11: 393-99, 2010)

- n=461 pazienti ipogonadici suddivisi in base alla [T]
- [PSA] basali significativamente (=0.02) > nei pz con T >200 ng/dl (1.24 ng/ml) vs pz con T <200 ng/dl (0.88 ng/ml)
- TRT → dopo 6 mesi aumento significativo del PSA: 0.32 ng/ml nei pz con T ipogonadismo) ma non (-0.03 ng aturation model

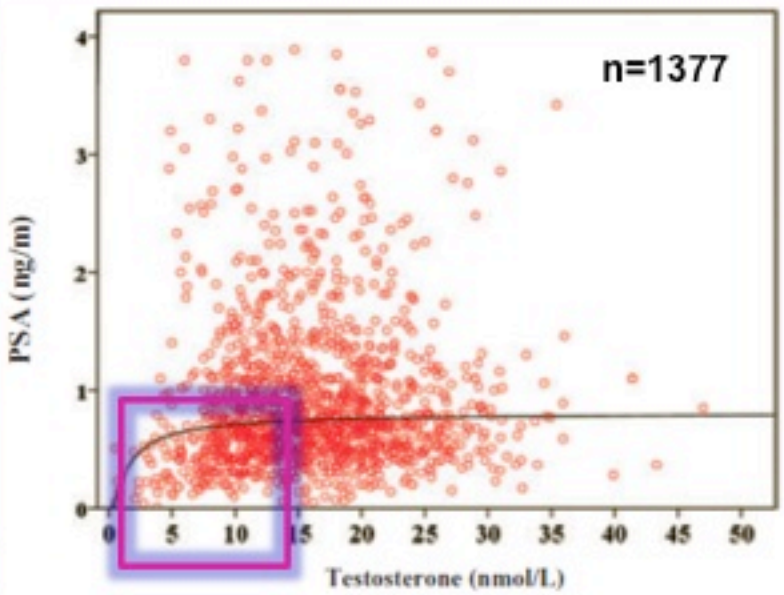

Figure 4 Relationship between testosterone and prostate-specific antigen levels as a scatter plot along with a best-fitting regression curve (calculated $R^2 = 0.034$).

The saturatio responds to the clinical thresh pogonadism

PSA is sensit at or below the near-severe nsensitive to T variation abov

Effect of Testosterone Replacement Therapy on Prostate Tissue in Men With Late-Onset Hypogonadism

A Randomized Controlled Trial

JAMA. 2006;296:2351-2361

Leonard S. Marks, MD
Norman A. Mazer, MD, PhD
Elahe Mostaghel, MD, PhD
David L. Hess, PhD
Frederick J. Dorey, PhD
Jonathan I. Epstein, MD
Robert W. Veltri, PhD
Danil V. Makarov, MD
Alan W. Partin, MD, PhD
David G. Bostwick, MD
Maria Luz Macairan, MD
Peter S. Nelson, MD

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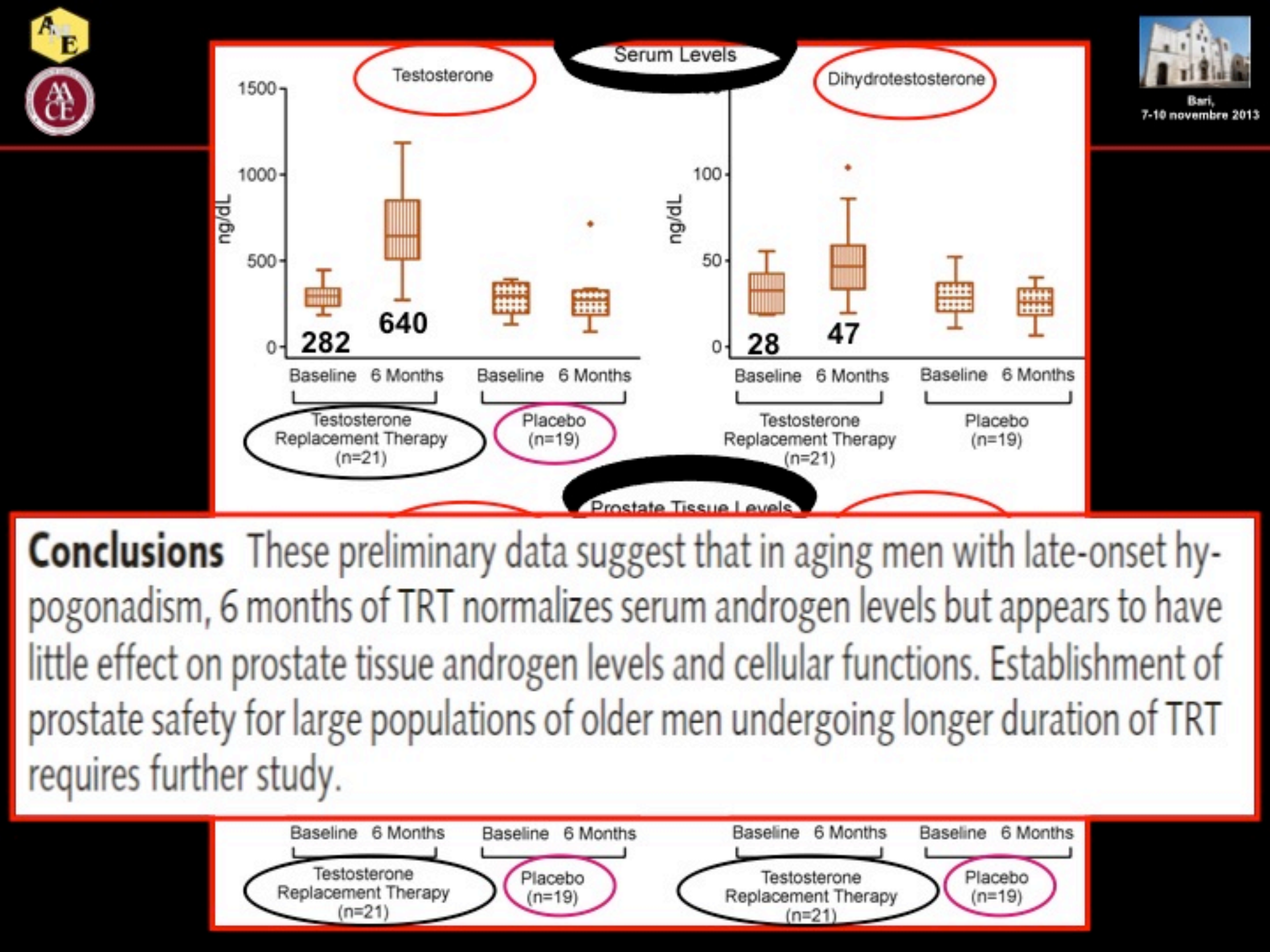
- **Metodi:**
- Randomizzato, doppio cieco
- 44 uomini (44-78 anni, mediana: 68 anni) con T plasmatico <3 ng/ml
- T enantato 150 mg i.m./2 sett o placebo per 6 mesi
- T, FT, DHT plasmatici
- Biopsie prostatiche e dosaggio tissutale di T, DHT (ng/g) ed espressione di Ki-67, AR

- **Risultati:**
- Nei pazienti trattati con T aumento significativo del T e del DHT nel plasma ma non nel tessuto prostatico
- Aumento (entro la norma) del PSA
- 4 casi di K prostata nel gruppo placebo, 2 nei T-trattati
- Non variazioni nella istologia prostatica, AR, biomarkers tissutali di proliferazione cellulare (Ki-67), angiogenesi (VEGF), PSA



Conclusions These preliminary data suggest that in aging men with late-onset hypogonadism, 6 months of TRT normalizes serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions. Establishment of prostate safety for large populations of older men undergoing longer duration of TRT requires further study.

Baseline 6 Months
Baseline 6 Months
Testosterone Replacement Therapy (n=21)
Placebo (n=19)
Baseline 6 Months
Baseline 6 Months
Testosterone Replacement Therapy (n=21)
Placebo (n=19)

Use of Testosterone Replacement Therapy in the United States and Its Effect on Subsequent Prostate Cancer Outcomes

Alan L. Kaplan and Jim C. Hu

OBJECTIVE To assess utilization trends and determine the effect of testosterone replacement therapy on outcomes in men who subsequently developed prostate cancer. **median age: 73 yrs**

METHODS We used linked Surveillance, Epidemiology, and End Results–Medicare data to identify 149,354 men diagnosed with prostate cancer from 1992 to 2007. Of those, 2,237 men (1.5%) underwent testosterone replacement therapy before their prostate cancer diagnosis. Propensity scoring methods were used to assess cancer-specific outcomes of testosterone replacement vs no replacement therapy.

RESULTS Testosterone replacement was associated with older age at cancer diagnosis, nonwhite race, and higher comorbidity ($P < .001$). No testosterone vs testosterone before the prostate cancer diagnosis was associated with higher grade (34% vs 30%, $P < .0001$) and more T4 (6.5% vs 4.3%, $P < .0001$) tumors. Mortality was decreased in men with ≥2 prostate-specific antigen (PSA) tests in the year before their cancer diagnosis. No significant difference was found between groups in overall survival, cancer-specific survival, or use of salvage androgen-deprivation therapy after initial treatment.

CONCLUSION Through our observational study design, we show that testosterone use was low throughout the study period. Testosterone use was not associated with aggressive prostate cancer and did not affect overall or disease-specific mortality. Although our findings support growing evidence that testosterone replacement is safe with respect to prostate cancer, confirmatory prospective studies are needed. UROLOGY 82: 321–326, 2013.

TESTOSTERONE REPLACEMENT THERAPY IN HYPOGONADAL MEN AT HIGH RISK FOR PROSTATE CANCER: RESULTS OF 1 YEAR OF TREATMENT IN MEN WITH PROSTATIC INTRAEPITHELIAL NEOPLASIA

ERNANI LUIS RHODEN AND ABRAHAM MORGENTALER*

THE JOURNAL OF UROLOGY®
Vol. 170, 2348–2351, December 2003

Materials and Methods: A total of 75 hypogonadal who completed 12 months of TRT were studied. All underwent prostate biopsy prior to initiating treatment. Of the men 55 had benign prostate biopsies (PIN−) and 20 had PIN without frank cancer (PIN+). All men with PIN underwent repeat biopsy to exclude cancer prior to the initiation of testosterone treatment. Prostate specific antigen (PSA), and total and free testosterone were determined prior to treatment and at 1 year. Repeat biopsy was performed for a change noted on digital rectal examination or for a PSA increase of 1 ng/l or greater.

Results: PSA was similar at baseline in men with and without PIN (1.49 ± 1.1 and 1.53 ± 1.6 ng/dl, $p > 0.05$) and after 12 months of TRT (1.82 ± 1.1 and 1.78 ± 1.6 ng/dl, respectively, $p > 0.05$). A slight, similar increase in mean PSA was noted in the PIN− and PIN+ groups (0.25 ± 0.6 and 0.33 ± 0.6 ng/dl, $p > 0.05$). One man in the PIN+ group had cancer after biopsy was performed due to abnormal digital rectal examination. Four additional men in the PIN− group and 2 in the PIN+ group underwent re-biopsy for elevated PSA and none had cancer. No differences were noted between the PIN− and PIN+ groups with regard to total and free testosterone at baseline and at 1 year ($p = 0.267$).

Conclusions: After 1 year of TRT men with PIN do not have a greater increase in PSA or a significantly increased risk of cancer than men without PIN. These results indicate that TRT is not contraindicated in men with a history of PIN.

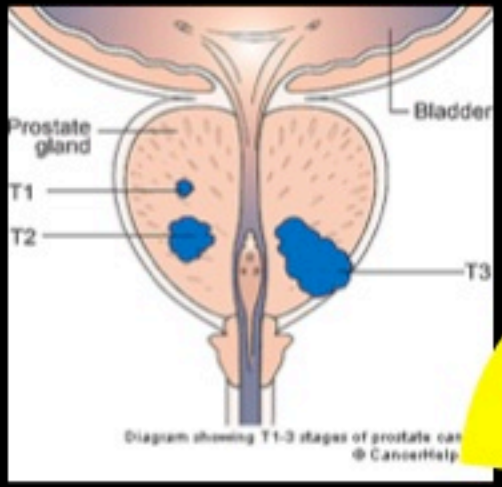
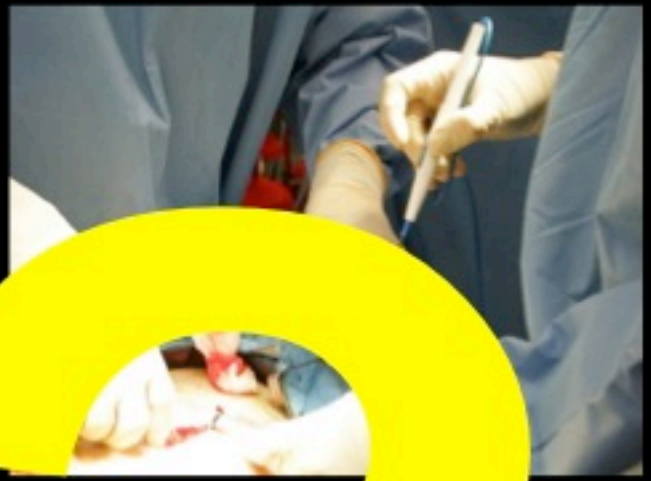
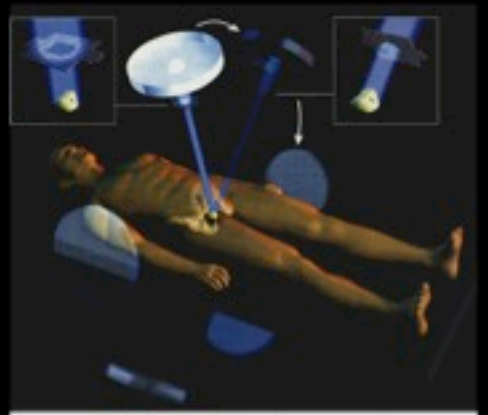


Diagram showing T1-3 stages of prostate can
© CancerHelp





Radioterapia a fasci esterni

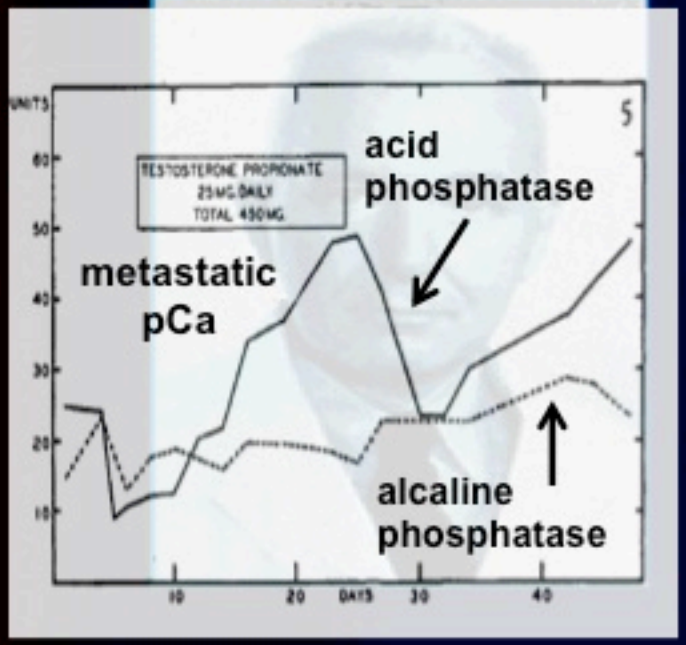
External beam radiotherapy

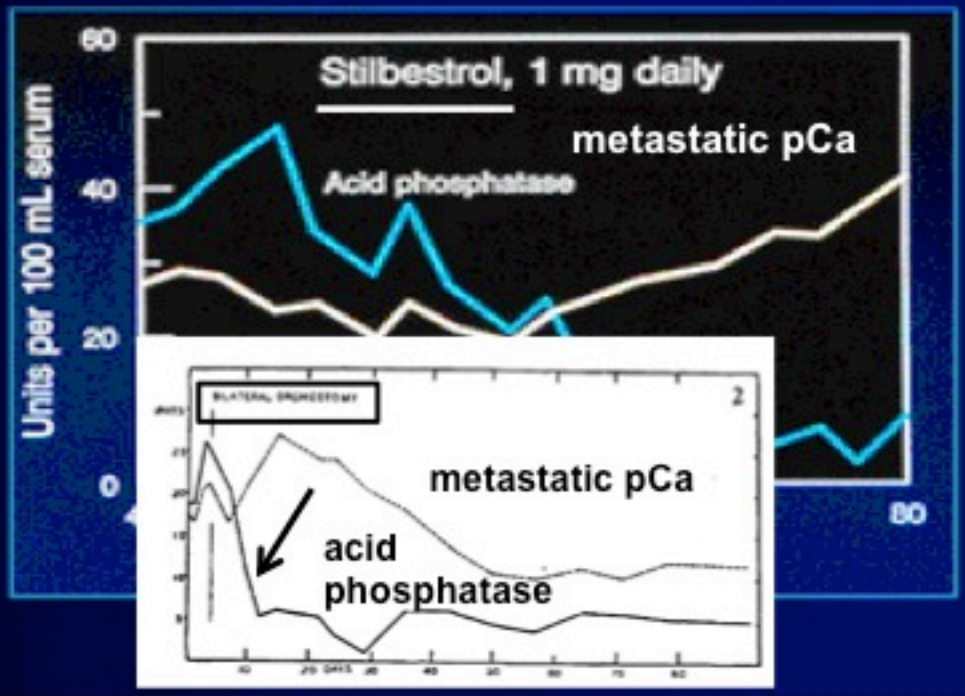
8 patients with advanced pCa: T administration in 3 pts, data on 2 pts (one previously castrated)

Charles Huggins and Hormonal Treatment of Prostate Cancer

Nobel Prize 1966

Huggins C and Hodges CV: Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941; 1: 293.





In 1941 Huggins and Hodges reported that **marked reductions in T by castration or estrogen treatment caused metastatic pCA to regress, and administration of exogenous T caused pCA to grow.** Remarkably, this latter conclusion was based **on results from only one patient.** **No pCa progression after T administration was seen in men who were hormonally intact.** Subsequent reports revealed no pCA progression with T administration, and some men even experienced subjective improvement.

Turning Conventional Wisdom Upside-Down

Abraham Morgentaler, MD[1,2]

Cancer September 1, 2011

tion of historical studies. Whereas it was well-known that several studies showed that T administration produced rapid cancer progression in androgen-deprived men with metastatic PCa, those very same studies revealed that T administration in hormonally intact men produced no negative effects.[1] Animal studies and PCa cell lines demonstrated a dose-response

concentrations elicited no further growth.[8] The resolution of the paradox is that there is a limit to the ability of androgens to stimulate PCa growth, and this limit is achieved at low androgen concentrations.[8]

Circumstantial evidence is a very tricky thing, answered (Sherlock) Holmes thoughtfully. It may seem to point very straight to one thing, but if you shift your own point of view a little, you may find it pointing in an equally uncompromising manner to something entirely different. Sir Arthur Conan Doyle. The Boscombe Valley Mystery.

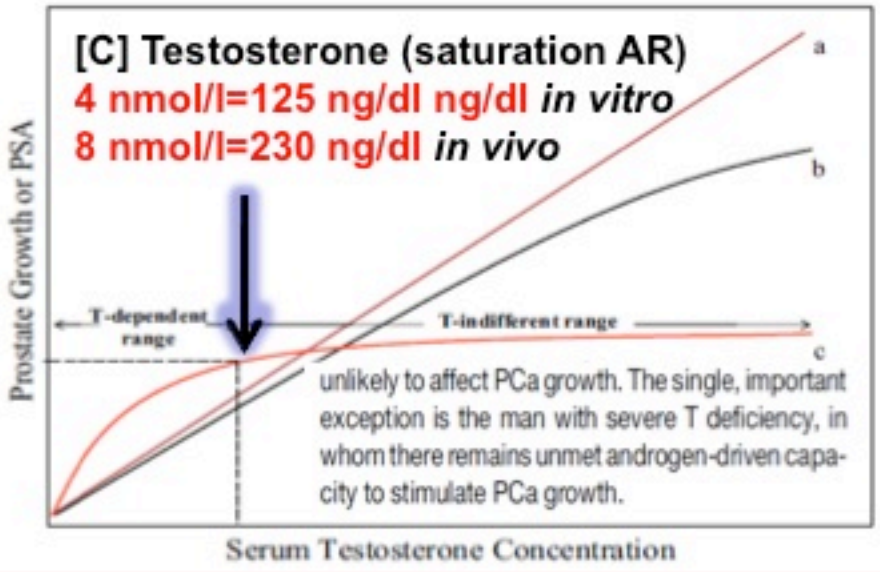
Testosterone Therapy in Men With Prostate Cancer: Scientific and Ethical Considerations

Abraham Morgentaler*,†

THE JOURNAL OF UROLOGY® Vol. 189, S26-S33, January 2013

Bari,
7-10 novembre 2013

Results: The prohibition against the use of testosterone therapy in men with a history of prostate cancer is based on a model that assumes the androgen sensitivity of prostate cancer extends throughout the range of testosterone concentrations. Although it is clear that prostate cancer is exquisitely sensitive to changes in serum testosterone at low concentrations, there is considerable evidence that prostate cancer growth becomes androgen indifferent at higher concentrations. The most likely mechanism for this loss of androgen sensitivity at higher testosterone concentrations is the finite capacity of the androgen receptor to bind androgen. This saturation model explains why



Goodbye Androgen Hypothesis, Hello Saturation Model

Abraham Morgentaler*

EUROPEAN UROLOGY 62 (2012) 765–767

0022-5347/98/1592-0441$03.00/0
THE JOURNAL OF UROLOGY

Vol. 159, 441–443, February 1998
Printed in U.S.A.

EFFECT OF EXOGENOUS TESTOSTERONE ON PROSTATE VOLUME, SERUM AND SEMEN PROSTATE SPECIFIC ANTIGEN LEVELS IN HEALTHY YOUNG MEN

CHRISTOPHER S. COOPER, PAUL J. PERRY, AMY E. T. SPARKS, JOHN H. MACINDOE, WILLIAM R. YATES AND RICHARD D. WILLIAMS

Purpose: We investigate and define the effects of exogenous testosterone on the normal prostate.

Materials and Methods: A total of 31 healthy volunteers 21 to 39 years old were randomized to receive either 100, 250 or 500 mg. testosterone via intramuscular injection once a week for 15 weeks. Baseline measurements of serum testosterone, free testosterone and prostate specific antigen (PSA) were taken at week 1. Semen samples were also collected for PSA content and prostate volumes were determined by transrectal ultrasound before testosterone injection. Blood was then drawn every other week before each testosterone injection for the 15 weeks, every other week thereafter until week 28 and again at week 40. After the first 15 weeks semen samples were again collected, and prostate volumes were determined by repeat transrectal ultrasound.

Results: Free and total serum testosterone levels increased significantly in the 250 and 500 mg. dose groups. No significant change occurred in the prostate volume or serum PSA levels at any dose of exogenous testosterone. Total semen PSA levels decreased following administration of testosterone but did not reach statistical significance.

Testosterone up to 1138-1994 ng/dl

Conclusions: Despite significant elevations in serum total and free testosterone, healthy young men do not demonstrate increased serum or semen PSA levels, or increased prostate volume in response to exogenous testosterone injections.

Editorial – referring to the article published on pp. 696–701 of this issue

Testosterone Deficiency and Prostate Cancer: Emerging Recognition of an Important and Troubling Relationship

Abraham Morgentaler *

Cause or effect ?

EUROPEAN UROLOGY 52 (2007) 623–625

Causa: ridotti livelli di T sembrano correlarsi a

- 1) sviluppo di tumore prostatico
- 2) aumentata aggressività (> Gleason) per aumento:

  i) espressione del R androgeni ii) attivazione di growth factors stimolatori iii) densità vascolare intratumorale
- 3) aumentata possibilità di recidiva dopo prostatectomia

Effetto:

- Tumore prostatico → aumentata produzione di inibina-α → inibizione dell'asse ipotalamo-ipofisi-gonadi → ↓ LH, FSH → ↓ T

Testosterone Replacement Therapy in Patients with Prostate Cancer After Radical Prostatectomy

THE JOURNAL OF UROLOGY® Vol. 190, 639-644, August 2013

Alexander W. Pastuszak,* Amy M. Pearlman,* Win Shun Lai,* Guilherme Godoy,* Kumaran Sathyamoorthy,* Joceline S. Liu,* Brian J. Miles,* Larry I. Lipshultz† and Mohit Khera‡,§

Materials and Methods: We performed a review of 103 hypogonadal men with prostate cancer treated with testosterone after prostatectomy (treatment group) and 49 nonhypogonadal men with cancer treated with prostatectomy (reference table 1B). Men in the treatment group were started on TRT after RP with a median interval of 12.3 months (IQR 7.8–16.8). Pretreatment serum hor-

Results: Median (IQR) patient age in the treatment group was 61.0 years (55.0–67.0), and initial laboratory results included testosterone 261.0 ng/dl (213.0–302.0), prostate specific antigen 0.004 ng/ml (0.002–0.007), hemoglobin 14.7 gm/dl (13.3–15.5) and hematocrit 45.2% (40.4–46.1). Median followup was 27.5 months, at which time a significant increase in testosterone was observed in the treatment group. A significant increase in prostate specific antigen was observed in the high risk and nonhigh risk treatment groups with no increase in the reference group. Overall 4 and 8 cases of cancer recurrence were observed in treatment and reference groups, respectively.

Conclusions: Thus, testosterone therapy is effective and, while followed by an increase in prostate specific antigen, does not appear to increase cancer recurrence rates, even in men with high risk prostate cancer. However, given the

International Journal of Impotence Research (2013) 25, 24–28

www.nature.com/ijir

ORIGINAL ARTICLE

Testosterone replacement therapy in the setting of prostate cancer treated with radiation

AW Pastuszak[1,4], AM Pearlman[2,4], G Godoy[1], BJ Miles[3], LI Lipshultz[1] and M Khera[1]

for prostate cancer (CaP), particularly those who have received radiation therapy. We performed retrospective review of 13 hypogonadal men with CaP, treated with brachytherapy or external beam radiotherapy who were subsequently treated with testosterone (T) between 2006 and 2011. Serum T, free T (FT), estrogen (E), sex hormone-binding globulin (SHBG), prostate-specific

median time to initiation of TRT after radiation treatment was 13.5 months

Median (interquartile range) age at TRT initiation was 68.0 (62.0–77.0) years, initial T 178.0 (88.0–263.5) ng dl^{-1}, FT 10.1 (5.7–15.0) pg ml^{-1} and PSA 0.30 (0.06–0.95) ng ml^{-1}. Median follow-up after TRT initiation was 29.7 months (range 2.3–67.3 months). At median follow-up, a significant increase in mean T (368.0 (281.3–591.0) ng dl^{-1}, $P=0.012$) and SHBG were observed, with no significant increases in Hgb, Hct, E, FT, or PSA (0.66 (0.16–1.35) ng ml^{-1}, $P=0.345$). No significant increases in PSA or CaP recurrences were observed at any follow-up interval. TRT in the setting of CaP after treatment with radiation therapy results in a rise

recurrences were observed at any follow-up interval. TRT in the setting of CaP after treatment with radiation therapy results in a rise in serum T levels and improvement in hypogonadal symptoms without evidence of CaP recurrence or progression.

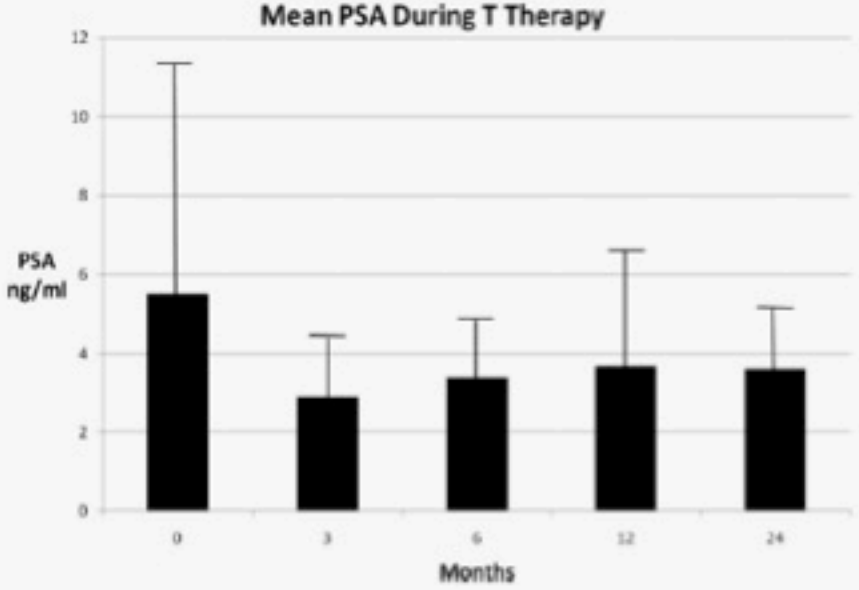
Testosterone Therapy in Men With Untreated Prostate Cancer

Abraham Morgentaler,*, † Larry I. Lipshultz,‡ Richard Bennett,§ Michael Sweeney,§ Desiderio Avila, Jr.§ and Mohit Khera‖

THE JOURNAL OF UROLOGY® Vol. 185, 1256-1261, April 2011

Materials and Methods: We report the results of prostate biopsies, serum prostate specific antigen and prostate volume in symptomatic testosterone deficient cases receiving testosterone therapy while undergoing active surveillance for prostate cancer.

Results: A total of 13 symptomatic testosterone deficient men with untreated prostate cancer re .5 years (range 1.0 to 8.1). Mean age sy was 6 in 12 men and 7 in 1. Mean s reased from 238 to 664 ng/dl (p <0.0 hange with testosterone therapy (5 ostate volume was unchanged. Mean r was found in 54% of followup biopsi g, and subsequent biopsies in 1 and no progression. No local prostate can rved.



PSA values during testosterone therapy

Conclusions: Test ostate cancer was not associated wit to medium term. These results are consistent with the saturation model, ie maximal prostate cancer growth is achieved at low androgen concentrations. The longstanding

Giovanni Corona[a,b], Mario Maggi[a,*]

EUROPEAN UROLOGY 63 (2013) 579–584

Bari,
7-10 novembre 2013

PCa subjects. However, it should be recognized that the number of reported cases is still small and heterogeneous. In the absence of randomized controlled trials, the concept of using TRT for PCa survivors is debatable. Accordingly, current recommendations suggest limiting TRT to symptomatic hypogonadal men successfully treated for PCa, after a prudent interval, although the length of that interval is not specified [4].

Is Testosterone a Friend or a Foe of the Prostate?

J Sex Med 2011;8:946–955

Emmanuele A. Jannini, MD,* Giovanni L. Gravina, MD, PhD,* Abraham Mortengaler, MD,†
Alvaro Morales, MD,‡ Luca Incrocci, MD, PhD,§ and Wayne J.G. Hellstrom, MD, FACS¶

available data suggest to the expert in sexual medicine that TTh can be cautiously considered in selected hypogonadal men previously treated for curative intent of low-risk PCa and without evidence of active disease. Jannini EA,

Should Hypogonadal Men With Prostate Cancer Receive Testosterone?

Abraham Morgentaler
Men's Health Boston
Harvard Medical School
Boston, Massachusetts

THE JOURNAL OF UROLOGY® Vol. 184, 1257-1260, October 2010

Bari,
7-10 novembre 2013

- **SI:**

- La capacità degli androgeni nello stimolare la crescita della prostata (e quindi anche del tumore prostatico) è limitata: **max binding in vitro del R degli androgeni: 4 nmol=125 ng/dl=saturazione** → la maggior parte degli uomini, anche quelli ipogonadici, hanno concentrazioni di T superiori a questo livello

- I livelli plasmatici di PSA non correlano con quelli di T

- Il tumore prostatico si manifesta in una fascia di età in cui i livelli di T si riducono e non nella giovane età in cui vi è il picco di T

- Dosi sovrafisiologiche di T per 10 mesi in volontari sani non modificano i livelli del PSA e il volume prostatico.

Should Hypogonadal Men With Prostate Cancer Receive Testosterone?

THE JOURNAL OF UROLOGY®
Vol. 184, 1257-1260, October 2010

Alvaro Morales
Centre for Applied Urological Research
Queen's University
Kingston, Canada

Bari,
7-10 novembre 2013

- **NO: saturation model** attraente ma completamente non provato e basato su modelli *in vitro ed* animali. Le osservazioni retrospettive (mancanza di effetti negativi del T in pz con tumore prostatico) erano inficiate dal fatto che il T era somministrato in pz trattati con CT, RT e P^{32}. Inoltre non fornisce standard numerici per i parametri più rilevanti (PSA, T, volume prostatico).

Una situazione completamente differente riguarda uomini con ipogonadismo sintomatico ed una storia di tumore prostatico trattato con successo

- **Dopo chirurgia:** questi pazienti, dopo un prudente periodo di sorveglianza (quanto lungo ? → finchè il PSA diventa indosabile), possono ricevere TRT (molecole a breve emivita: gel/orale)
- **Dopo RT:** questi pazienti, quando è stato raggiunto un nadir stabile nei livelli di PSA (>6 mesi post-RT), possono ricevere TRT

Effect of testosterone administration to men with prostate cancer is unpredictable: a word of caution and suggestions for a registry

Alvaro Morales

BJUI
2011 BJU INTERNATIONAL | 107, 1369–1373

biopsy: PCa
T < 300 ng/dl

FIG. 1. Changes in PSA levels (blue line) in a patient with PCa receiving TTh (red line) over 4 years. After an initial increase the levels have remained stable on testosterone supplementation.

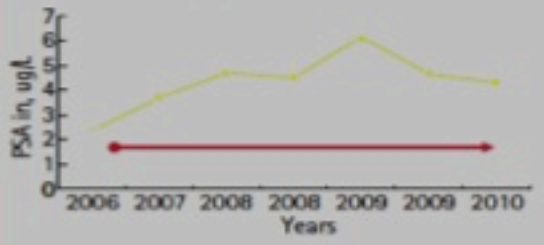
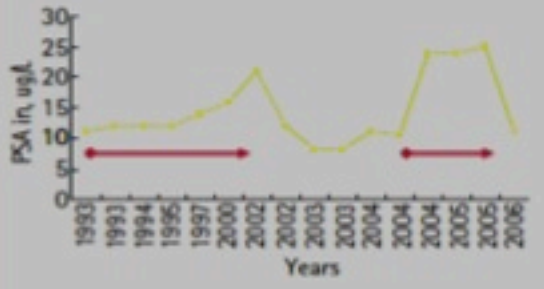


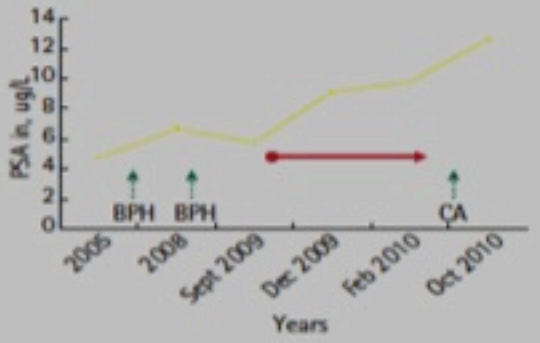
FIG. 2. Another patient in whom, after a stable period, there was an increase in PSA values with return to the pre-treatment nadir upon interruption of TTh. Re-initiation of TTh caused a rapid increase in PSA followed by a precipitous decline after TTh was discontinued.



would be reason for discontinuation of TTh, while a return to pretreatment PSA levels would permit re-initiation of TTh.

FIG. 3. Another patient in whom the onset of TTh resulted in a prompt and marked increase in PSA levels. This patient opted for definitive surgery with good early biochemical results.

FIG. 4. In this patient a sub-clinical PCa was discovered. Two previous biopsies (arrows) were negative for PCa. After TTh the values of PSA increased promptly, leading to a new biopsy showing the presence of PCa.



Use of Testosterone Replacement Therapy in Patients with Prostate Cancer

Curr Urol Rep (2011) 12:223–228

Tanya B. Dorff · Nicholas J. Vogelzang

Vol. 184, 1257-1260, October 2010

Bari,
7-10 novembre 2013

TRT if «no residual disease» exists:
PSA <0.2 ng/ml after prostatectomy
PSA <2 ng/ml after RT or brachytherapy

> 300 pts treated with TRT after treatment (RP, RT, brachytherapy) for prostate cancer→ recurrence ~1%

Table 2 - Criteria to consider before initiating testosterone therapy in men with history of treated prostate cancer

The clinical picture is consistent with a diagnosis of testosterone deficiency.
The patient must understand that safety data are limited and that there is an unknown degree of risk of PCa progression or recurrence.
The patient must be willing and able to provide informed consent.
No medical contraindications to testosterone therapy (eg, erythrocytosis) exist.
There is an undetectable or stable PSA level.
Clinicians must be prepared for the possibility of PCa recurrence or progression, which will occur in some men regardless of testosterone therapy but may be attributed to testosterone therapy by patients, family, or other clinicians.
Use testosterone therapy with extreme caution in men at high risk for PCa recurrence or progression.
Do not recommend testosterone therapy for men currently receiving any form of ADT.

REVIEW

Could Testosterone Have a Therapeutic Role in Prostate Cancer?

UROLOGY JOURNAL Vol. 10 | No. 1 | Winter 2013

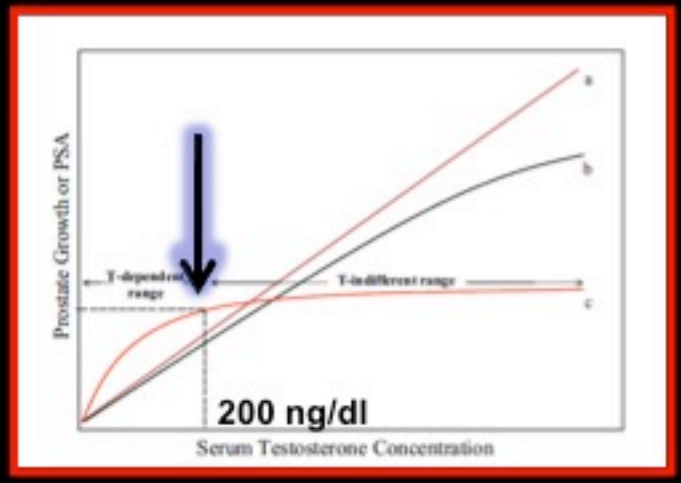
Konstantinos Stamatiou, Nikolaos Pierris

Results: The androge and progression of PCa. The latter is ass and more precisely, with its conversion f oliferation and sur-vival of prostatic cell t conversion is due to functional changes ormal genomic, but also novel non-genon nal prostatic epithe-lial cells. Thus, treatr se, all center on the regulation and manip owever offer strong evidence of a direct apoptotic action induced by activation of the membrane androgen receptor by testosterone-albumin conjugates.

CONCLUSIONI (I)

Bari,
7-10 novembre 2013

- Il R degli androgeni a livello prostatico possiede una limitata capacità di essere attivato e nel range di [C] di T ridotte (fino a 120-200 ng/dl) oltre le quali esiste un effetto plateau (saturazione) senza ulteriore stimolazione della crescita prostatica e del PSA



- Ridotti livelli plasmatici di T (causa o effetto ?) sembrano correlarsi ad una maggiore aggressività (> Gleason score) del tumore prostatico secondaria a i) modificazioni del R androgenico ii) attivazione di growth factors stimolatori iii) aumento della densità vascolare

- La TRT nell'ipogonadismo sintomatico non induce lo sviluppo di un tumore della prostata ma aumenta il PSA generalmente entro il range normale

CONCLUSIONI (II)

Bari,
7-10 novembre 2013

- E' necessaria, tuttavia, una accurata selezione dei pazienti con ipogonadismo sintomatico che possano beneficiare della TRT che includa una valutazione iniziale e durante il follow-up del PSA (e del volume prostatico)

- Una particolare attenzione va riservata ai pazienti con severo ipogonadismo, i.e. con T <150 ng/dl, per le caratteristiche proprie di attivazione del recettore androgenico a livello prostatico a queste concentrazioni di testosterone dopo avvio di TRT

- In assenza di trial clinici randomizzati, la TRT (molecole a breve emivita) in pazienti con ipogonadismo sintomatico operati o radio-trattati con successo per tumore della prostata può essere iniziata dopo un prudente periodo di sorveglianza clinica e biochimica (PSA). I livelli plasmatici di T in terapia vanno mantenuti nel range medio-basso della norma.