UNIVERSITY OF CALIFORNIA,
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Assessment of Preoperative Low Free Testosterone on Erectile Function in Men undergoing Radical Prostatectomy

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

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2020

DEDICATION

To

my parents, my significant other, and my friends

in recognition of their unwavering belief and tireless support

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ABSTRACT OF THE THESIS

The Protective Effect of Free Testosterone on Sexual Function in Men with Prostate Cancer undergoing Radical Prostatectomy

by
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Master of Science in Biomedical and Translational Science

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Professor Thomas E. Ahlering, Chair

The relationship between testosterone and prostate cancer is both complex and understudied. Impact of testosterone on disease aggressiveness, overall health status, and sexual function are of particular interest in both prostate cancer patients and in aging men. As such, the present study seeks to explore the impact of free testosterone on sexual function in prostate cancer patients (PCa) undergoing radical prostatectomy.

From 2009 to 2019, 783 men with localized PCa were treated with robot-assisted radical prostatectomy (RARP). Total testosterone and sex hormone binding globuin (SHBG) was collected from all patients and free testosterone (cFT) was prospectively calculated. Sensitivity analysis was performed to identify relevant cut-points in age, free testosterone, and sexual function scores. Impact of free testosterone (cFT), age, comorbidity status, and disease characteristics were considered as covariates and linear regression models were generated to predict sexual function.

In sensitivity analysis, men over the age of 60 had significantly lower cFT, higher serum prostate specific antigen (PSA) and prostate weight. Additionally, these men also had a higher proportion with high-risk (GGG 9-10) and high-volume (p-stage T3/T4) disease. After adjusting covariates in linear regression, cFT was an independent predictor of preoperative IIEF-5 scores for men above the age of 60 years (p=0.001, Beta: 0.140, 95% CI: 0.165 – 0.690). In addition, prostate weight was a significant covariate of preoperative IIEF-5 scores for men above 60 years of age (p=0.013, Beta: -0.110, 95% CI: -0.066 – -0.008). cFT appears to be an independent predictor of preoperative sexual function in older men with PCa.

These results highlight the deleterious effects of long-term exposure to low cFT. We emphasize that cFT (over total testosterone) should be systematically checked in all men regardless of age. Furthermore, testosterone replacement therapy should be considered as an early intervention strategy in at-risk patients.

INTRODUCTION

Adult-onset hypogonadism (AOH) is caused by decreased levels of circulating androgens, with the most clinically significant factor being poor testosterone release from the testes (1,2). This disorder consists of a broad constellation of symptoms including decreased sexual function, diminished lean body mass, loss of bone density, depressive mood, poor cognition, and sleep disturbances (1,3–5). In adult males, primary hypogonadism is commonly due to direct injury from trauma or disease of the testes, while secondary hypogonadism is due to dysfunction in the higher levels of the hypothalamic-pituitary-gonadal axis (6–10). AOH is likely a combination of primary and secondary hypogonadism as these men present with low levels of testosterone as well as normal-to-low levels of luteinizing hormone (LH), indicating failure of the testes as well as the hypothalamus and pituitary gland (11,12).

The true prevalence of AOH is difficult to ascertain due to differing thresholds patients have in how well they tolerate their symptoms before presenting to their physician (2,13–15). As adult men experience a yearly drop of 0.8% and 2% of their serum TT and FT, respectively, it is likely that men with AOH concordantly begin to develop indolent comorbidities without identification and treatment in the early phases of their disease (6,7,16,17). The Massachusetts Male Aging Study (MMAS), one of the largest longitudinal studies on aging males, reported even greater rates of decline of 1.6% in TT and 3% in FT per year for men between 40- to 70-years of age (7). In a study analyzing the MMAS, Araujo et al. estimated a baseline 6.0% prevalence of hypogonadism for 40- to 69-year old men that rose to 12.3% at 8.8 years follow-up (18). This would represent approximately 481,000 new cases of hypogonadism per year in the United States for men 40-69 years old (18). Lowered levels of testosterone have been associated with poorer overall health and increased risk of developing metabolic syndrome disorders including type 2 diabetes, hypertension, and obesity (19). As hypogonadism and aging greatly overlaps in symptomatology and risk of comorbidities, there has been a modern

resurgence of research in the fluctuating levels of testosterone of the aging male and the possible benefits for testosterone replacement therapy (TRT) (20–22).

BACKGROUND

Measuring Testosterone

AOH in the aging male is a nebulous condition with imprecise laboratory parameters (23). Further compounding the issue is the inaccuracy laboratory tests are often marred with when measuring testosterone levels (23). Measuring testosterone is not a precise science as levels can fluctuate from a wide variety of causes (13,23). The most consistent are the diurnal changes coinciding with the circadian rhythm as testosterone will peak in the early morning and trough during the evening (24). Thus, it is strongly recommended that patients being evaluated for hypogonadism have their laboratory levels drawn between 07:00 AM – 11:00 AM (13,25). Acute illness, such as respiratory infections and sepsis, as well as physiological stressors in the form of surgery and bodily injury have been well-documented to decrease levels of testosterone (26–30). In one study, young men with respiratory infections experienced a 10% transient decrease in their testosterone levels during the acute phase of the disease (31). Men with chronic diseases, such as cancer and liver disease, experience even greater decrease in testosterone levels as well as an increased risk for early-onset AOH (29,32). Further complicating clinical evaluation is the 32% within-subject variation testosterone levels may have when comparing values drawn one day to the next (33). For these reasons, repeated levels of TT and investigations into FT levels are required before considering TRT (12,34).

Total versus Free Testosterone

Conventionally, TT has been the mainstay for measuring androgen levels due its wide availability and familiarity as the first step in the diagnosis of AOH (12,13,19,34). In erectile dysfunction (ED), the EAU, British Society of Sexual Medicine, SMSNA, and AUA all agree that

TT levels are essential (12,34–36). It is well-known that testosterone levels and sexual function are individually associated with aging in an inverse fashion (7,37,38). However, the relationship between TT levels and sexual function, especially in older men, is not as clear (39–41). This may be attributed to rising levels of SHBG with relatively stable TT, resulting in lower levels of FT in aging men (6,9). As such, when a patient presents with low to borderline levels of TT, societal guidelines recommend follow-up measurements that include FT (1,12,19,34). Some studies have demonstrated the clinical utility measuring FT may have as low levels have been associated with greater risk for insulin resistance, metabolic syndrome, and cardiovascular disease as well as poor cognitive function and Alzheimer's disease (42–47).

Measuring Sexual Function

While a variety of questionnaires exist to measure male sexual function, none are as ubiquitous as the International Index of Erectile Function (IIEF) (48). The IIEF was initially validated with 15-items for clinical trials (49). It was the measurement of choice in the original studies on sildenafil and has been used in more than 50 clinical trials since (48,50). A simplified version was created with 5-items (IIEF-5) and has been validated for daily, clinical practice (51). It is available in over 32 languages and a myriad of studies have shown its efficacy in sexual function among wide ethnic and geographic backgrounds (52).

Study Aims

The relationship between aging and testosterone is further complicated in prostate cancer patients and, especially, in those considering radical prostatectomy as a treatment option. Impact of testosterone on disease aggressiveness, overall health status, and sexual function are of particular interest due to the complex relationships between androgens, possible disease progression, and side effects of definitive treatment. In this regard, the present study

seeks to explore the impact of free testosterone on sexual function in prostate cancer patients (PCa) undergoing radical prostatectomy.

METHODS

Patient Selection

The database utilized in this study has been reviewed and approved by the University of California, Irvine's Institutional Review Board (HS# 1998-84) with all patients providing written informed consent prior to being included. Data collection was performed in compliance with the Health Insurance Portability and Accountability Act with all values stored in an anonymous fashion.

This was a retrospective cohort analysis performed on a prospectively managed database of 923 men with localized PCa treated by robot-assisted radical prostatectomy (RARP) between December 2009 to August 2019 from a single, high-volume surgeon. One hundred fifty patients were excluded as they had a history of TRT.

Preoperative levels of prostate-specific antigen (PSA), IIEF-5, body mass index (BMI), prostate volume, TT, and SHBG were systematically recorded. Patients were instructed to have TT and SHBG levels drawn before 10:00am. A validated calculator was utilized to determine cFT from preoperative TT and SHBG values (53). To accurately reflect PSA levels in patients taking 5α-reductase inhibitors, PSA levels were multiplied by a factor of 2. IIEF-5 scores were subtracted by 7 points if patients were using phosphodiesterase type 5 (PDE5) inhibitors. Postoperatively, pathologic Gleason score (pGS) and tumor stage (pT) were noted.

Primary Statistical Analysis

Effect of aging on free testosterone was considered via sensitivity analysis. The database was divided by 3 different age cut-offs of 55-, 60-, and 65- years of age (i.e., <55 vs. >55, <60 vs. >60, <65 vs. >65). Sensitivity analyses were conducted via Pearson's correlations.

Univariate analysis was then performed to determine the significant difference in clinical demographics between the younger and older cohorts. Significant covariates of age, cFT, and sexual function were identified using two-tailed, Student t-tests and Fisher's exact tests. Sexual function was assessed as a continuous variable and via the IIEF-5. Two linear regression models were created, one for each cohort, to assess whether cFT was predictive of preoperative sexual function after adjusting for significant covariates. In the linear regression models, pGS and pT were treated as binomial categorical variables with pGS 1 – 3 and pT2 as reference groups, respectively. The threshold for significance was considered to be $p<0.05$.

Secondary Statistical Analysis

Impact of cFT on overall health status and comorbidities profiles were considered. A random number generator on IBM SPSS® Statistics was utilized to randomly select 100 patients from each cohort, creating a 200-patient sample pool. Univariate analysis was performed to determine whether the clinical demographics in the new sample was representative of the overall patients in the database. Through a retrospective chart review of the electronic medical record system, Charlson Comorbidity Index (CCI) scores were tabulated for each patient in the sample group. Again, significant covariates of age, cFT, and sexual function were identified using two-tailed, Student t-tests and Fisher's exact tests. Six more linear regression models were created, three for each cohort, to assess whether cFT was predictive of preoperative sexual function after adjusting for significant covariates. pGS and pT were treated as binomial categorical variables with pGS 1 – 3 and pT2 as reference groups, respectively. The threshold for significance was considered to be $p<0.05$.

RESULTS

Sensitivity Analysis

Sensitivity analysis showed 60 years of age to be the most specific cut-off, with primary endpoint of IIEF-5 score. (R=0.167 for men >60-years of age) (Table 1) (54).

Table 1. Pearson's Correlation between Preoperative cFT and IIEF-5 scores at various age cutoffs.

	Pearson's R	p-value
<55 Years	-0.26	0.789
≥55 Years	0.145	**<0.001**
<60 Years	-0.041	0.515
≥60 Years	0.167	**<0.001**
<65 Years	0.06	0.195
≥65 Years	0.133	**0.017**

Impact of Age on Free Testosterone

Of the 783 men included in this study, 260 were younger than 60-years and 523 older than 60-years of age. Men over 60 years of age had significantly higher serum PSA (8.9 ng/dL vs. 6.9 ng/dL, p=0.001), prostate volume (56.7 mL vs. 46.8 mL, p<0.001), and SHBG (50.8 nmol/L vs. 40.8 nmol/L, p<0.001), but lower IIEF-5 scores (17.9 vs. 21.8, p<0.001) and cFT (5.9 ng/dL vs. 6.9 ng/dL, p<0.001). Additionally, a higher proportion of the older men also had high-risk (pGS 5: 16% vs. 8%, p<0.001) and high-volume (pT3/4: 43% vs. 29%, p<0.001) disease. Further clinical demographics can be found in Table 2.

Table 2: Clinical Demographics of Younger versus Older Patients with Prostate Cancer.

	< 60 years n=260 **Mean (SD)**	**≥ 60 years** n=523 **Mean (SD)**	**p-value**
Age (years)	55.0 (4.1)	67.4 (4.8)	**<0.001**
PSA (ng/dL)	6.9 (5.0)	8.9 (11.5)	**0.001**
IIEF-5	21.8 (5.2)	17.9 (7.4)	**<0.001**
BMI (kg/m2)	27.1 (3.2)	27.0 (3.5)	0.664
Prostate Volume (mL)	46.8 (14.4)	56.7 (22.1)	**<0.001**
Preoperative TT (ng/dL)	375.8 (147.4)	379.5 (159.5)	0.753
Preoperative SHBG (nmol/L)	40.8 (18.4)	50.8 (22.3)	**<0.001**
Preoperative FT (ng/dL)	6.9 (3.0)	5.9 (2.4)	**<0.001**
	N (%)	**N (%)**	**p-value**
Nerve Sparing			**<0.001**
Bilateral	232 (89)	404 (77)	
Unilateral	25 (10)	75 (14)	
None	3 (1)	44 (8)	
Pathologic Grade			**<0.001**
1	60 (23)	72 (14)	
2	115 (44)	195 (37)	
3	51 (20)	134 (26)	
4	14 (5)	39 (7)	
5	20 (8)	83 (16)	
Pathologic Stage			**<0.001**
pT2	185 (71)	298 (57)	
≥pT3	75 (29)	225 (43)	

In correlative analysis and in the cohort of men <60-years of age, there was no association between cFT and IIEF-5 (R2=0.0003) (Figure 1a.). For the older cohort, there was a 0.45 drop in IIEF-5 scores for every unit decrease in cFT (R2=0.0222) (Figure 1b).

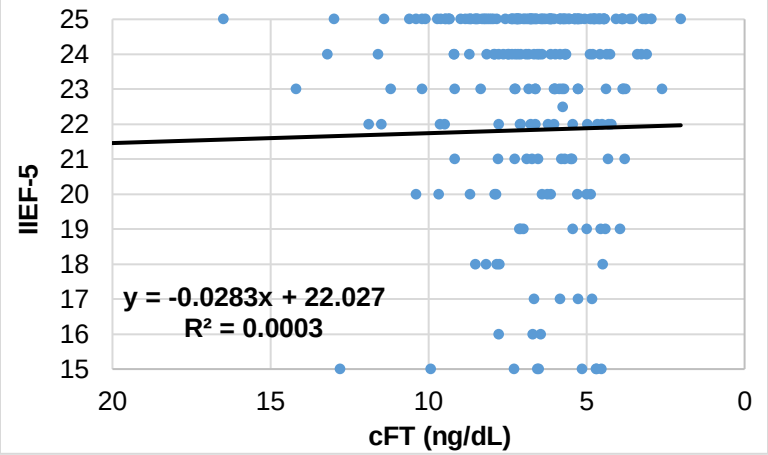

Figure 1a. Correlation between cFT and IIEF-5 scores for men <60 years of age.

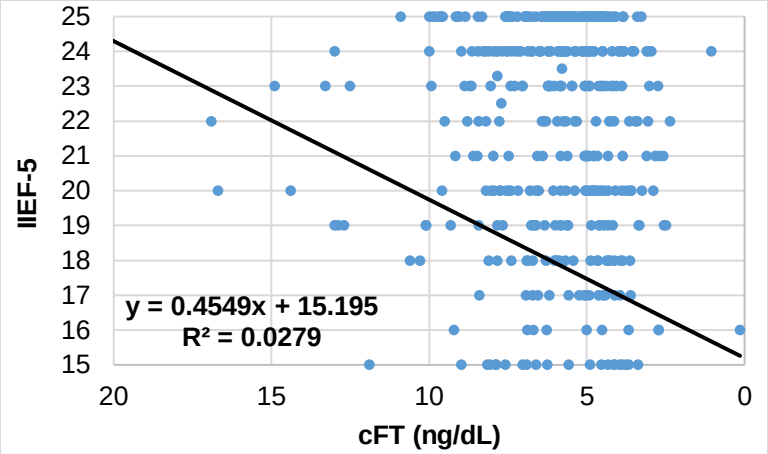

Figure 1b. Correlation between cFT and preoperative IIEF-5 scores for men ≥60 years of age.

After adjusting for significant covariates with linear regression, cFT was an independent predictor of preoperative IIEF-5 scores only for men above the age of 60 years (Beta: 0.140, 95% CI: 0.165 – 0.690, p=0.001) (Table 2b). Prostate volume was also significantly associated with preoperative IIEF-5 scores for men >60 years of age (Beta: -0.110, 95% CI: -0.066 – -0.008, p=0.013).

Table 2a. Predictors of Preoperative IIEF-5 in patients <60 years.

	B	Std. Error	Beta	t	Sig.	95.0% CI for B Lower	Upper
Constant	21.860	1.337		16.348	<0.0001	19.226	24.493
cFT (cont.)	-0.057	0.111	-0.033	-0.514	0.608	-0.275	0.161
PSA (cont.)	0.066	0.071	0.064	0.933	0.352	-0.073	0.205
Prostate Volume (cont.)	0.006	0.023	0.016	0.253	0.800	-0.039	0.050
pGS [1-4 (ref) vs. 5]	-0.628	1.265	-0.033	-0.497	0.620	-3.119	1.862
pT [2 (ref) vs. 3/4]	-1.120	0.762	-0.099	-1.469	0.143	-2.621	0.381

Table 2b. Predictors of Preoperative IIEF-5 in patients ≥60 years.

	B	Std. Error	Beta	t	Sig.	95.0% CI for B Lower	Upper
Constant	17.697	1.296		13.658	<0.0001	15.151	20.242
cFT (cont.)	0.428	0.134	0.140	3.201	**0.001**	0.165	0.690
PSA (cont.)	0.043	0.029	0.066	1.479	0.140	-0.014	0.100
Prostate Volume (cont.)	-0.037	0.015	-0.110	-2.501	**0.013**	-0.066	-0.008
pGS [1-4 (ref) vs. 5]	-1.085	0.950	-0.053	-1.143	0.254	-2.951	0.781
pT [2 (ref) vs. 3/4]	-0.984	0.697	-0.065	-1.411	0.159	-2.353	0.386

When age was introduced as a significant covariate for each age cohort, it was an independent predictor of preoperative IIEF-5 scores within each cohort (Table 3a-b).

Table 3a. Predictors of Preoperative IIEF-5 in patients <60 years.

	B	Std. Error	Beta	t	Sig.	95.0% CI for B Lower	Upper
Constant	33.701	4.702		7.167	<0.001	24.440	42.961
Age (cont.)	-0.224	0.080	-0.177	-2.811	**0.005**	-0.381	-0.067
cFT (cont.)	-0.166	0.139	-0.075	-1.194	0.233	-0.439	0.108
PSA (cont.)	0.045	0.070	0.043	0.635	0.526	-0.094	0.183
Prostate Volume (cont.)	0.011	0.023	0.031	0.494	0.621	-0.033	0.056
pGS [1-4 (ref) vs. 5]	-0.454	1.253	-0.024	-0.362	0.717	-2.921	2.013
pT [2 (ref) vs. 3/4]	1.056	0.753	0.093	1.401	0.162	-0.428	2.539

Table 3b. Predictors of Preoperative IIEF-5 in patients ≥60 years.

	B	Std. Error	Beta	t	Sig.	95.0% CI for B Lower	Upper
Constant	52.492	4.568		11.490	<0.001	43.517	61.468
Age (cont.)	-0.530	0.064	-0.346	-8.225	**<0.001**	-0.657	-0.404
cFT (cont.)	0.342	0.134	0.106	2.553	**0.011**	0.079	0.605
PSA (cont.)	0.027	0.027	0.042	0.999	0.318	-0.026	0.081
Prostate Volume (cont.)	-0.019	0.014	-0.057	-1.369	0.172	-0.047	0.008
pGS [1-4 (ref) vs. 5]	-0.821	0.891	-0.040	-0.921	0.358	-2.572	0.931
pT [2 (ref) vs. 3/4]	0.236	0.660	0.016	0.358	0.721	-1.061	1.534

Impact of Comorbidity Status on Free Testosterone

In a randomly selected sample of 200 patients, the median CCI score was 2. 4.5% of patients had no comorbidities, 31.8% had 1, and the remaining 53.7% of patients had ≥2 comorbidities. When analyzing for correlations between comorbidity status and sexual function, men with higher CCI scores were more likely to have a lower IIEF-5 score ($R= -0.309$, $p<0.001$).

Combined with age analysis, men over 60 years of age had significantly higher serum PSA (8.9 ng/dL vs. 6.6 ng/dL, $p=0.008$), prostate volume (58.8 mL vs. 47.2 mL, $p<0.001$), and SHBG (50.8 nmol/L vs. 40.8 nmol/L, $p<0.001$), but lower IIEF-5 scores (18.2 vs. 21.4, $p=0.001$). Older men also had significantly worse CCI scores (3.03 vs. 1.23, $p<0.001$). cFT was lower in the older men, but not significantly different (5.9 ng/dL vs. 6.5 ng/dL, $p=0.053$). A higher proportion of the older men also had high-risk (pGS 5: 24% vs. 6%, $p<0.001$) and high-volume (pT3/4: 45% vs. 29%, $p=0.02$) disease. Further clinical demographics can be found in Table 4.

Table 4. Clinical Demographics of the Randomly Selected Sample Patients with CCI Scores.

	< 60 years n=100 Mean (SD)	**≥ 60 years** n=100 Mean (SD)	p-value
Age (years)	54.9 (3.7)	66.9 (5.3)	**<0.001**
PSA (ng/dL)	6.6 (4.1)	8.9 (7.1)	**0.008**
IIEF-5	21.4 (5.8)	18.2 (7.2)	**0.001**
CCI	1.23 (0.7)	3.03 (0.9)	**<0.001**
BMI (kg/m2)	27.2 (3.1)	27.7 (3.8)	0.375
Prostate Volume (mL)	47.2 (14.5)	58.8 (23.5)	**<0.001**
Preoperative TT (ng/dL)	350.5 (114.7)	373.7 (158.7)	0.238
Preoperative SHBG (nmol/L)	38.8 (16.4)	49.3 (21.8)	**<0.001**
Preoperative FT (ng/dL)	6.5 (2.1)	5.9 (2.2)	0.053
	N	**N**	p-value
Nerve Sparing			**0.003**
Bilateral	90	71	
Unilateral	7	21	
None	3	8	
Pathologic Grade			**0.001**
1	18	11	
2	52	34	
3	19	26	
4	5	5	
5	6	24	
Pathologic Stage			**0.02**
pT2	71	55	
≥pT3	29	45	

After adjusting for significant covariates, including CCI, with linear regression, cFT again was an independent predictor of preoperative IIEF-5 scores only for men above the age of 60 years (Beta: 0.323, 95% CI: 0.456 – 1.632, p=0.001) (Table 5b). CCI (Beta: -0.333, 95% CI: -4.145 – -1.176, p=0.001) and pGS (Beta: -0.208, 95% CI: -6.899 – -0.104, p=0.044) were also significantly associated with preoperative IIEF-5 scores for men >60 years of age.

Table 5a. Predictors of Preoperative IIEF-5 in Sample Group Patients <60 years.

	B	Std. Error	Beta	t	Sig.	95.0% CI for B Lower	Upper
Constant	25.655	5.638		4.551	0.000	14.460	36.851
cFT (cont.)	-0.452	0.285	-0.165	-1.587	0.116	-1.019	0.114
CCI (cont.)	0.473	0.884	0.055	0.535	0.594	-1.283	2.230
BMI (cont.)	-0.062	0.203	-0.032	-0.303	0.762	-0.465	0.342
PSA (cont.)	0.000	0.147	0.000	-0.002	0.998	-0.292	0.292
Prostate Volume (cont.)	0.007	0.042	0.017	0.158	0.875	-0.077	0.090
pGS [1-4 (ref) vs. 5]	-3.340	2.514	-0.137	-1.329	0.187	-8.332	1.652
pT [2 (ref) vs. 3/4]	-0.506	1.333	-0.040	-0.380	0.705	-3.153	2.141

Table 5b. Predictors of Preoperative IIEF-5 in Sample Group Patients ≥60 years.

	B	Std. Error	Beta	t	Sig.	95.0% CI for B Lower	Upper
Constant	27.469	5.760		4.769	0.000	16.029	38.909
cFT (cont.)	1.044	0.296	0.323	3.527	**0.001**	0.456	1.632
CCI (cont.)	-2.660	0.747	-0.333	-3.560	**0.001**	-4.145	-1.176
BMI (cont.)	-0.149	0.188	-0.077	-0.788	0.433	-0.523	0.226
PSA (cont.)	-0.032	0.100	-0.032	-0.325	0.746	-0.231	0.166
Prostate Volume (cont.)	-0.025	0.031	-0.083	-0.823	0.413	-0.087	0.036
pGS [1-4 (ref) vs. 5]	-3.502	1.711	-0.208	-2.047	**0.044**	-6.899	-0.104
pT [2 (ref) vs. 3/4]	-1.124	1.623	-0.078	-0.693	0.490	-4.347	2.099

DISCUSSION

Aging has been shown to be independently associated with AOH, comorbid illness, and sexual function separately. However, the interaction between these three factors in the aging male has yet to be fully elucidated. To our best knowledge, this is the first study to demonstrate cFT as an independent predictor of sexual function in older men after adjusting for significant covariates including comorbid illness. While TT was comparable between younger and older men, cFT was significantly lower in men >60-years of age. In a prospective cohort study of 3,654 men, Yeap et al. found TT concentration to remain steady with advancing age while FT declined, similarly to our findings (8). FT and LH have also been shown to be inversely correlated in aging men, suggesting poorer hypothalamic-pituitary response with lower levels of circulating FT (55,56). While 60-years was the cutoff chosen in this study, we believe that the negative consequences of AOH is not restricted to this age limit and can afflict both the young and old. During our sensitivity analyses, there was significant association found between cFT and sexual function at every age cutoff (Table 1). Furthermore, when age was reintroduced into

our multivariate models, it predicted sexual function for both age cohorts (Table 3a-b). While our cFT findings may be more pronounced in older men, we believe that younger adults are also at risk of experiencing the negative side effects of AOH prior to developing overt laboratory patterns shown in this study (Table 3a-b). Overall, our findings demonstrate how low cFT can have deleterious effects on men even with eugonadal levels of TT. As TRT may have protective benefits in men suffering from low levels of testosterone, cFT should be drawn in conjunction with TT to detect the process of AOH earlier in young adults.

Early Testosterone Studies

Dr. Huggins received the Nobel Prize in 1966 for his work demonstrating that manipulation of hormones could treat cancer, resulting in the first systemic approach to the treatment of PCa (57). The paper published in 1941 was titled the Studies on Prostate Cancer Part I and involved 47 men with PCa, eight of whom had metastases or highly elevated acid phosphatase, an older and less specific marker for PCa (58). Among the eight with advanced disease, three were subjected to injection of testosterone and their acid phosphatase levels were then measured. Only one of the three injected with testosterone had a sustained elevation in their acid phosphatase levels (58). The results from the single patient was interpreted as being the first demonstration that excess androgens, in the form of testosterone injections, promotes growth of PCa (59).

Testosterone and the Prostate

On top of inducing male sexual traits and organs, testosterone is known to regulate multiple parameters of health including lean muscle mass, bone density, lipid levels, immune response and the nervous system (60,61). A surge in androgens causes the prostate to swell in volume 10-fold during puberty, while, in adulthood, DHT will promote a more linear prostatic growth, which has been implicated as the pathophysiology of benign prostate hypertrophy

(BPH) (62–64). In landmark studies published in 1941, Dr. Charles Huggins and Dr. Clarence Hodges demonstrated that surgical or hormonal castration resulted in regression of metastatic PCa, which solidified the “androgen hypothesis” as the main model for PCa pathogenesis (58). Their work paved the way for setting androgen deprivation therapy as a mainstay of PCa treatment, which continues to be utilized today for those with advanced stages of disease (65–67). More recently, studies at the cellular level have shown that PCa cell lines will grow and die in response to androgen supplementation or withdrawal respectively (68–70). In a stepwise fashion, the association of testosterone as the fuel to the fire of PCa had been cemented in the minds of physicians, researchers, and the public alike.

Modern Understanding of Testosterone and the Prostate

With the prevailing “androgen hypothesis” and evidence of the efficacy of androgen deprivation therapy, any history of PCa was considered as strict contraindication for TRT for over 65 years (71,72). This fear based on historical evidence eventually came under scrutiny in the 1990s and 2000s with the introduction of the “saturation model”, which was born to reconcile the emergence of publications reporting no increased risk for PCa progression among patients receiving TRT (73–75). This model posited that the androgen-receptors on prostate cells are only responsive to fluctuations in serum testosterone within significantly low ranges of androgen, close to that of hormone castration levels (73). Beyond a certain androgen receptor saturation point, however, any additional rises in serum testosterone would not confer any added risk for malignant prostatic proliferation (73). This model could then explain the associations seen in the work by Huggins & Hodges as the vast majority of their patient pool had been castrated prior to the study (58).

With the advancements in both scientific understanding and treatment efficacy, it is estimated that there will be over 4 million survivors of PCa by 2024 (76). As the risks for both AOH and PCa increase with age, TRT for those with a history PCa has come to the forefront of

exciting scientific findings. Kaplan et al. found that among 1,181 men with a history of PCa who received TRT, there was no increase in PCa-specific mortality (75). More surprisingly, Ahlering et al. recently published a study in 2020 detailing a 54% reduction in biochemical PCa recurrence for those who received testosterone replacement after prostatectomy of low-grade prostate disease (77). The neutral, to even protective, findings of TRT post-prostatectomy is likely rooted in the oncologic burdens fueled by metabolic syndrome disorders (78–81). A population study of the Prostate Cancer Database Sweden (PCBaSe) stratified 118,543 men based on CCI scores and found that those with increasing comorbidities suffered from more severe PCa disease in both grade and tumor stage (82). After adjusting for PCa grade, size, and type of oncologic treatment received, CCI lost its effect on PCa-specific mortality while maintaining effect for other-cause (OC) mortality (82). This phenomena of CCI's independent association with OC-mortality instead of PCa-mortality, after radical treatment and adjustment for tumor type, has been replicated in multiple other studies (83–87). It stands to reason that with men where radical prostatectomy is definitive therapy, the disorders of metabolic syndrome must be controlled to extend their lives. In our study, older men had poorer general health and, after adjusting for cFT, CCI was found to be independently associated with preoperative sexual function. This may indicate IIEF's ability to represent the general well-being of patients pre-prostatectomy. Bittner et al. and Jeong et al. found lower IIEF scores to be associated with lower overall survival rates as well as higher pGS and larger tumor volume, respectively (88,89). While further work must be done before considering IIEF as a surrogate for general health influencing PCa-specific survival, we believe that measurement of testosterone levels and sexual function have deeply rooted roles in maximizing both quality and length of life.

Strengths and Limitations

This is one of the first studies comparing cFT levels between younger and older men with PCa. While TT measurements may be more readily available, FT levels more accurately

represent the bioavailable testosterone levels accessible for physiologic activity. This study also investigated and adjusted for testosterone levels, sexual function, and comorbid disease in PCa. We were able to replicate the clinical utility of cFT measurements in older men as well as demonstrate CCI and IIEF's relationship in PCa. As IIEF is a widely available questionnaire in the field of urology, it would be of great benefit if further research was performed to demonstrate IIEF's association with PCa outcomes. Furthermore, all patients were treated by a single, high-volume surgeon. Therefore, patient outcomes were less likely to be affected by surgical technique.

While there were unique findings in this study, we were able to appreciate the limitations of our research. Firstly, this was a retrospective study on a prospectively managed database. CCI was not a datapoint prospectively managed, thus, it was limited to 200 patients who were randomly selected. Furthermore, the composition of the patients was not varied in terms of ethnic and socioeconomic status. While a homogenous database may lend itself to more clear statistical results, the findings in this study may not be immediately applicable to patients with varying backgrounds. Lastly, this was a study a very select subgroup of the general male population without a control group to compare to. Inferences from our findings must be tethered to an oncologic background as all of our patients had PCa that was eventually treated surgically.

CONCLUSIONS

These results highlight the deleterious effects of long-term exposure to low cFT. We emphasize that cFT (over total testosterone) should be systematically checked in all men regardless of age. Furthermore, testosterone replacement therapy should be considered as an early intervention strategy in at-risk patients.

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