NUNOTOMADA
UROLOGIA & CIRURGIA RECONSTRUTIVA

TESTOSTERONE REPLACEMENT THERAPY. **WHAT IS THE REAL RISK?** WHAT TO DO IN **PROSTATE CANCER ?**

UROUP MADRID 2014

TESTOSTERONE REPLACEMENT THERAPY (TRT)

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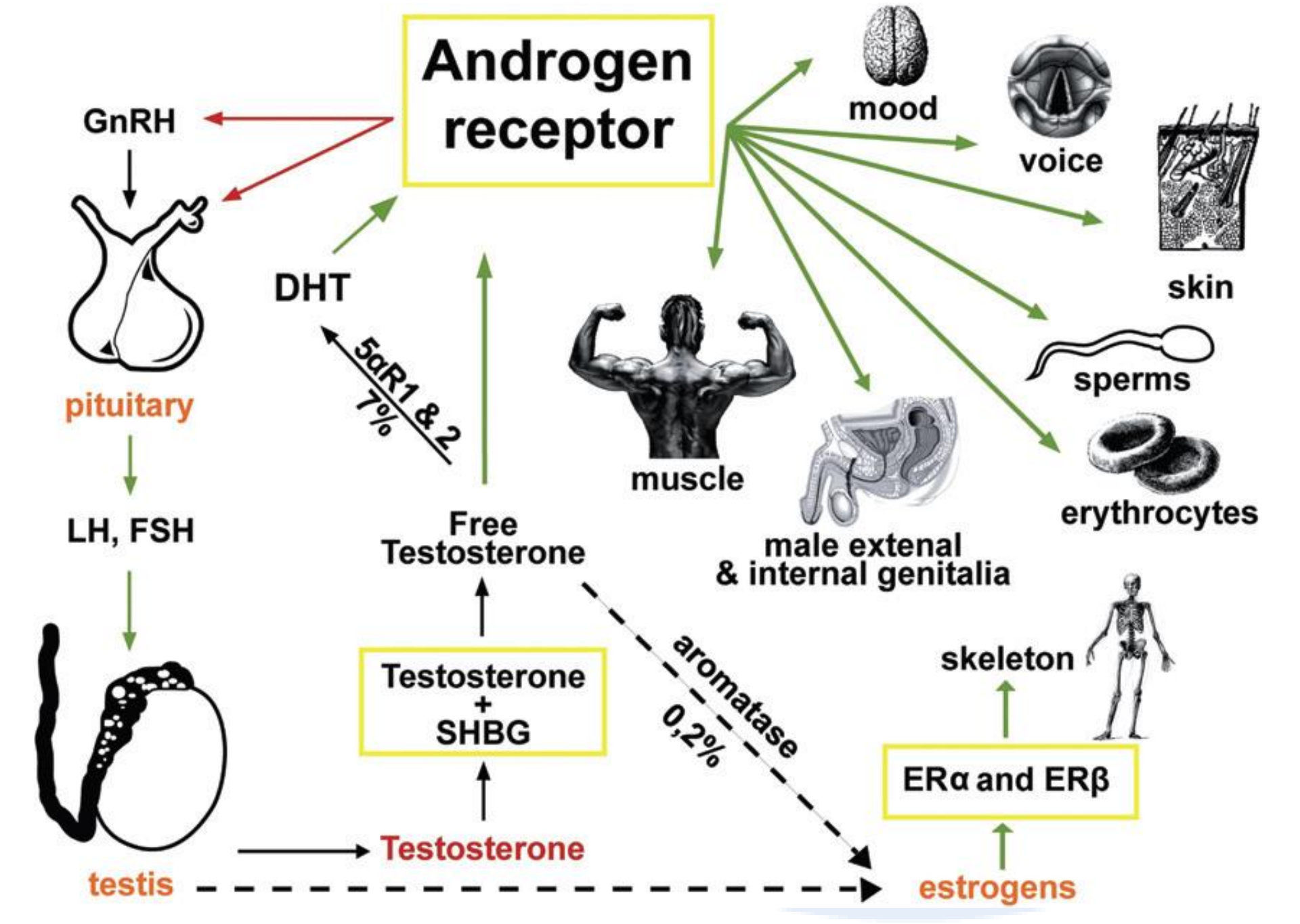
ESGURS



J Sex Med 2013;10:245-84.

Testosterone: Target Organs

brain
libido, aggression

skin
hair growth, balding,
sebum production

muscle
increase in strength
and volume

liver
synthesis of serum proteins

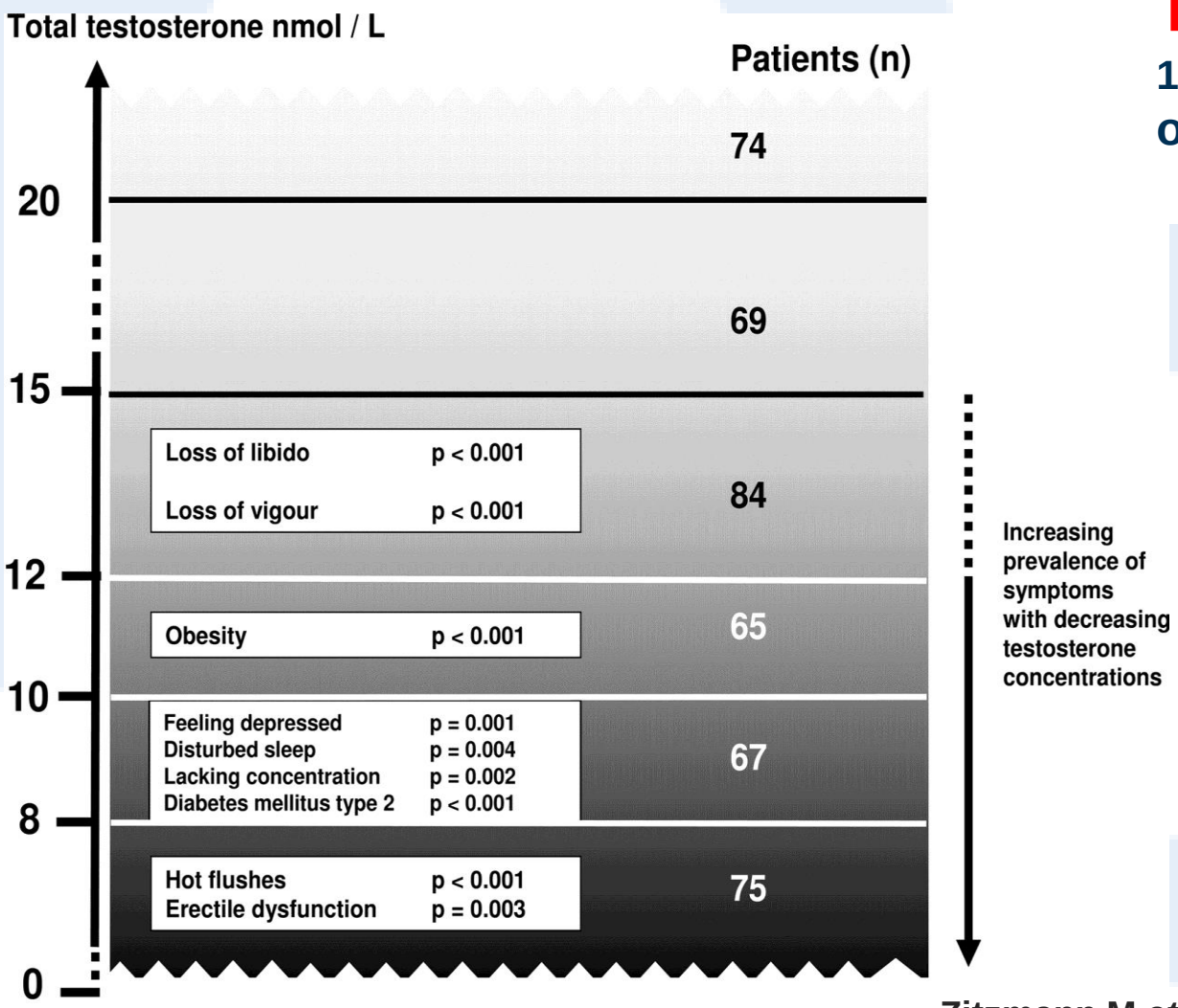
kidney
stimulation of
erythropoietin production

male sexual organs
penile growth
spermatogenesis
prostate growth and function

bone marrow
stimulation of stem cells

bone
accelerated linear growth
closure of epiphyses

Overview of symptom-specific concentrations of TT levels below which the prevalence of the respective symptom starts to increase



TDS

17%- 39 % middle- and older-aged men

Zitzmann M *et al*. J Clin Endocrinol Metab 2006

TRT

TDS

ED

¿?

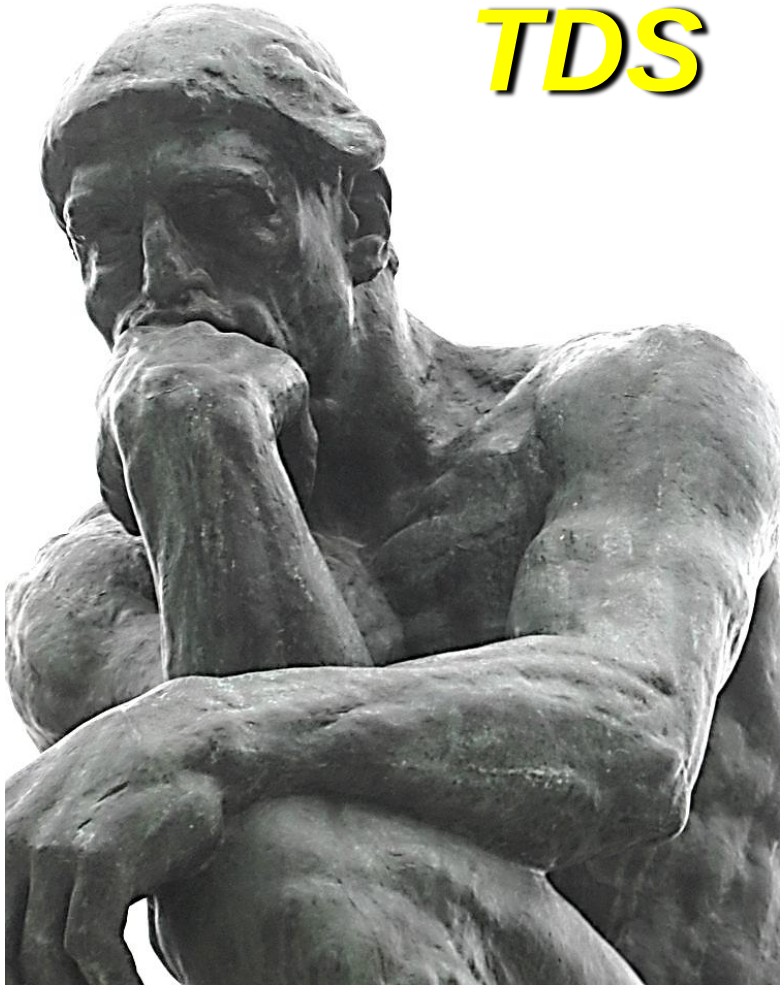
¿?

Prostate cancer

Overall mortality

¿?

¿?



CV mortality

¿?

ED Treatment

Testosterone supplementation

in *Testosterone Deficiency Syndrome (TDS)* according to Aging Male (ISSAM) guidelines

- **Many men who do not respond to PDE5-I present low Testosterone**
- **Testosterone replacement converts more than 50% of these cases in PDE5-I responders**

Improved well being? Endothelial function? PDI5 and NOS expression?

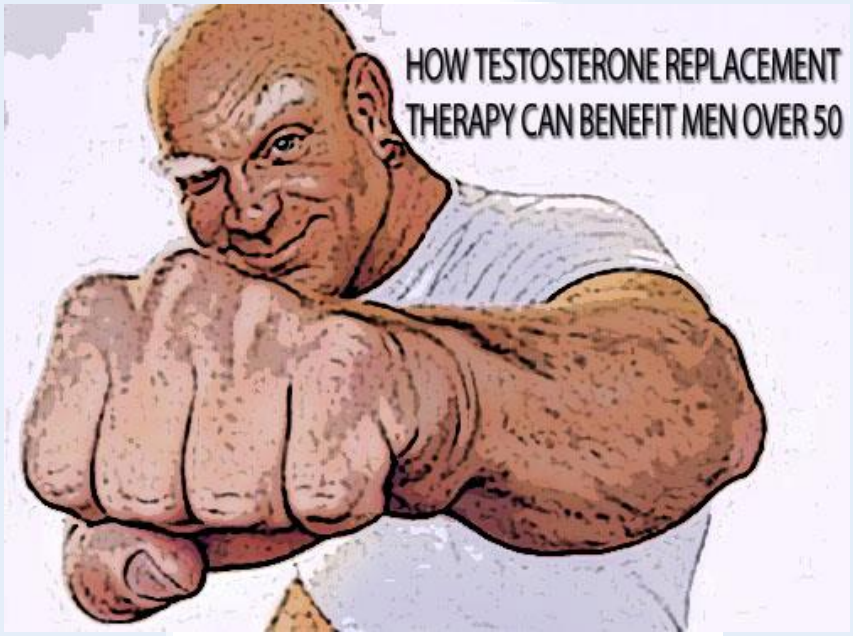
Direct effects on Corpus cavernosum structure and function?

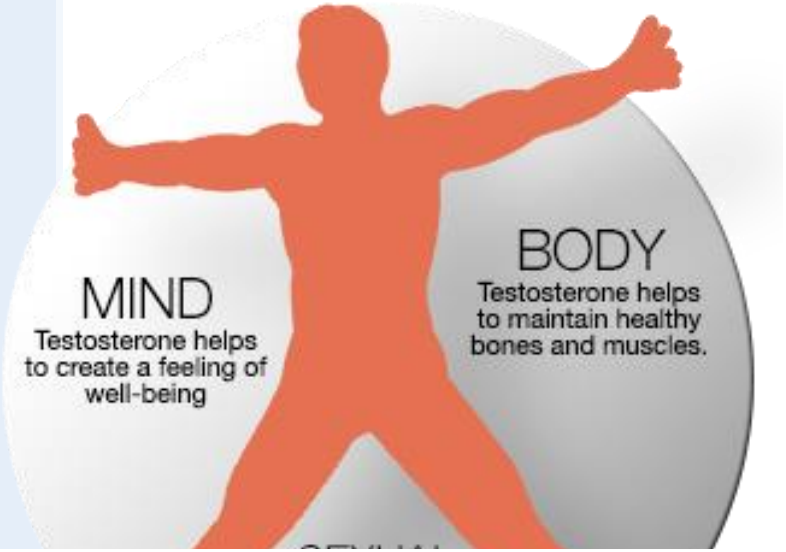
Tomada I *et al*. Age 2013

Authors	No. of subjects/hypogonadism	Sildenafil response at baseline	Overall efficacy/adverse events
Aversa et al. [9]	20/no	Failure	80%/none
Kalinchenko et al. [25]	120/yes	Failure	70%/none
Shabsigh et al. [10]	75/yes	Failure	70%/not evaluated
Chatterjee et al. [36]	12/yes	Not evaluated	100%/none
Shamloul et al. [26]	40/no	Failure/present	Improved/none
Greenstein et al. [37]	49/yes	Not evaluated	63%/18% skin irritation
Hwang et al. [27]	32/yes	Failure	57%/none
Rosenthal et al. [28]	24/yes	Failure	92%/1% headache
Tas et al. [38]	23/yes	Not evaluated	34%/none

Greco EA *et al*. Eur Urol 2006

TRT

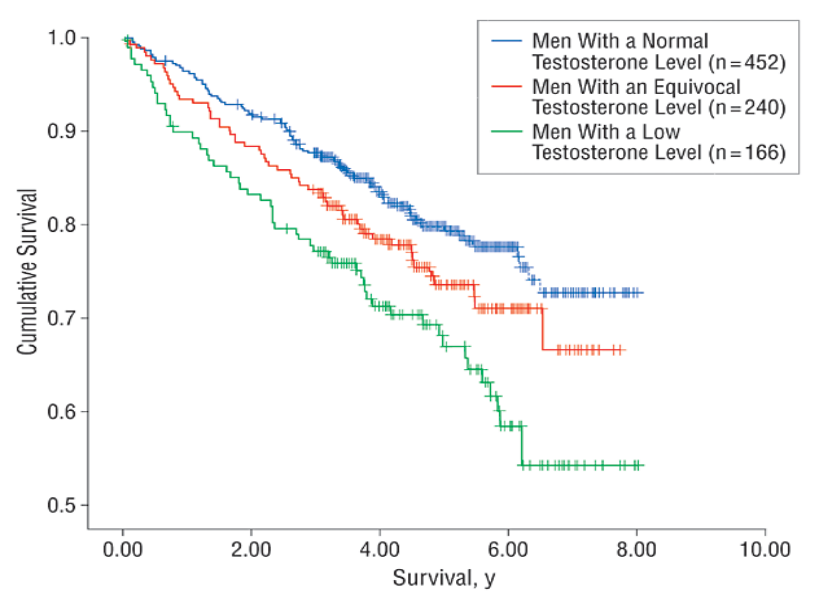


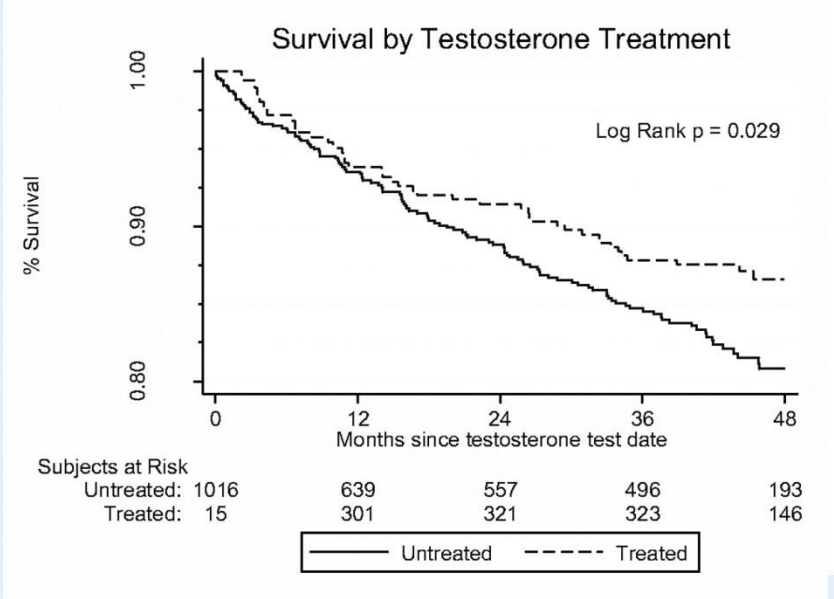


Benefits	Potential risks
Maintains secondary sexual characteristics	Acne, oily skin
Improves libido and erectile dysfunction	Gynecomastia
Increases lean/muscle mass and strength	Weight gain/fluid retention at initiation of treatment
Decreases weight, body fat and visceral obesity	Lipids (decrease in HDL)
Increases bone mass	Prostate (benign prostatic hyperplasia and prostate cancer)*
Improves energy and vitality	Increased hemoglobin, hematocrit and red cell count
Improves mood and depression*	Sleep apnea*
Coronary vasodilatation, reduces cardiovascular disease risk*	Increased cardiovascular adverse effects*

Expert Opin Pharmacother 2014;15:1247-64

Low serum testosterone and mortality in Male Veterans



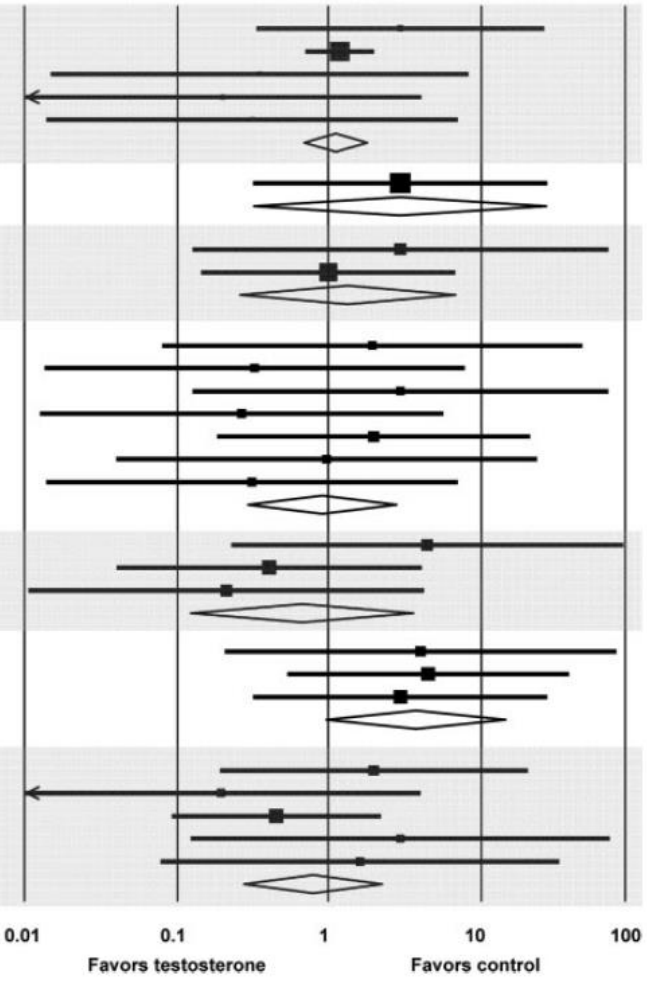


Unadjusted Kaplan-Meier survival curves for the 3 testosterone level groups. Men with low and equivocal testosterone levels had a significantly shorter survival than men with normal testosterone levels (P = 0.001).

Shores *et al*. JAMA 2006
Shores *et al*. J Clin Endocrinol Metab 2012

TRT outcomes

	RR	Lower limit	Upper limit	Events / Total testosterone	Events / Total control
Brockenbrough, 2006	3.00	0.34	26.56	3 / 21	1 / 21
Copenhagen Study Group, 1986	1.19	0.72	1.98	33 / 134	18 / 87
Malkin, 2006	0.35	0.01	8.35	0 / 37	1 / 39
Snyder 1999, 2001	0.20	0.01	4.07	0 / 54	2 / 54
Svartberg, 2004	0.31	0.01	7.09	0 / 15	1 / 14
All cause mortality	**1.12**	**0.70**	**1.81**		
Snyder 1999, 2001	3.00	0.32	27.94	3 / 54	1 / 54
Arrhythmia	**3.00**	**0.32**	**27.94**		
English, 2000	3.00	0.13	70.30	1 / 25	0 / 25
Snyder 1999, 2001	1.00	0.15	6.84	2 / 54	2 / 54
Coronary bypass surgery	**1.35**	**0.26**	**6.96**		
Copenhagen Study Group, 1986	1.96	0.08	47.47	1 / 134	0 / 87
Emmelot-Vonk, 2008	0.32	0.01	7.88	0 / 113	1 / 110
English, 2000	3.00	0.13	70.30	1 / 25	0 / 25
Morley, 1993	0.27	0.01	5.70	0 / 9	1 / 7
Snyder 1999, 2001	2.00	0.19	21.41	2 / 54	1 / 54
Steidle, 2003	0.97	0.04	23.72	1 / 307	0 / 99
Svartberg, 2004	0.31	0.01	7.09	0 / 15	1 / 14
Myocardial infarction	**0.91**	**0.29**	**2.82**		
Chiang, 2007	4.52	0.23	88.38	2 / 20	0 / 18
Harman, 2003	0.40	0.04	4.09	1 / 21	2 / 17
Malkin, 2006	0.21	0.01	4.24	0 / 37	2 / 39
Newly diagnosed diabetes	**0.67**	**0.12**	**3.67**		
Harman, 2003	4.09	0.21	79.88	2 / 21	0 / 17
Nair, 2006	4.59	0.55	38.63	4 / 27	1 / 31
Snyder 1999, 2001	3.00	0.32	27.94	3 / 54	1 / 54
Prostate Biopsy	**3.82**	**0.97**	**15.00**		
Amory, 2004 & Page, 2005	2.00	0.19	20.61	2 / 24	1 / 24
Emmelot-Vonk, 2008	0.19	0.01	4.01	0 / 113	2 / 110
Marks, 2006	0.45	0.09	2.20	2 / 21	4 / 19
Snyder 1999, 2001	3.00	0.12	72.05	1 / 54	0 / 54
Steidle, 2003	1.62	0.08	33.53	2 / 307	0 / 99
Prostate cancer	**0.79**	**0.28**	**2.28**		



Fernández-Balsells MM *et al*. J Clin Endocrinol Metab 2010

After more than 30y, recent fears concerning CV security emerge …

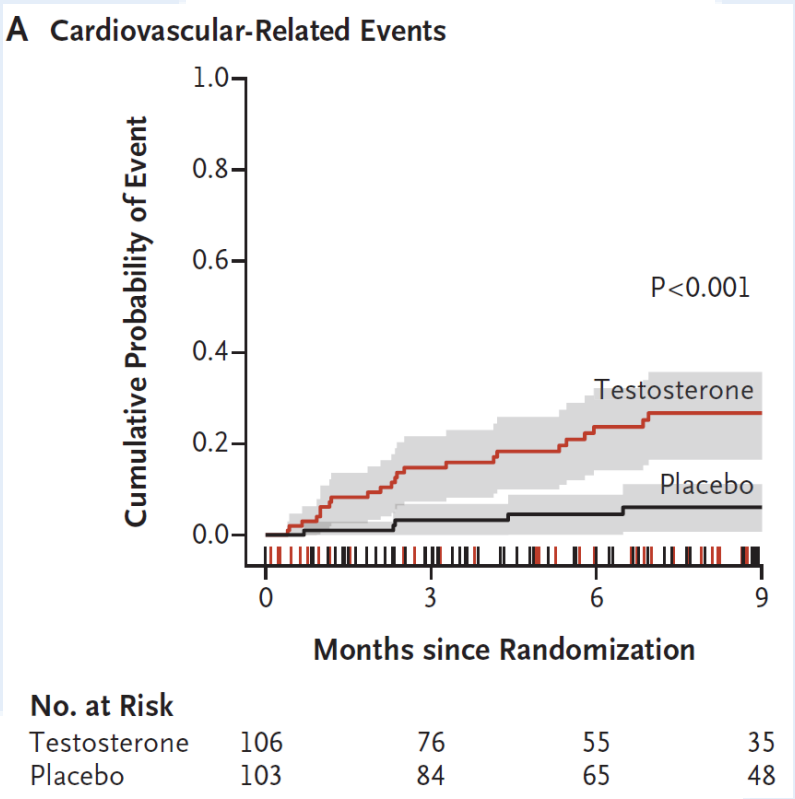


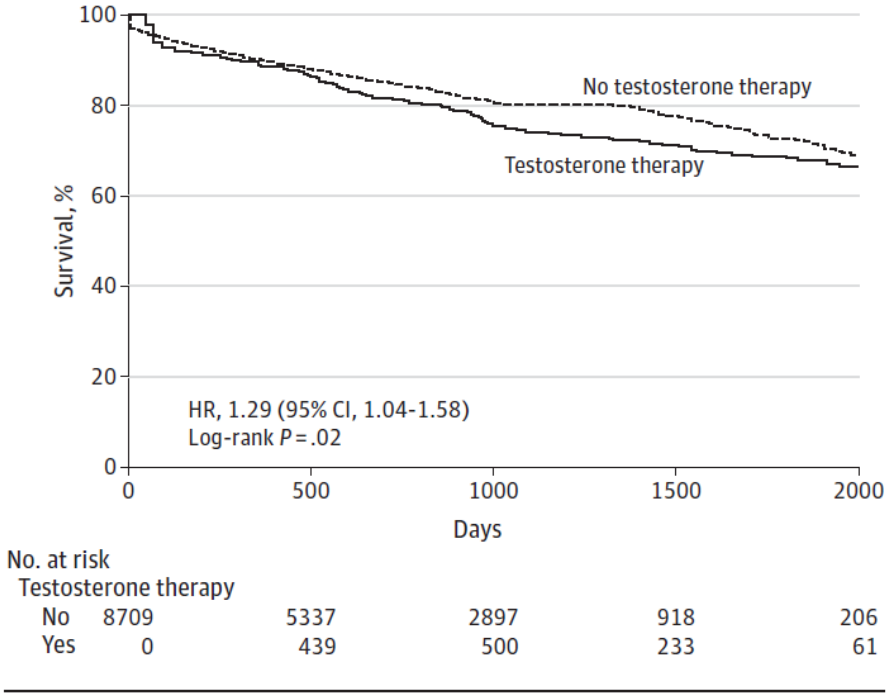
Table 3. Subjects with One or More Cardiovascular-Related Adverse Events.*

Subject No.	Adverse Event	MedDRA-Classified Cardiac Event	Cardiovascular-Related Event
			no. of events
Testosterone group			
1	Acute coronary syndrome and chest pain	1	2
2	Chest pain		1
3	Syncope		1
4	Syncope		1
5	Myocardial infarction treated with angioplasty and placement of pacemaker	1	1
6	Myocardial infarction	1	1
7	Angioplasty and coronary-artery bypass grafting		1
8	Peripheral edema		1
9	Peripheral edema		1
10	Ectopy on ECG (premature ventricular contractions, couplets)	1	1
11	Left ventricular strain pattern during exercise testing	1	1
12	ST-segment depression during exercise testing		1
13	Elevated blood pressure		1
14	Atrial fibrillation with rapid ventricular rate and shortness of breath and exacerbation of congestive heart failure, which necessitated hospitalization	2	2
15	Stroke		1
16	Elevated blood pressure and atrial fibrillation	1	1
17	Peripheral edema		1
18	Peripheral edema		1
19	Elevated blood pressure		1
20	Tachycardia with fatigue	1	1
21	Death, suspected myocardial infarction	1	1
22‡	Peripheral edema		1
23	Congestive heart failure exacerbation	1	1
Placebo group			
1	Syncope resulting in hospitalization		1
2	Tachycardia		1
3	Elevated blood pressure		1
4	Arrhythmia–ectopy noted on ECG before exercise testing	1	1
5	Carotid bruit and carotid-artery plaque identified on ultrasonography		1

Basaria S *et al*. N Engl J Med 2010

After more than 30y, recent fears concerning CV security emerge …

Figure 2. Kaplan-Meier Survival Curves With Testosterone Therapy Evaluated as a Time-Varying Covariate



But…

The actual percentage of men with CV events in the T group was less than half that in the no T group (10.1% vs 21.2%).

Opposite conclusion solely after complex adjustments for more than 50 variables

Miscategorized more than 1000 individuals and contamination by inclusion of 100 women…

Vigen R *et al*. JAMA 2013

After more than 30y, recent fears concerning CV security emerge …

Data base 55.593 Prescriptions T

Table 1. Rates of myocardial infarction per 1,000 persons per year (PY) in men under age 65 years and those age 65 years and older, in pre- and post-prescription intervals for an initial prescription for testosterone therapy rate ratios (RR) and 95% confidence intervals (CI).

	All Ages	Age <65 Years	Age ≥65 Years
Patients (N)	55,593	48,539	7,054
Pre-prescription			
Cases	193	156	37
Rate per 1,000 PY (95%CI)	3.48 (3.02, 4.01)	3.22 (2.75, 3.77)	5.27 (3.81, 7.27)
Post-prescription			
Cases	65	45	20
Rate per 1,000 PY (95%CI)	4.75 (3.72, 6.05)	3.76 (2.81, 5.04)	11.52 (7.43, 17.86)
Rate Ratio (post/pre) (95%CI)	1.36 (1.03, 1.81)	1.17 (0.84, 1.63)	2.19 (1.27, 3.77)

Excess risk for men > 65y and those with pre-existing heart disease

But…

No data on hypogonadism diagnosis.

No mention of T levels

No monotorization of T, haematocrit or PSA

Finkle *et al*. PLoS One 2014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TESTOSTERONE REPLACEMENT THERAPY. WHAT IS THE REAL RISK? WHAT TO DO IN PROSTATE CANCER ?

Testosterone and Prostate Cancer: Mith or Truth ??

Androgens ↔ Prostate

Complex interaction – needs androgens for development and undergoes atrophy without them

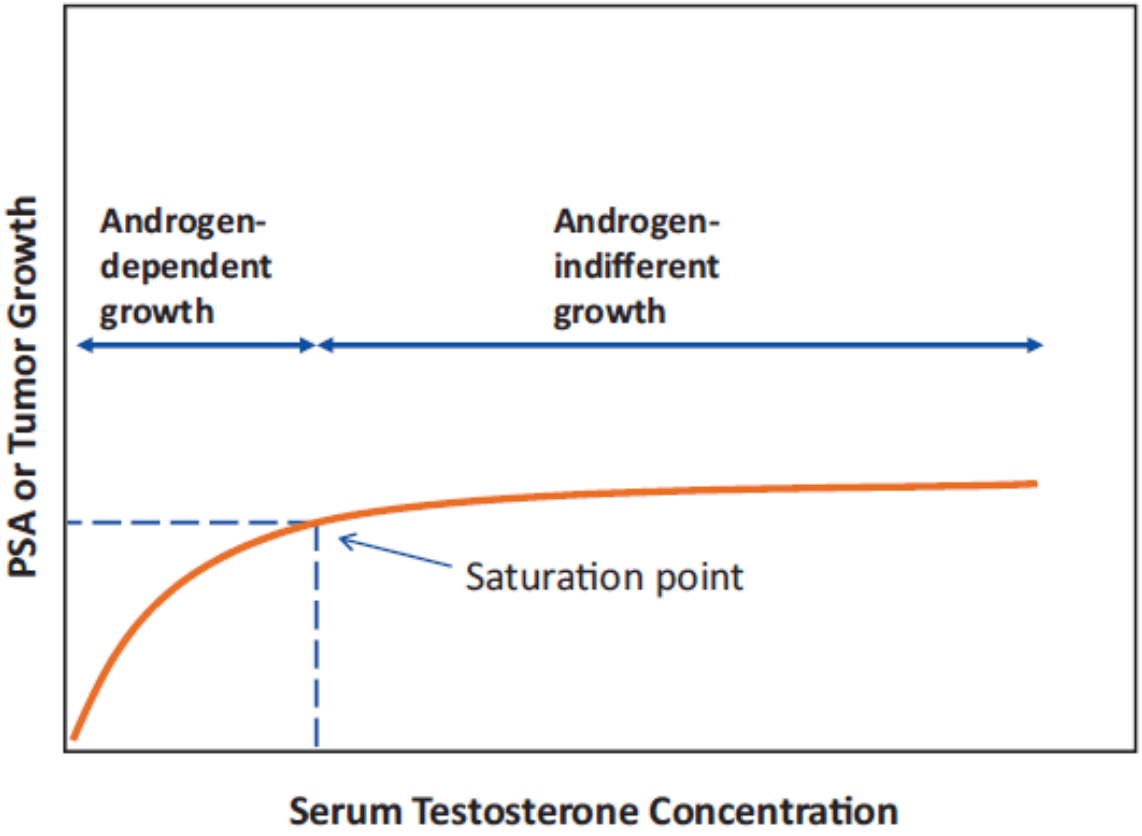
But pathologic growth stimulated by androgens?

First studies

Huggins and Hodges
Fowler and Whitmore

→ **Testosterone Replacement Therapy unfavourable response in metastatic Prostate Cancer**

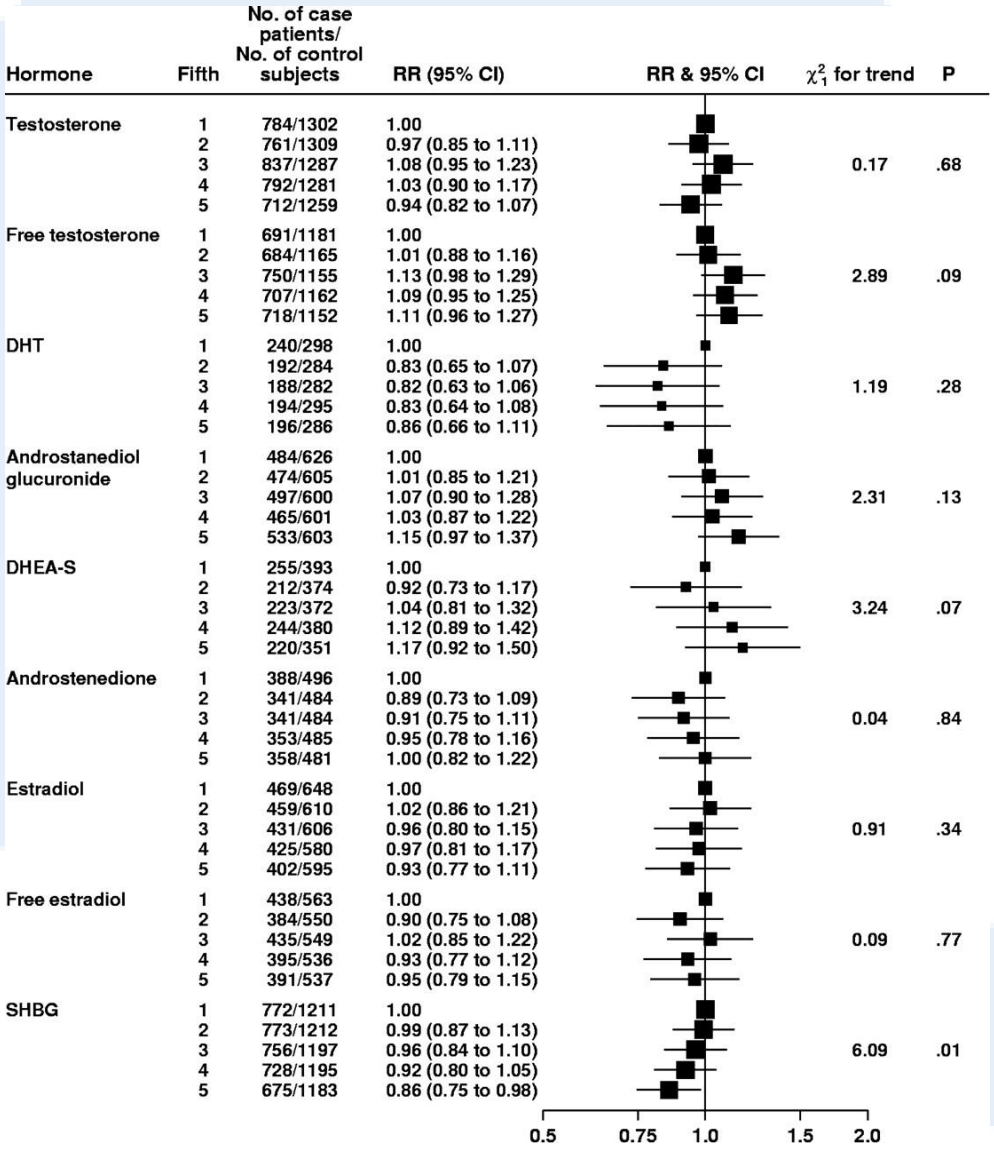
Testosterone and Prostate cancer growth



Saturation Model

Morgentaler A. Urol Clin North Am 2007

T and Prostate Cancer incidence



Hormone	Fifth	No. of case patients/ No. of control subjects	RR (95% CI)	χ^2_1 for trend	P
Testosterone	1	784/1302	1.00		
	2	761/1309	0.97 (0.85 to 1.11)		
	3	837/1287	1.08 (0.95 to 1.23)	0.17	.68
	4	792/1281	1.03 (0.90 to 1.17)		
	5	712/1259	0.94 (0.82 to 1.07)		
Free testosterone	1	691/1181	1.00		
	2	684/1165	1.01 (0.88 to 1.16)		
	3	750/1155	1.13 (0.98 to 1.29)	2.89	.09
	4	707/1162	1.09 (0.95 to 1.25)		
	5	718/1152	1.11 (0.96 to 1.27)		
DHT	1	240/298	1.00		
	2	192/284	0.83 (0.65 to 1.07)		
	3	188/282	0.82 (0.63 to 1.06)	1.19	.28
	4	194/295	0.83 (0.64 to 1.08)		
	5	196/286	0.86 (0.66 to 1.11)		
Androstanediol glucuronide	1	484/626	1.00		
	2	474/605	1.01 (0.85 to 1.21)		
	3	497/600	1.07 (0.90 to 1.28)	2.31	.13
	4	465/601	1.03 (0.87 to 1.22)		
	5	533/603	1.15 (0.97 to 1.37)		
DHEA-S	1	255/393	1.00		
	2	212/374	0.92 (0.73 to 1.17)		
	3	223/372	1.04 (0.81 to 1.32)	3.24	.07
	4	244/380	1.12 (0.89 to 1.42)		
	5	220/351	1.17 (0.92 to 1.50)		
Androstenedione	1	388/496	1.00		
	2	341/484	0.89 (0.73 to 1.09)		
	3	341/484	0.91 (0.75 to 1.11)	0.04	.84
	4	353/485	0.95 (0.78 to 1.16)		
	5	358/481	1.00 (0.82 to 1.22)		
Estradiol	1	469/648	1.00		
	2	459/610	1.02 (0.86 to 1.21)		
	3	431/606	0.96 (0.80 to 1.15)	0.91	.34
	4	425/580	0.97 (0.81 to 1.17)		
	5	402/595	0.93 (0.77 to 1.11)		
Free estradiol	1	438/563	1.00		
	2	384/550	0.90 (0.75 to 1.08)		
	3	435/549	1.02 (0.85 to 1.22)	0.09	.77
	4	395/536	0.93 (0.77 to 1.12)		
	5	391/537	0.95 (0.79 to 1.15)		
SHBG	1	772/1211	1.00		
	2	773/1212	0.99 (0.87 to 1.13)		
	3	756/1197	0.96 (0.84 to 1.10)	6.09	.01
	4	728/1195	0.92 (0.80 to 1.05)		
	5	675/1183	0.86 (0.75 to 0.98)		

Serum concentrations of sex hormones were not associated with the risk of prostate cancer !

Roddam AW *et al*. J Natl Cancer Inst 2008
Muller RL *et al*. Eur Urol 2012

T and Prostate Cancer incidence

Inverse relationship

Rhoden EL *et al*. J Urol 2008

Lower levels associated to:

- **More advanced stage**
- **Higher Score de *Gleason***
- **Biochemical recurrence after Radical prostatectomy**

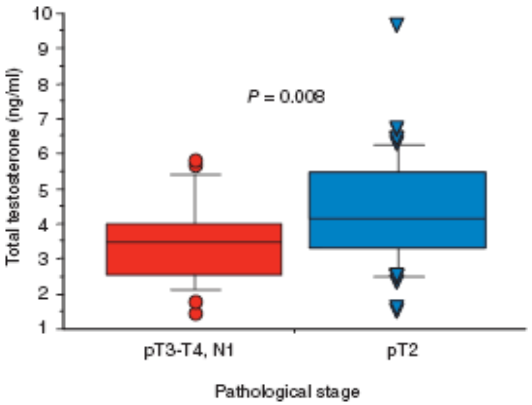


Fig. 1 High pretreatment total testosterone levels predict organ-confined disease in patients treated with radical prostatectomy (Imamoto *et al.* 2005[16]).

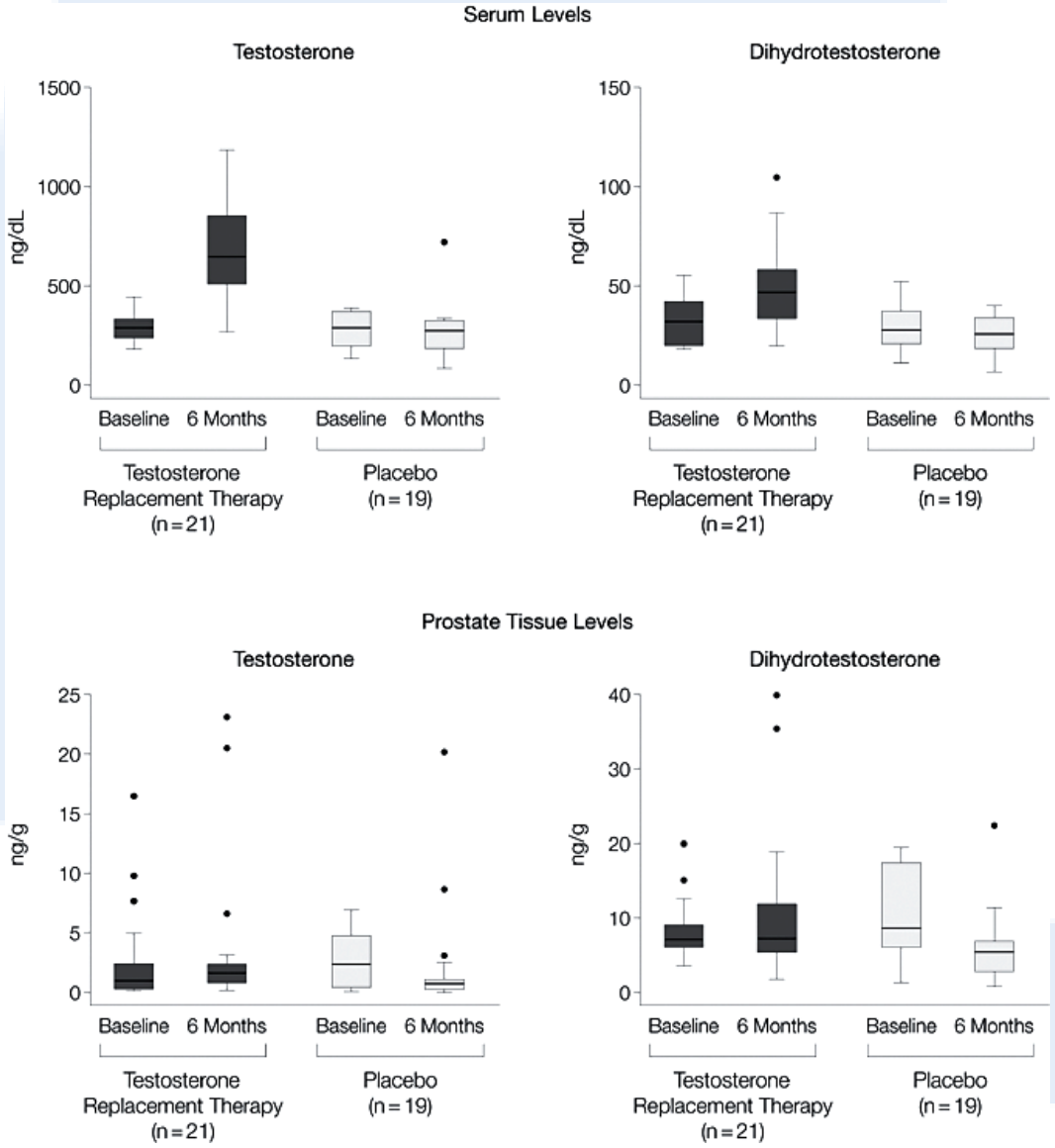
Table 1 Univariate analysis of relationship between pretreatment testosterone levels and clinical and pathological factors (Yano *et al.* 2007[13])

Variable	Testosterone (ng/mL)			*P*
	Mean	Median	Range	
Diagnosis				0.090
Cancer	3.90	3.725	0.90–12.7	
Not cancer	3.66	3.650	0.10–8.56	
DRE				0.806
Positive	3.89	3.670	0.09–8.56	
Negative	3.75	3.735	0.16–12.7	
Pathological Gleason score				0.030
≤6	4.21	3.95	0.90–12.7	
7–10	3.73	3.62	0.09–9.35	
Pathological differentiation				<0.010*
Well-differentiated	4.85	4.355	1.39–12.7	
Moderately differentiated	3.80	3.68	0.90–9.35	
Poorly differentiated	3.71	3.54	0.09–7.74	

*Well-differentiated *vs* moderately differentiated, poorly differentiated, or both. DRE, digital rectal examination.

Imamoto T *et al*. Eur Urol 2005
Yano M *et al*. Eur Urol 2007
Yamamoto S *et al*. Eur Urol 2007
Mearini L *et al*. Urol Int 2008
Garcia-Cruz E *et al*. BJU 2012

TRT and Prostate cancer



"… normalizes serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions."

Marks *et al*. JAMA 2006

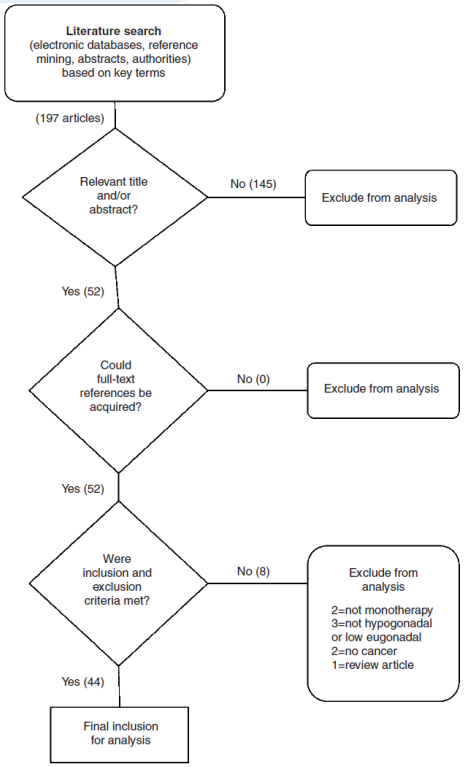
TRT and Prostate Cancer

Meta Analyses

19 studies

- **TRT (n=651) vs Placebo (n=433)**

Calof *et al*. J Gerontology 2005



***No differences*:**

- **Prostate cancer**
- **PSA>4**
- **Score IPSS**

None demonstrated that testosterone therapy for hypogonadism increased prostate cancer risk or increased Gleason grade of cancer detected in treated vs untreated men.

Testosterone therapy did not have a consistent effect on prostate-specific antigen levels.

There is no evidence that testosterone therapy increases the risk of prostate cancer in hypogonadal men.

Shabsigh R *et al*. Int J Impot Res 2009

TRT and Prostate Cancer Incidence

The incidence of PCa during long-term TRT was equivalent to that expected in the general population

Feneley & Carruthers. J Sex Med 2012

Testosterone use was not associated with aggressive prostate cancer and did not affect overall or disease-specific mortality

Kaplan & Hu. Urology 2013

Table 2. Unadjusted and adjusted prostate cancer-specific outcomes for testosterone replacement therapy before prostate cancer diagnosis vs no testosterone replacement therapy

Variable	Categories	No TRT No. (%)	TRT No. (%)	*P* Value	No-TRT No. (%)	TRT No. (%)	*P* Value
Grade	Well	9722 (6.6)	160 (7.2)	<.0001	6.6	6.8	<.0001
	Moderately	87,084 (59.2)	1444 (64.6)		59.2	63.5	
	Poorly	50,311 (34.2)	633 (28.3)		34.2	29.7	
Clinical stage	T1	58,807 (40.0)	932 (41.7)	<.0001	40.0	41.6	<.0001
	T2	74,210 (50.4)	1152 (51.5)		50.5	50.1	
	T3	4580 (3.1)	73 (3.3)		3.1	4.0	
	T4	9520 (6.5)	80 (3.6)		6.5	4.3	
Initial treatment	ADT	24,878 (16.9)	321 (14.4)	.006	16.9	12.3	<.0001
	RP	27,034 (18.4)	401 (17.9)		18.4	20.0	
	RT	74,391 (50.6)	1181 (52.8)		50.6	53.1	
	WWAS	20,814 (14.2)	334 (14.9)		14.1	14.7	

ADT, androgen-deprivation therapy; RP, radical prostatectomy; RT, radiotherapy; WWAS, watchful waiting with active surveillance; other abbreviation as in Table 1.

TRT and risk of Prostate cancer

0022-5347/03/1706-2348/0
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DOI: 10.1097/01.ju.0000091104.71869.8e

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*

From the Division of Urology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

TABLE 1. *Patient characteristics*

No. pts	75
Mean age ± SD (range)	59.6 ± 9.0 (42–77)
Mean ng/dl PSA ± SD (range)	1.54 ± 1.5 (0.3–9.4)
Mean ng/dl TT ± SD (range)	295.9 ± 119.3 (74–776)
Mean ng/dl FT ± SD (range)	1.04 ± 0.33 (0.4–1.9)
No. biopsy:	
Without PIN	55
With PIN	20

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.

TRT after definitive Prostate cancer treatment

Study	No. of patients	Intervention	Follow-up, mo	Gleason score (no. of patients)	Pretreatment PSA	Post-treatment PSA	Pretreatment testosterone, ng/dl	Post-treatment testosterone, ng/dl	Comments
Agarwal et al. [39]	10	RP	19	6 (2) 7 (7) 8 (1)	<0.1	<0.1	197	591	No PSA recurrences
Kaufman et al. [38]	7	RP	24	6 (6) 7 (1)	<0.1	<0.1	97	434	No PSA recurrences; longest follow-up = 12 yr
Khera et al. [40]	57	RP	13	≤6 (24) 7 (26) 8 (4)	0.005	0.005	255	459	No PSA recurrences
Pastuszak et al. [41]	103	RP	27.5	<6 (1) 6,7 (72) ≥8 (9)	0.004	0.007	261	460	Included 26 men with high-risk PCa and positive margins or nodes or Gleason score >8; comparison group of 49 men with RP without testosterone therapy; four PSA recurrences in the testosterone therapy group (4%), eight recurrences in the comparison group (16%)
Sarosdy [42]	31	Brachytherapy	60	5 (3) 6 (19) 7 (6) 8/9 (3)	NA	<1	188	489	No PSA recurrences
Morales et al. [43]	5	EBRT	14.5	6 (2) 7 (1) 8 (2)	0.1–0.97	<0.1–1.08	150 (5.2 nmol/l)	507 (17.6 nmol/l)	One patient had a transitory increase in PSA; none had PSA increase >1.5 ng/ml
Pastuszak et al. [44]	13	Brachytherapy and EBRT	29.7	6 (4) 7 (7) 8 (2)	0.30	0.66	178	368	No PSA recurrences
Morgentaler et al. [8]	13	AS	30	6 (12) 7 (1)	5.5	3.6	238	664	Follow-up biopsies in all men; no definite PCa progression in any patient; no increase in mean PSA or prostate volume; no cancer in 54% of follow-up biopsies
Morales et al. [45]	6	AS	NA	6 (5) 8 (1)	5.66	NA	259 (9 nmol/l)	NA	Variable PSA response in several men; no follow-up biopsies reported; one man subsequently underwent RP

PSA = prostate-specific antigen; RP = radical prostatectomy; PCa = prostate cancer; NA = not available; EBRT = external-beam radiation therapy; AS = active surveillance.

Khera M *et al*. Eur Urol 2014

TRT after definitive Prostate cancer treatment

Importance of conducting studies in the AS population

- No change in mean PSA and P volume
- No definite Prostate cancer progression

Strict follow up – PSA, DRE and Biopsies

BUT

Large, prospective, randomized trials are in need…

Bayler College of Medicine Clinical trial NCT00848497

Testosterone gel + Sildenafil daily after radical prostatectomy

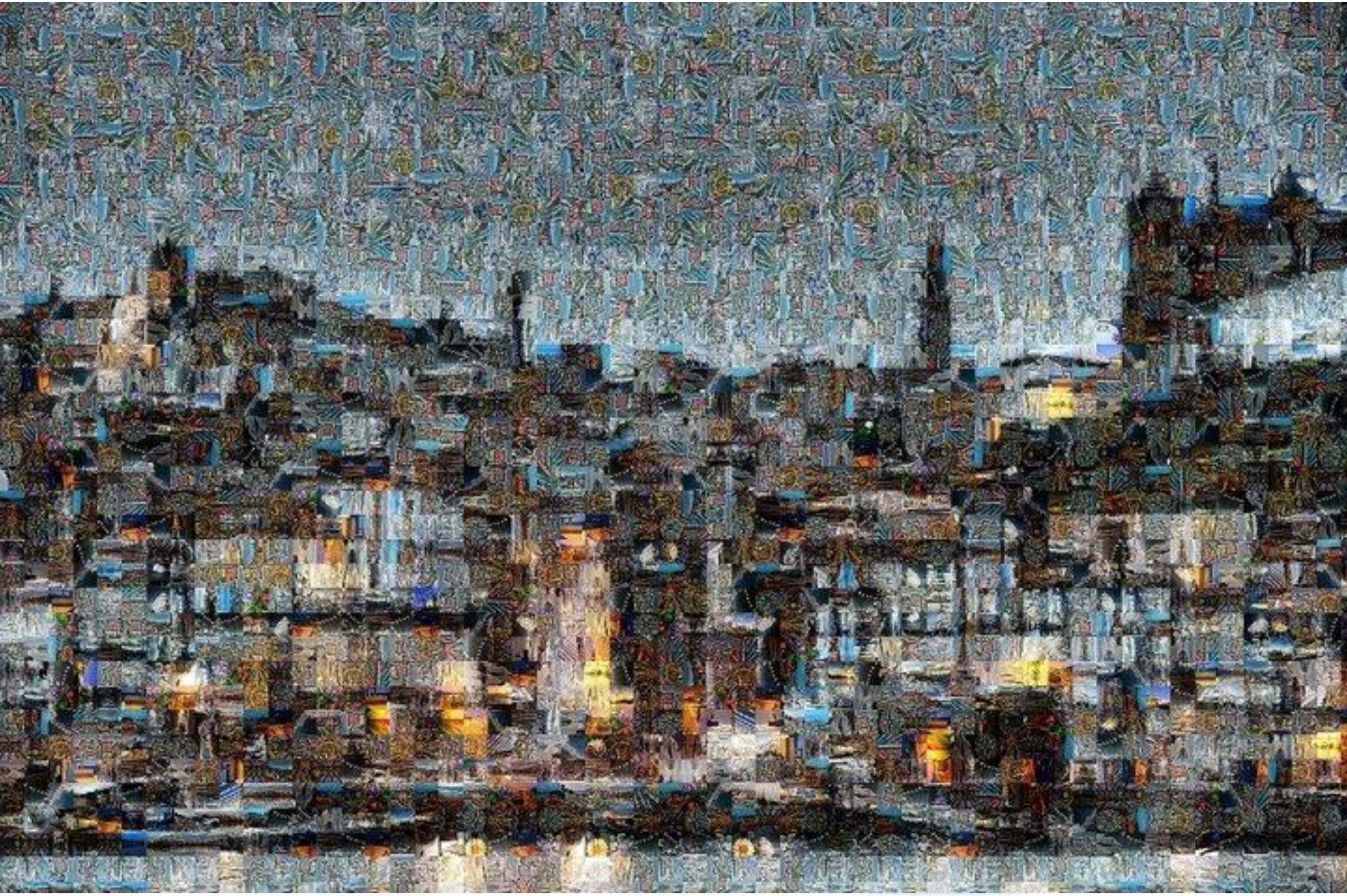
Final remarks

- Low T is associated with higher CV risk
- T may act as biomarker of poor health or even may be a protective evolutionary factor that decreases energy expenditure in men with poor or declining health status
- Although TRT has been associated with a decrease in CV risk, recent studies suggest TRT should be avoided in older patients and those with previous heart disease

Final remarks

- No evidence for increased risk for PCa in normal range of T
- Lower T is even associated with several parameters of bad prognosis for PCa
- TRT still contraindicated in patients diagnosed with PCa
- TRT may be considered for TDS patients after definitive PCa treatment, but informed consent must be obtained for each case and sctrict follow up is mandatory

Ribeira do Porto



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