The Impact of Low Free Testosterone on Prostate Cancer: High-Risk Disease, Recurrence, and Testosterone Replacement after Radical Prostatectomy

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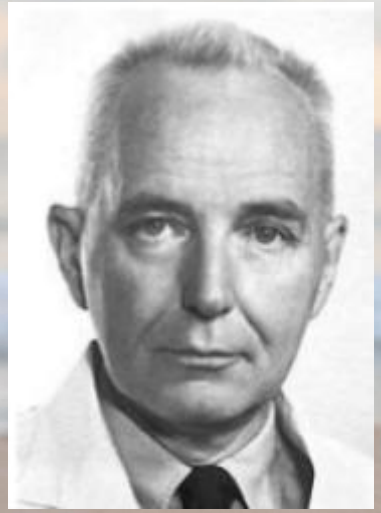
Prostate Cancer and Testosterone



Charles Huggins

- **1941** – 21 patients with advanced Prostate Cancer (PC) underwent castration with dramatic improvement!
- **1966** – Nobel Prize in Medicine
- **Origin of the Truth/Myth** – Testosterone causes Prostate Cancer.

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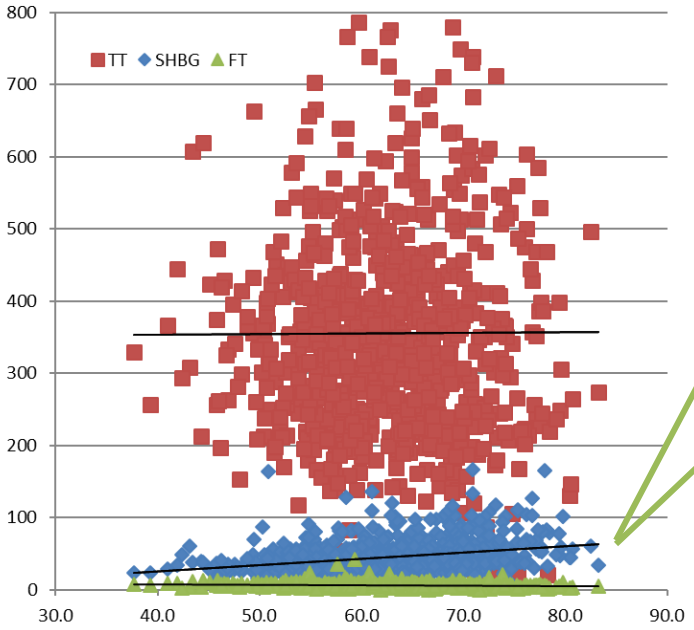
Introduction & Objective

- Historically, treating low serum testosterone in men with PC has been “contra-indicated” due to fear of exacerbating the disease.
- Recent studies, however, have reported that testosterone replacement therapy (TRT) in men with low risk PC has not resulted in exacerbation.
- **Objective: Observational Study of Serum T levels to Evaluate:**
- **1. If Total and/or Free Testosterone (cFT) impact PC aggressiveness and progression.**
- **2. Assess the benefits and risks of TRT in men (PC low risk) following RARP with sexual dysfunction or low T symptoms.**

Methods – Study Population

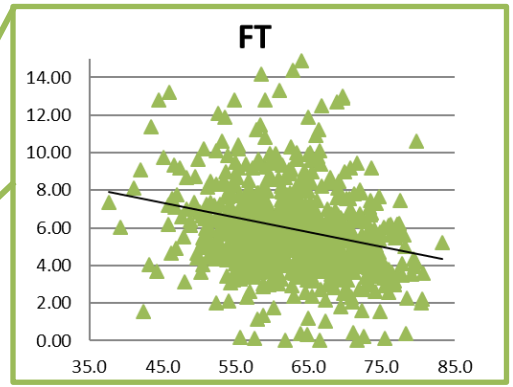
- December 2009 to June 2018, 850 patients underwent RARP for primary treatment of localized prostate cancer
- Prospective collection of total testosterone (TT), sex hormone binding globulin (SHBG), and calculated free testosterone (cFT).
- 152 / 850 (18.2%) were prescribed testosterone replacement therapy (TRT) if:
  - Pathologically-confirmed low and intermediate risk cancer
  - Undetectable PSA levels (PSA<0.05)
  - Low baseline and/or 3-month postoperative cFT levels < 5.7ng/dL, **or**
  - Reduced erectile function recovery

Men with Prostate Cancer
Testosterone and Age



Age

- **TT was stable over the decades!**
- **SHBG rose!**
- **cFT dropped ~ 50% from 40-80 yrs**



Age

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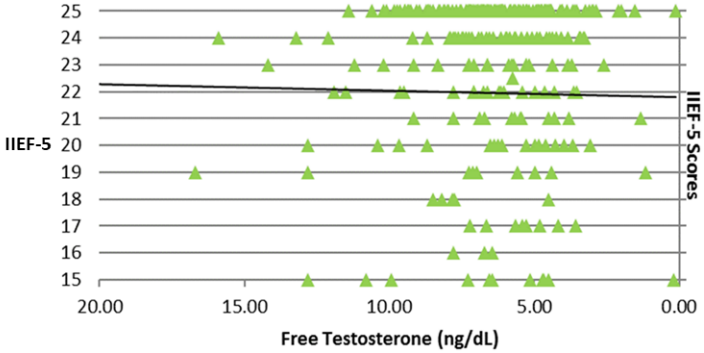
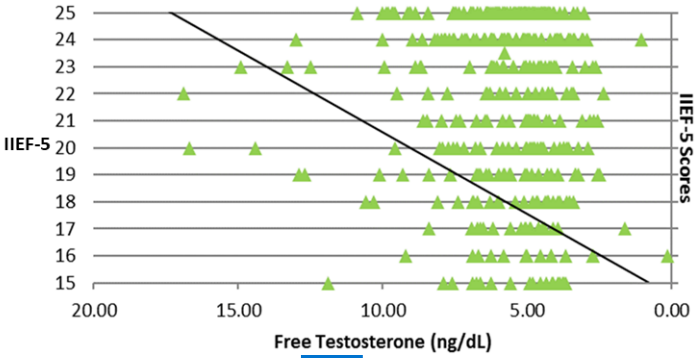
Impact of FT on Sexual Function prior to RARP

40-60 yr FT vs. IIEF-5



Men age 40 – 60: FT had very little impact on IIEF-5 scores

60-80 yr FT vs. IIEF-5



Whereas men 61 – 80: each ng drop of FT reduced IIEF-5 scores 30%

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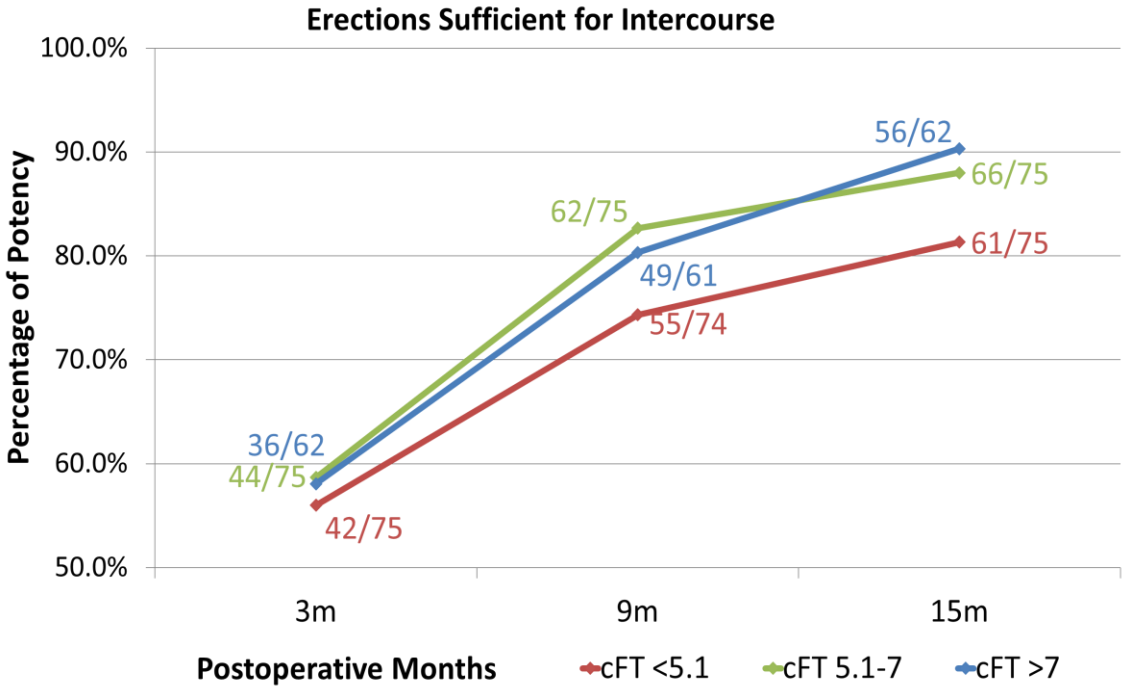
Preop cFT vs Postop Sexual fxn

Of 840 men undergoing RARP, 212 met the above-mentioned inclusion criteria.

Of the 212 patients:

- 75 (35.4%) had preoperative cFT less than 5.1 ng/dL (low),
- 75 (35.4%) had preoperative cFT between 5.1 and 7 ng/dL (middle), and
- 62 (29.2%) had preoperative cFT greater than 7 ng/dL (high).



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TRT and postop Sexual Function Recovery Compared to Controls

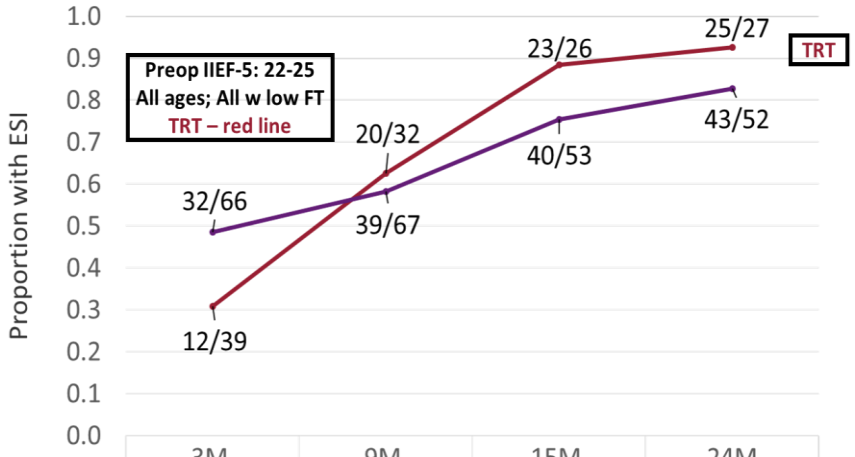
Of the 212 patients, 123 (58%) men had a preoperative IIEF-5 score between 22 and 25 and cFT < 5.1 ng/dL.

40/123 (32.5%) received TRT, while 83/123 (67.5%) did not.

At 3, 9, and 15 months post RARP, potency recovery was:

49%, 58%, 76%, 83% Untreated

31%, 63%, 89%, 93% TRT

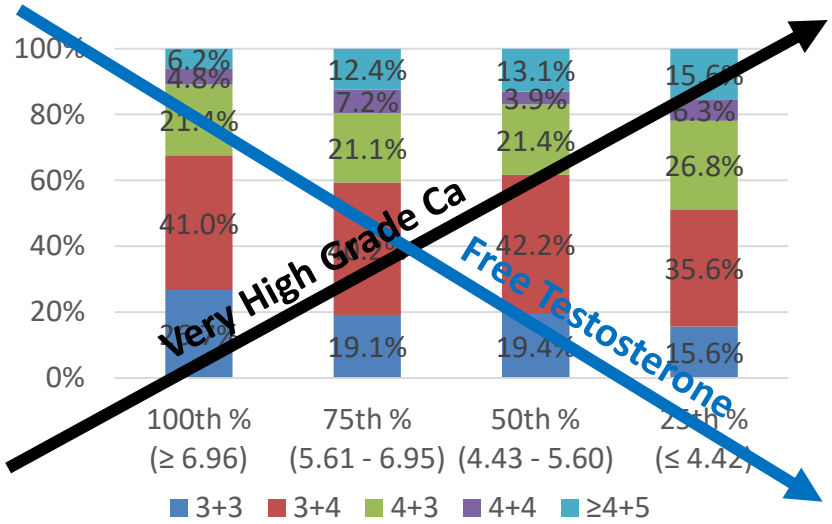


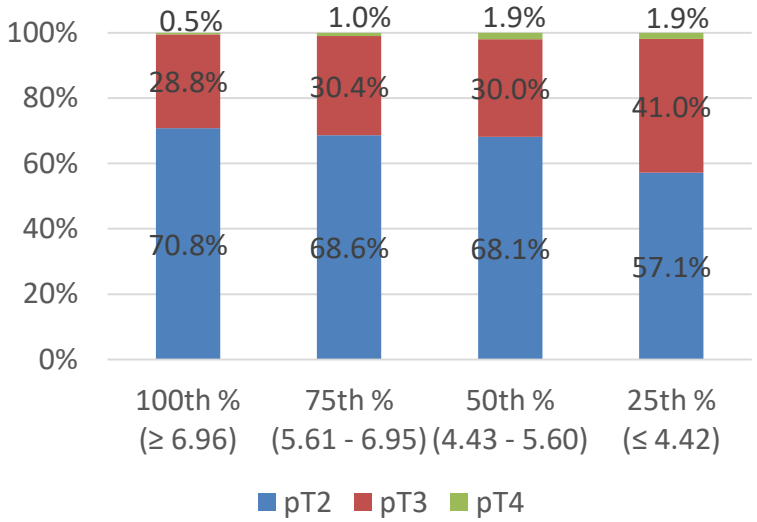
	3M	9M	15M	24M
TRT	0.308	0.625	0.885	0.926
Control	0.486	0.582	0.755	0.827

Pathological and BCR Outcomes

- **Primary outcome**: impact of low cFT on pGG, p-stage, and BCR.
- 830 consecutive patients underwent RARP, with prospectively-drawn total testosterone (TT), sex hormone binding globulin (SHBG), and calculated free testosterone (cFT) preop and 3 months postop.
- **Secondary outcome**: impact of TRT on BCR and time to-BCR
- Study Group: A subset of 152 Hypogonadal men with low-risk PC and undetectable PSAs were placed TRT.
- Control Group: 419 matched controls risk based 1st on p-GG and 2nd p-Stage. Secondary adjusted analysis based on cFT levels.

Low cFT on GGG, p-stage





- Prevalence of high-risk, high-volume disease was significantly higher for patients with cFT in the lowest quartile, when compared to those in the highest quartile.

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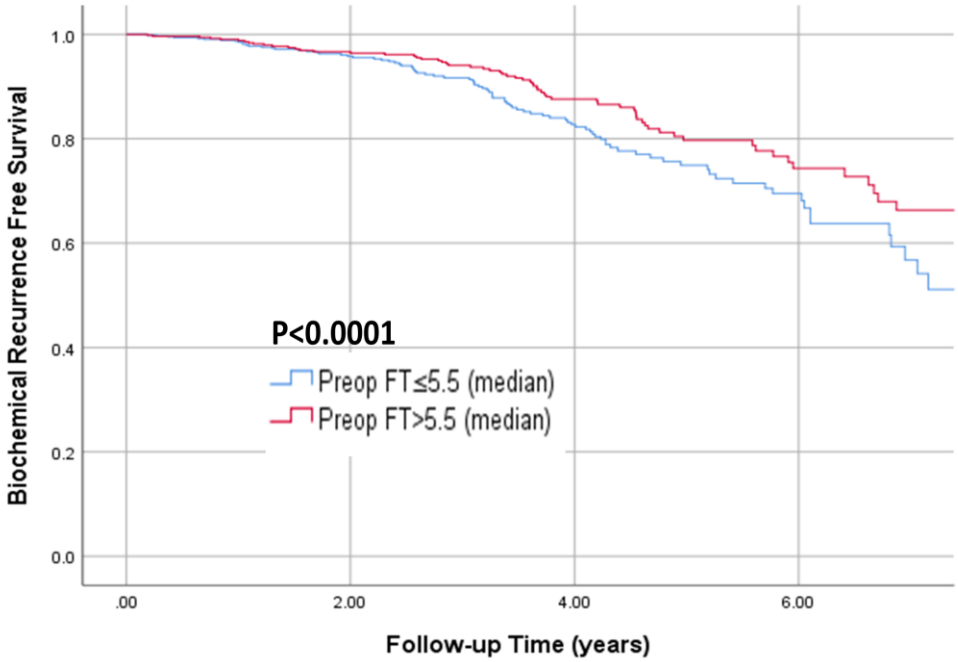
Preop cFT vs BCR

Table 1. Logistic Regression of Factors predicting Post-RARP recurrence, including endogenous preoperative cFT.

	B	S.E.	Wald	Sig.	OR	95% C.I.	
						Low	High
Age, cont.	0.02	0.016	1.534	0.216	1.02	0.989	1.052
Preoperative PSA, cont.	0.101	0.018	31.526	**<0.001**	1.106	1.068	1.146
GGG [<4+5 (ref) vs. 9-10]	1.734	0.244	50.583	**<0.001**	5.661	3.511	9.128
p-stage [pT2 (ref) vs. pT3/T4]	1.531	0.237	41.655	**<0.001**	4.625	2.905	7.364
Preoperative FT, cont.	-0.449	0.235	3.639	**0.046**	0.638	0.402	0.999



- Figure 1 illustrates a cox regression for BCR-free survival, stratifying patients by preoperative cFT. 415 patients had a preoperative cFT≤5.5 that was compared to 415 patients with preoperative FT >5.5.
- After adjusting for preoperative PSA, BMI, and age, low cFT was significantly associated with increased likelihood of GGG 9-10 (P=0.036), stage pT3/T4 (P=0.047), and BCR within 3-years post-RP (P<0.0001).

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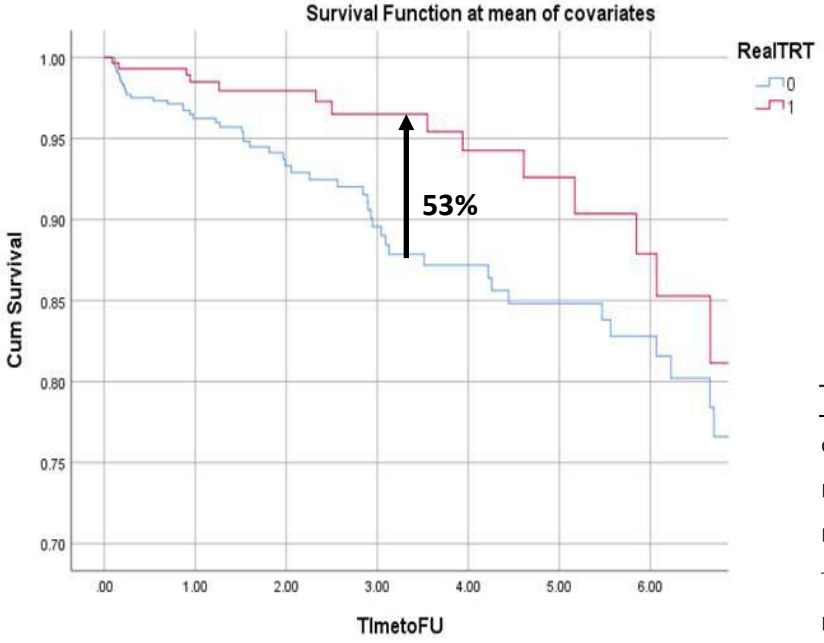
UCI Prostate cancer study 2009-2019:

Testosterone Replacement and Recurrence (N=571)



TRT exerted a protective effect with a **53%** reduction in BCR at a median 3.1 years.

	B	SE	Wald	P	OR	95%CI	
Gleason Grade Group [1-4 (ref) vs. 5]	1.664	0.311	28.673	<0.001	5.28	2.872	9.708
Preoperative Free Testosterone (cont.)	-0.14	0.063	4.911	0.027	0.869	0.768	0.984
Pathologic Stage [pT2 (ref) vs. pT3/pT4]	1.407	0.268	27.638	<0.001	4.084	2.417	6.901
Testosterone Therapy [TRT (ref) vs. cont.]	-0.616	0.313	3.88	0.049	0.54	0.292	0.997
Preoperative PSA (cont.)	0.058	0.012	23.651	<0.001	1.06	1.035	1.085

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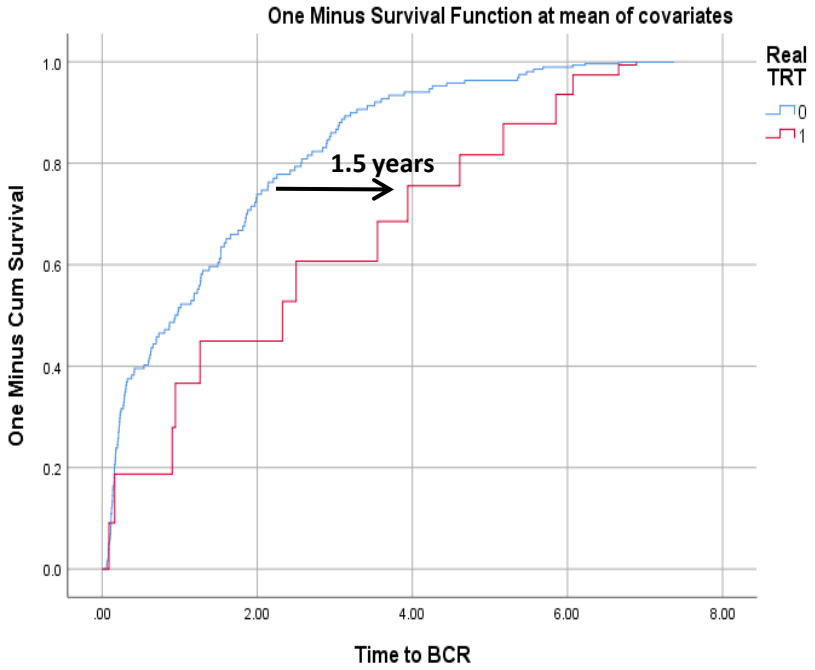
Testosterone Replacement and Recurrence (N=571)



For men who did recur, TRT delayed disease progression **by 1.5 years.**

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Testosterone and Prostate Cancer: A Tale of Two Cities and Separating Myth from Reality

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Association of the extent of therapy with prostate cancer in those receiving testosterone therapy in a US commercial insurance claims database

David S. Lopez, Danmeng Huang, Konstantinos K. Tsilidis, Mohit Khera, Stephen B. Williams, Randall J. Urban, Orestis A. Panagiotou, Yong-fang Kuo, Jacques Baillargeon, Albert Farias, Trudy Krause ... See fewer authors

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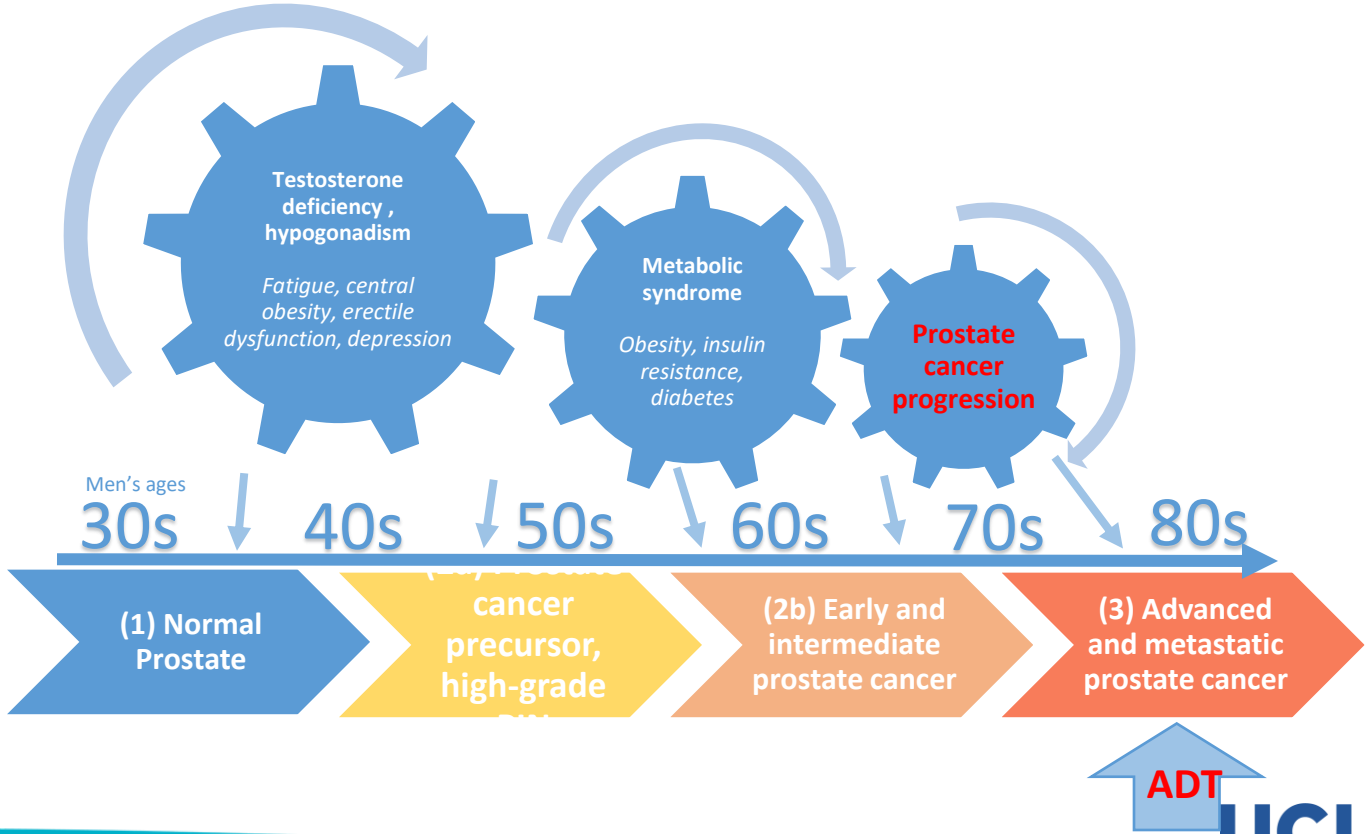
matched men free of prostate cancer.

33% reduced association of PCa after comparing the highest category (>12) of TTh injections with the lowest (1-2 injections) category (HR = 0.67, 95% CI: 0.54-0.82).

1. TRT had wide favorable risk prostate cancer (OR, 1.35; 95% CI, 1.16 to 1.56) and lower risk of aggressive prostate cancer (OR, 0.50; 95% CI, 0.37 to 0.67).

Increased use of TTh was inversely associated with PCa and this remained significant only among nondiabetics.

Interrelationship between Testosterone, Testosterone Deficiency, Metabolic Syndrome and Late PC Androgen Receptor Influences.



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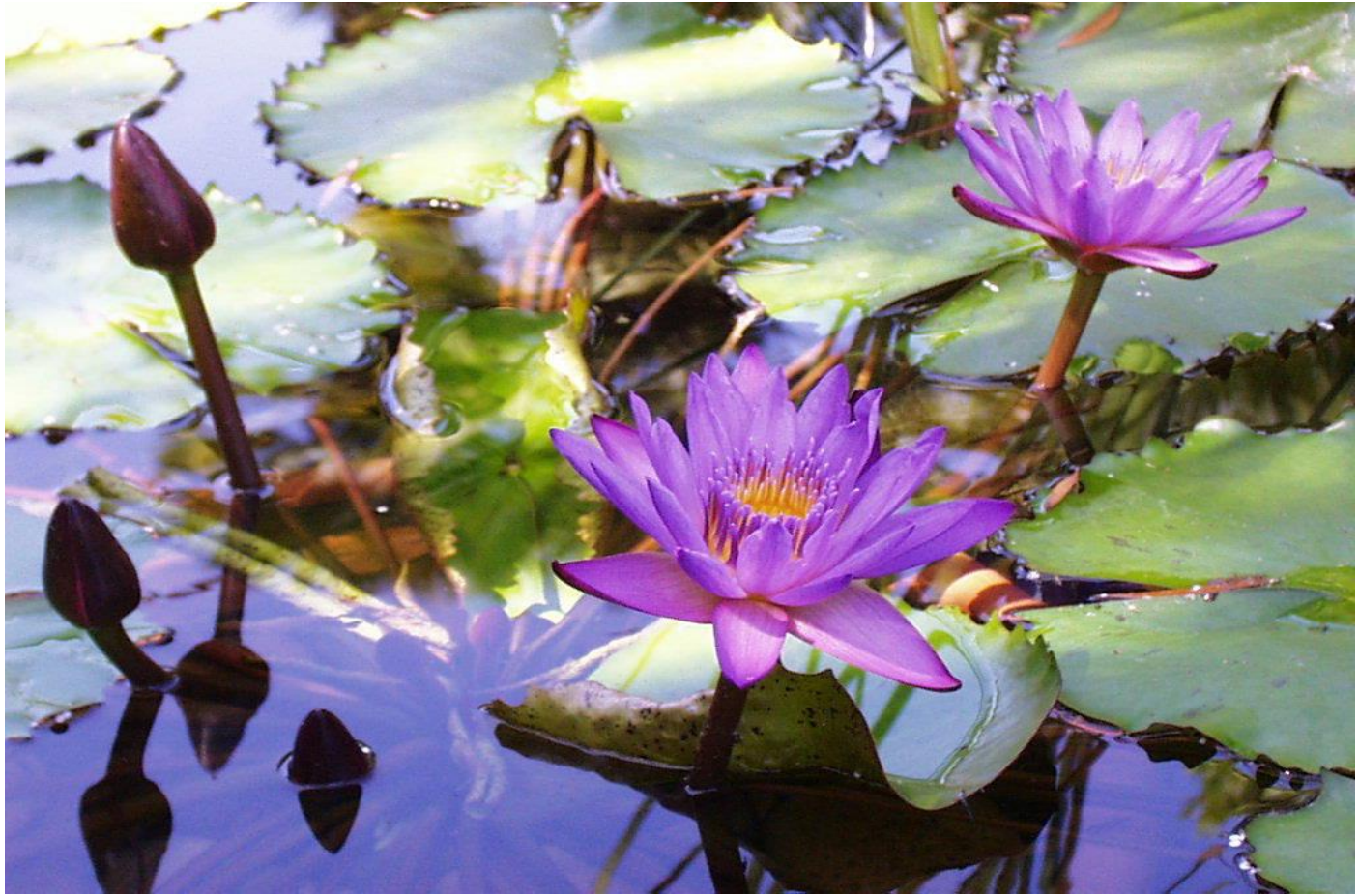
EMERGING ROLE OF TOTAL AND FREE TESTOSTERONE IN PROSTATE CANCER?

- **1** “Low testosterone” is not accurately determined by Total Testosterone!
- **2** Sex Hormone Binding Globulin and the calculated “Free Testosterone” appears to drive the critical impact of “Testosterone” in CaP.
- **3** Low FT in men with normal sexual function (IIEF-5: 22-25) reduces recovery of sexual function following RARP regardless of good nerve sparing surgery.

Conclusion

- Low cFT contributes to high-risk PC via increased GGG, p-stage, and likelihood of recurrence.
- Men with low cFT benefit oncologically with TRT – via a 53% reduction in BCR and a 1.5-year delay in “time to BCR”.
- These results argue the previous notions that high testosterone furthers PC progression and suggests the need for prospective studies assessing benefit of TRT in PC patients.



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