

Testosterone Treatment and Prostate Cancer Risk

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Disclosure

Consultant:

- Coloplast
- Biote

Advisory Board:

- Boston Scientific
- Progyny

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- Boston Scientific
- Coloplast
- Endo

Case: 66 year old man with decreased libido, erectile dysfunction, and decreased energy

“I don’t have the strength that I used to”

Testosterone 252 ng/dl (normal 348-1197ng/dl)

Free Testosterone 4.8 ng/dl (normal 6.6-18.1)

FSH, LH and Prolactin all normal

PSA 1.1 ng/dl

Hematocrit 46%

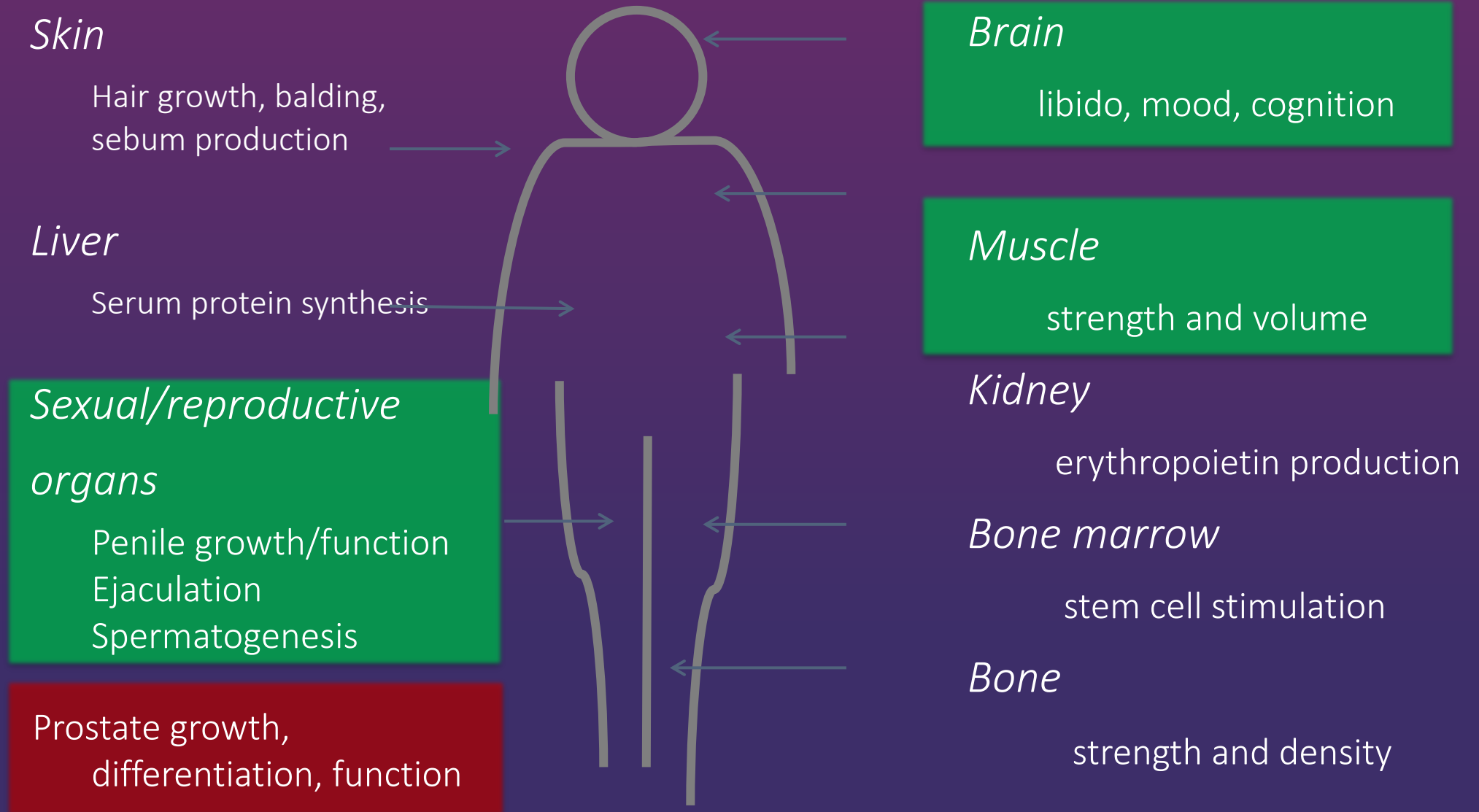
Would you treat him with
testosterone?

Does testosterone treatment place this man at higher risk for prostate cancer?

Testosterone therapy is appropriate treatment for patients with clinically significant testosterone deficiency, after full discussion of potential adverse effects

Adapted from AUA Position Statement on Testosterone Therapy, 2015

The Effects of Androgen





Adverse Events of Testosterone Therapy in a RCT of Intermediate-Frail and Frail Older Men

Number (%) of Adverse Events		
	Testosterone (n= 130)	Placebo (n = 132)
Serious	6 (4.6)	3 (2.3)
Mild/Moderate	10 (7.7)	7 (5.3)
Skin rash	11 (8.5)	14 (10.6)

Adverse events:

MI, **Prostate cancer**, death from ruptured aneurysm, lung cancer, esophagus cancer, Pulmonary embolism, heart failure, abdominal aneurysm, pericarditis

The Effect of TRT on Prostate Cancer: Meta-analysis

	OR	95% CI	Events/Total # Subjects Testosterone	Control	# Trials
12 months or less or testosterone therapy					
Prostate biopsy	2.79	0.57-13.64	6/387	0/212	4
Prostate cancer	0.74	0.26-4.65	7/778	5/390	5
12 to 36 months of testosterone therapy					
Prostate biopsy	2.37	0.86-6.53	13/314	5/266	5
Prostate cancer	0.99	0.24-4.02	3/191	3/188	3

The Veteran's Affairs Testosterone Treatment Study

A Pharmacoepidemiologic study of hypogonadal U.S. Veterans aged 40 to 89 years from 2002 to 2012



T *R*ex Study

Hypothesis

Treatment with exogenous testosterone increases the risk of prostate cancer

1. Initiator of cancer
2. Promotor of cancer
3. “increased likelihood of diagnosis”

Most concerned about the risk of aggressive prostate cancer due to its worse health outcomes

Setting for Observational Study

Excellent setting in which to respond to testosterone treatment safety questions:

1. Large population of men (~8M users in a year)
2. National electronic health record
3. National prescription dispensing data
4. testosterone treatment relatively common
5. VA Central Cancer Registry
6. Can easily include CMS data
7. Uniformity of health care access

Basic Study Design



Cohort of men with low Testosterone

1. Men aged 40-89 years
2. Cohort entry at first lab measure of low endogenous T
3. Users of VA primary care: 2 or more outpatient visits in 12 months before cohort entry
4. Exclusion: histories of prostate cancer, prostate biopsy, PSA not measured, PSA ≥ 4.0 ng/dL, T treatment prior to cohort entry

Basic Study Design



Basic Study Design



Incident Aggressive Prostate Cancer

- ✓ Gleason grade ≥ 8
- ✓ prostate specific antigen (PSA) ≥ 20 ng/dl
- ✓ pathological stage T3 (pT3) or greater
- ✓ lymph node metastasis (N+)
- ✓ distant metastasis (M+)

Incident “Any” Prostate Cancer

Death

End of Study

Exposure-Outcome Models

- NEVER use versus EVER use (analogous to intention to treat)
- Time-varying cumulative dose, calculated by summing the amount of delivered testosterone over the period of study

Screening Bias

Testosterone treatment increases PSA screening

- Increases rate of prostate biopsy
- Increases likelihood of detecting cancer

Possible remediation

- Adjustment for time-varying PSA screening intensity (<6 m, 6-12 m, >12 m) to create fairer comparisons of exposure groups

Association Analysis

- Time-to-event models
- Covariate adjustments
 - Fixed: age, race, region, BMI, hospitalization in year before cohort entry
 - Time varying: PSA screening, presence-absence of 26 medical comorbidities

Results

- 147,593 with low T of whom 56,833 (39%) initiated T during follow-up
 - 1.35M prescriptions
 - 64% IM, 27% patches, 10% gels
 - Mean cumulative duration: 14.6 months (SD 16.8 months)
- Median follow-up: 3.0 y (9.8 y max)
- Comorbidities similar across treatment groups (modal age 60-64 years)

Table 1. Baseline Characteristics of Men with Low Testosterone, 2002 to 2012		
Baseline Comorbidities	Treated (n=58,617)	Not Treated (n=88,976)
CAD (hard outcomes)	7,333 (13%)	12,578 (14%)
CAD (soft outcomesb)	17,732 (30%)	29,142 (33%)
Chronic Heart Failure	5,109 (9%)	9,343 (11%)
Chronic Liver Failure	2,179 (4%)	3,837 (4%)
Chronic Lung Disease	14,582 (25%)	22,516 (25%)
Chronic Pain	2,755 (5%)	3,483 (4%)
CVD (hard outcomesb)	859 (1%)	1,786 (2%)
CVD (soft outcomesb)	4,003 (7%)	7,446 (8%)
Diabetes	25,777 (44%)	39,644 (45%)
Sexual dysfunction	35,078 (60%)	42,831 (48%)
Frailty	389 (1%)	745 (1%)
Hyperlipidemia	21,156 (36%)	30,630 (34%)
Hypertension	46,632 (80%)	70,704 (79%)
Major Depression	12,829 (22%)	16,046 (18%)
Malignancy	2,385 (4%)	4,405 (5%)
Morbid Obesity	6,583 (11%)	8,220 (9%)
Osteoporosis	3,004 (5%)	4,839 (5%)
PVD	5,885 (10%)	10,442 (12%)
Polycythemia	395 (1%)	452 (1%)
Sleep Apnea	14,359 (25%)	17,311 (19%)
Smoking	20,074 (34%)	31,593 (36%)
TBI	1,607 (3%)	2,360 (3%)
DVT/PE	2,194 (4%)	3,603 (4%)

Serum T Levels at Cohort Entry and Follow-Up*

Total Testosterone Level (ng/dL)			
	No T Treatment	Topical T Treatment	Intramuscular T Treatment
Number of men	31,540	14,385	15,794
Baseline T, Mean (SD)	217.2 (128.1)	179.4 (81.4)	178.5 (78.3)
Follow-up T, Mean (SD)	280.3 (158.6)	272.30 (154.4)	365.8 (310.1)
Change in T, Mean (95% CI)	63.1 (61.4-64.7)	92.9 (90.5-95.4)	187.3 (182.4-192.1)

*Among Men Treated and Not Treated with T

Ever-Never Testosterone Treatment Results

Aggressive Incident Prostate Cancer				
T Treatment	PY	Events	IR (95%CI)	HR (95%CI)
Never treated	335,878	190	0.57 (0.49-0.65)	1.0 (ref)
Ever treated	212,719	123	0.58 (0.48-0.69)	0.89 (0.70-1.13)
Any Incident Prostate Cancer				
Never treated	335,878	848	2.52 (2.36-2.70)	1.0 (ref)
Ever treated	212,719	591	2.78 (2.56-3.01)	0.90 (0.81-1.01)

PY: person-years

IR: unadjusted incidence rate per 1000 PY

HR: adjusted hazard ratio

CI: confidence interval

Cumulative Testosterone Treatment Results

Aggressive Incident Prostate Cancer				
T (mg)	PY	Events	IR (95%CI)	HR (95%CI)
1-399	37,602	28	0.74 (0.51-1.08)	1.0 (ref)
400-799	33,841	20	0.59 (0.38-0.92)	0.78 (0.44-1.38)
800-1599	39,521	28	0.71 (0.49-1.03)	0.86 (0.50-1.45)
1600-3199	38,599	26	0.67 (0.49-0.99)	0.78 (0.46-1.34)
≥3200	45,750	15	0.33 (0.20-0.54)	0.34 (0.18-0.64)

PY: person-years

IR: unadjusted incidence rate per 1000 PY

HR: adjusted hazard ratio

CI: confidence interval

Cumulative Testosterone Treatment Results

Any Incident Prostate Cancer				
T (mg)	PY	Events	IR (95%CI)	HR (95%CI)
1-399	37,602	103	2.74 (2.26-3.32)	1.0 (ref)
400-799	33,841	82	2.42 (1.95-3.01)	0.84 (0.63-1.12)
800-1599	39,521	113	2.86 (2.38-3.44)	0.90 (0.69-1.18)
1600-3199	38,599	125	3.24 (2.71-3.86)	0.94 (0.72-1.23)
≥3200	45,750	124	2.71 (2.27-3.23)	0.72 (0.55-0.95)

PY: person-years

IR: unadjusted incidence rate per 1000 PY

HR: adjusted hazard ratio

CI: confidence interval

By Testosterone Route of Administration

Aggressive Incident Prostate Cancer		
	Intramuscular only	Topical only
T Treatment	HR (95% CI)	HR (95% CI)
Never	1.0 (ref)	1.0 (ref)
Ever	0.93 (0.68-1.27)	0.92 (0.667-1.26)

By Testosterone Route of Administration

Aggressive Incident Prostate Cancer		
	Intramuscular only	Topical only
T (mg)	HR (95% CI)	HR (95% CI)
1-399	1.0 (ref)	1.0 (ref)
400-799	1.11 (0.44-2.85)	0.45 (0.18-1.11)
800-1599	1.13 (0.47-2.76)	0.54 (0.23-1.28)
1600-3199	0.68 (0.26-1.79)	0.84 (0.38-1.85)
≥3200	0.40 (0.14-0.1.11)	0.53 (0.19-1.43)

Interpretation

The use of testosterone does NOT appear to increase risk of prostate cancer

- Consistent for ever-never and cumulative dose
- Similar results for aggressive and any prostate cancer
- Similar results by mode of T administration

66 year old man with decreased libido,
mild erectile dysfunction and decreased
energy

Would you treat him with testosterone?

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Questions

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