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THE RELATIONSHIP BETWEEN PSA AND TOTAL TESTOSTERONE LEVELS IN MEN WITH PROSTATE CANCER

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Abstract

Background: PSA secretion is a testosterone (T) dependent process. Published data suggest that a low T level is an independent predictor of higher-grade prostate cancer (PC).

Aim: To evaluate the relationship between T and PSA in patients with PC.

Methods: All men diagnosed with PC with a recorded pre-treatment total T level measurement were included in this analysis. We analyzed demographic, clinical, and pathological data. Patients were stratified according to pretreatment PSA levels: <2 ng/mL, 2–4 ng/mL, >4 ng/mL. Low T was defined as total T < 10.4 nmol/L (300 ng/dL), very low T < 6.9 nmol/L (200 ng/dL).

Outcomes: T levels by PSA groups according to the PC pathology.

Results: In this retrospective study, mean patient age was 61 years among 646 men. The distribution by PSA group was: 8% (<2), 17% (2–4), and 76% (>4). The mean T level across the entire cohort was 13 nmol/L (374 ng/dL). Overall, 30% had a T level < 10.4 nmol/L (300 ng/dL). The mean total T level by PSA group was: <2 ng/mL, 7 nmol/L (206 ng/dL); 2–4 ng/mL, 13 nmol/L (362 ng/dL); >4 ng/mL, 14 nmol/L (393 ng/dL), p<0.001. PSA <4 ng/mL was a significant predictor of low T in men with PC GS ≥8. PSA <2 ng/mL was a significant predictor of very low T independent of the PC pathology.

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Clinical implications: These findings suggest that clinicians should consider measuring T levels when a patient diagnosed with PC GS ≥8 and PSA level <4ng/ml, and for each patient with PSA level <2 ng/ml independent of the PC pathology.

Strengths & limitations: Our study has several strengths including (i) inclusion of a large population of men, (ii) use of a database which is audited and reviewed for accuracy annually, and (iii) use of an accurate T assay (LCMS). Nonetheless, there are limitations: (i) the subjects of the study are from a single institution, and (ii) we did not measure free T levels.

Conclusion: In men with PC with GS ≥8, PSA level <4 ng/mL predicts low T. PSA <2 ng/ml predicts very low T independent of the PC pathology.

Keywords

Testosterone; PSA; Prostate Cancer; Testosterone Deficiency; Hypogonadism

INTRODUCTION

Rates of both low serum testosterone (T) and prostate cancer (PC) increase with age, both impacting the health and quality of life of older men.[1] Studies have reported a prevalence of PC between 1–10%, with a probability of up to 14% lifetime diagnosis.[1–4] Up to 5% of older adults will have symptomatic low T levels.[5] The prevalence of low T levels in male across of age spectrum is highly variable ranging between 5% to 50%. This is related to factors such as type of assays used, time of the day blood drawn, comorbidities profile in different population, and the inclusion of symptomatic and non-symptomatic patients in certain patient cohorts. The Baltimore Longitudinal Study of Aging, based on laboratory measurements only, published a prevalence of low T of 12%, 20%, 30% and 50% in men in their 50s, 60s, 70s, and 80s, respectively.[1, 5, 6] Low T may impact men's overall health, with increased risks of lower bone mineral density, pre-diabetes/diabetes, metabolic syndrome, and major adverse cardiovascular events.[1, 7]

PC is an androgen-dependent cancer[8] and so is prostate-specific antigen (PSA) production.[9, 10] PSA is a serine protease involved in fertility, by contributing to the dissolution of the seminal fluid after ejaculation.[11] PSA production is dependent on T. T and dihydrotestosterone (DHT) bind and activate the androgen receptor in the cytoplasm of both benign and malignant prostate cells. This complex then passes into the nucleus, increasing the expression of PSA.[9] There is likely a threshold level of T required for optimal PSA production, consistent with the previously described "saturation model" for T stimulation of the androgen receptor.[1, 12]

For the last 30 years, PSA testing has been the cornerstone of PC screening, playing a critical role in diagnosing and monitoring men with PC.[13, 14] Historically, men with elevated PSA levels have undergone further evaluation and prostate biopsy. Studies have shown that the prevalence of PC increases in men with low T.[8, 15, 16] Low serum total T level has been shown to be associated with a higher stage and higher PC grade.[15]. It is also worth noting that low T levels are also associated with an increased likelihood of extra-prostatic extension, positive surgical margins andf biochemical recurrence for patients treated with

RP. [17, 18] Despite that, no society PC guideline includes serum T level measurement as an integral part of the patient assessment.

The present study aimed to evaluate the relationship between T and PSA in patients diagnosed with PC.

METHODS

Study Population:

After institutional review board approval was obtained (IRB 16–459), the computerized database of PC patients treated at our institution between 1998 to 2018 was reviewed. For this study, the inclusion criteria included men (i) diagnosed with organ confined PC, abnormal digital rectal exam or high PSA level, (ii) who had PSA and total T levels measured (iii) within 90 days prior to the date of their RP (iv) measured within 30 days of each other and (v) T levels measured with liquid chromatography mass spectometry (LCMS) before noon. Patients were subdivided based on PC surgical pathology into two groups: Gleason Sum (GS) 6–7 and (ii) GS ≥8. Men with androgen deprivation therapy, neo-radiation therapy or non-organ confined prostate cancer were exclusions. We also gathered and described demographic, comorbidity, and surgical pathology data including positive seminal vesicle invasion (SVI), positive surgical margins (SM), and positive lymph node involvement (LNI).

Laboratory measurement:

Patients were subdivided into three groups according to their PSA levels before RP: <2ng/mL; 2–4 ng/mL, and >4 ng/mL. Samples for total T levels were drawn before noon. Low T was defined as total T < 10.4 nmol/L (300 ng/dL), per AUA guidelines,[7] and patients with T < 6.9 nmol/L (200 ng/dL) were defined as having very low T. The use of LCMS offers analytical specificity superior to that of immunoassays with a well documented lower coefficient of variation. [19]

Statistics:

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). Descriptive statistics were reported as mean ± standard deviation (SD) or median (IQR) for continuous variables and as percentages for categorical variables. PSA and low T rates were calculated overall and by patient subsets (PSA level and pathology groupings). An overall association between PSA group and mean total T level group was tested via analysis of variance (ANOVA). Next, PSA association to rates of low T and very low T were tested within patient GS. The GS 6/7 group was subdivided into favorable or unfavorable surgical pathology. Favorable pathology was defined as negative SVI, negative SM, and negative LNI. Unfavorable surgical pathology included one or a combination of positive SVI, positive SM, and/or positive LNI. GS ≥8 was grouped irrespective of the surgical pathology. Multivariable logistic regression model analyses were performed. Age and diabetes were considered as potential covariates in multivariable analyses, dependent on significant association with T level groupings. Data published by Abdollah et al showed that Diabetes was an independent predictor of high-grade Gleason score, however this study

did not evaluate T levels.[20] Logistic regression models were fitted for each outcome: low T and very low T, regressed on PSA group, within each patient subset, and according to the PC pathology group, so that six models were tested (three GS groups and two separate outcomes). For each model, the lower PSA groups' (<2 ng/mL or 2–4 ng/mL) effect was assessed in comparison to the PSA group over 4 ng/mL. Results were reported as odds ratios (OR) with a 95% confidence interval (CI). The mean total T level preradical prostatectomy was plotted against continuous PSA values by the PC pathology according to the GS/pathology group, using a cubic spline smoothing function.[21] Type I error was set to 0.05 for all comparisons.

RESULTS

Study Population:

646 men met the study criteria with all the requisite data recorded. The study population had a median age of 61 (55–66) years, and 11% had diabetes, 6% coronary artery disease, 14% obstructive sleep apnea, 45% hypertension, and 49% dyslipidemia. 8% were current smokers and 32% former smokers. Age and prevalence of comorbidities as well as smoking status did not vary by GS significantly. Regarding PC pathology, 81% had a GS 6–7, and the remaining 19% had a GS ≥8; 16% had positive SVI, 23% positive SM, and 19% positive LNI. Patients with GS ≥8 had a higher frequency of positive SVI (41%), positive SM (33%), and positive LNI (51%). Table 1 summarizes the patients' GS/pathology group characteristics and comorbidities.

Laboratory measurements:

The median PSA level was 5.8 (4.1–8.9) ng/mL. 8% of men had a PSA level of <2 ng/mL, 17% between 2–4 ng/mL, and 76% a PSA level >4 ng/mL. The mean total T level across the entire cohort was 13±6 nmol/L (374±172 ng/dL); 30% had a total T level <10.4 nmol/L (300 ng/dL) and 11% <6.9 nmol/L (200 ng/dL). Patient laboratory results are presented in Table 1. The mean total T level by PSA group was 7±9 nmol/L (206±245 ng/dL) for PSA <2 ng/mL; 13±6 nmol/L (362±158 ng/dL) for PSA 2–4 ng/mL; and 14±5 nmol/L (393±156 ng/dL) for PSA >4 ng/mL ($p<0.001$). Diabetes rates, but not age, varied significantly with decreasing T level; 10% of men with low T had diabetes, 19% of men with very low T while only 8% of men with normal T levels ($p=0.01$). Figure 1 illustrates the prevalence of low T among PSA groups. Table 2 summarizes the patients' T profiles.

Predictors of low T levels:

PSA level <4 ng/mL was a significant predictor of low T in patients with a GS ≥8. There were higher odds of having low T or very low T within this group as PSA values decreased below 4 ng/mL in models adjusted for diabetes. Men with PSA <2 ng/mL group had 31 times the odds of having low T (OR = 30.9, 95% CI = 3.9 – 241) and almost 40 times of very low T (OR = 37.6, 95% CI = 9.5 – 149), compared to the PSA >4 ng/mL group. The PSA 2–4 ng/mL group also had significantly higher odds of both low T (OR = 8.49, 95% CI = 1.7 – 41) and very low T (OR = 5.90, 95% CI = 1.6 – 22). Within the GS 6/7 groups, both favorable and unfavorable, surgical pathology pretreatment, PSA < 2 ng/mL was significantly associated with very low T (OR = 9.08, 95% CI 2.8–29, and OR = 6.36,

95% CI = 1.1–38, respectively). Table 3 summarizes the logistic regression models between PSA grouping according to PC GS groups and low T and very low T. Figure 2 illustrates graphically the magnitude of the difference in low T rates for GS ≥8.

DISCUSSION

PC is highly prevalent in older men and represents almost 11% of all new cancer diagnoses in men, with an estimated 191,930 new cases in the U.S in 2020, according to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.[22] The screening, diagnosis, and monitoring of PC are typically based on PSA levels. Papsidero measured PSA quantitatively in the blood for the first time in 1980, and Stamey was the first to describe the clinical use of PSA as a marker of PC.[23] While far from a perfect test, PSA has been widely used to screen, diagnose, and monitor PC since 1991.[14] According to AUA PC guidelines, screening is recommended for men between 55 and 70, with PSA and digital rectal exams.[24]

The data vary widely regarding the prevalence of low T levels in the general population ranging from 2–50%, depending upon the population studied and assays used to measure T levels, among other factors. [25–29] According to the American Urological Association and its evaluation and management of T deficiency guideline, low T increases the risk for cardiovascular disease, diabetes, and low bone mineral density.[7] The overall prevalence of symptomatic low T has been reported to be as high as 5%; however, exact rates are difficult to ascertain.[5] This is largely due to variations in the T cut-off values used to define low T, the assays used to measure T, the forms of T measured (free and total), the timing of the T lab draws, and the heterogeneity of the populations studied. [7, 25–28, 30]

In the prostate cells, PSA production depends on T levels.[9, 10] Morgentaler et al, presented the saturation model[31] in which the androgen receptors are saturated after T levels reach 8.7 nmol/L (250 ng/dL). In men with low T, the PSA production is optimized, and these men may see greater PSA generation when T levels are in normal range. Rising PSA in patients with low T after T therapy has also been documented. In a cohort of 451 men with low T who received T treatment for 12 months, Khera et al. observed that a higher proportion of men with T levels ≤ 8.7 nmol/L (250 ng/dL) had a PSA increase compared to men with T levels > 8.7 nmol/L (250 ng/dL) (22% vs. 14%).[32] Rhoden et al. found similar results, in a study of 48 men with low T; higher PSA increases were detected in men with T levels < 8.7 nmol/L (250 ng/dL) compared to men with T levels ≥ 8.7 nmol/L (250 ng/dL) (mean PSA changes 0.33 vs. 0.25 ng/mL respectively).[33] Morgentaler et al. demonstrated that age (≥60 years) and low T were factors associated with greater PSA increases following normalization of T levels.[34]

Low serum total T level is an independent predictor of higher stage and higher grade PC.[15, 35] This is possibly related to the delayed diagnosis of PC, given the inability of some of these men to generate PSA due to their low T levels, impairing the screening process. Pichon et al. in a study that included 937 patients, and assessed T using immunoassay. As they reported low serum testosterone (< 300 ng/dL, 14.8%, 137 men had low T) as an independent risk factor for high Gleason score (4+3, 4+4, and 4+5). This group of men also

had higher rate of Gleason pattern 4. However, no difference in PSA was observed between normal and low T level groups.[35] This study did not report the mean T levels of each of the study groups. No difference in PSA between low and normal T level groups was identified. There are a number of plausible explanations for this, one of which was a low prevalence of low T in this study; and they used an accurate assay to assess total T level. In our study, we have a higher proportion of men with low T (around 1/3 of the sample size), and we used LCMS to assess total T levels. Wang et al. studied 379 patients with and without PC with two or more T assessments within five years; T decreases of more than 0.3 nmol/L (10 ng/dL) per year increased the odds of PC by 14%. If the reduction of T was ≥1 nmol/L (30 ng/dL) per year, the PC risk increased 5-fold.[36] Rastrelli et al. conducted a study of 3156 men without PC, with PSA levels <4 ng/mL. They found that men with low PSA (<0.65 ng/mL) were more likely to have low testosterone (<8 nmol/L or 232 ng/dL). While only 9% of the entire cohort had T levels <8 nmol/L (232 ng/dL), over half of these men had a PSA <0.65 ng/mL, suggesting that PSA could play a decisive role in monitoring or even diagnosing men with low T.[37]

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, in a cohort of 4073 men without PC, demonstrated that men with low T levels at baseline, <10nmol/L (288 ng/dL), had higher rate of PC diagnosis during follow up compared to men with greater baseline T levels.[38] In a multicenter, double-blinded, placebo-controlled trial of of 790 patients ≥65 years of age with low T levels (mean ≤ 9.5 nmol/L, 275 ng/dL), Cunningham et al. found that half of the cases with PC had a pathology GS ≥8.[39] Garcia-Cruz et al. reported in a cohort of 137 patients with PC, that patients with GS ≥8 had lower T levels (mean T = 12 nmol/L, 347 ng/dL) compared to 16 nmol/L (452 ng/dL) for GS 6 and 15 nmol/L (441 ng/dL) for GS 7.[40] Watts et al, in data analysis of 20 prospective studies, reported that the lowest percentile free T levels had the lowest risk of PC.[41] However, this study has several major methodological issues to consider: (i) total T levels assay was not reported, but it is likely highly variable among the 20 different studies (ii) free T levels were analyzed using a calculated method which is known to be notoriously inaccurate, and were based on a constant albumin concentration, (iii) a higher proportion of the T lab measurements at a time point years of difference from surgery, and (iv) it is not clear by the authors chose a cut-off of the highest 20% as the threshold to establish normal free T levels. Most of the studies demonstrate that PSA and T are correlated. Evidence published suggests that low T can lead to falsely low PSA levels, especially in men with PC, a finding that is supported by our study.

Our study found that a low PSA level is a predictive factor of low T levels in a cohort of patients with PC, especially when the PC pathology is GS ≥8. In our cohort, the prevalence of low T and very low T were significantly higher in the group with GS ≥8 compared to the groups with GS 6/7 (low T 52% vs. 24.7%, p<0.001, and very low T 29% vs. 7.1, p<0.001, respectively). Additionally, the likelihood of low T and very low T was significantly higher in patients with GS ≥8 and PSA 2–4 ng/mL (OR 8.5 and 6, respectively) and much higher with GS ≥8 and PSA <2 ng/mL (OR 30 and 37, respectively). Patients with GS 6/7, with or without favorable pathology, and PSA <2 ng/mL also had a significantly higher likelihood of very low T (favorable pathology OR 9.1 and unfavorable pathology OR 6.4). This finding reinforces the previous concept that low T levels are associated with higher-grade PC.

Accordingly, our results indicate that it would be beneficial to measure total T levels in patients diagnosed with PC as part of their diagnostic process, especially in patients with GS ≥8 and those with low PSA levels. Studies have also suggested that androgen receptor (AR) expression increases in men with higher Gleason sum scores.[42, 43] Men with Gleason sum 7, 8, or 9 have demonstrated an increase in the expression rate of AR, both intracellularly and on the membrane.[42] However, none of these studies have associated these findings with T levels. Nonetheless, it is reasonable to infer that this may be explained due to low T levels circulating.

Our study has several strengths including (i) inclusion of a large population of men, (ii) use of a database which is audited and reviewed for accuracy annually by the institution, (iii) use of an accurate T assay (LCMS) (iv) performed at a single lab. Nonetheless, there are limitations: (i) the subjects of the study are from a single institution, (ii) we did not measure free T levels, (iii) we did not assess PC-specific mortality, which will be part of future analysis, which may be a stronger indicator of the clinical significance of biochemical recurrence, and (iv) we did not evaluate the ratio between prostate volume, prostatic tumor volume and PSA levels. Nonetheless, we believe that this study is significant and should encourage clinicians to test T levels alongside PSA levels in patients diagnosed with PC as part of their diagnostic process, especially in patients with GS ≥8 and those with low PSA levels.

CONCLUSION

In men with PC, PSA levels <4 ng/mL and PC with a GS ≥8 are predictive of low T levels. PSA <2 ng/ml predicts very low T independent of the PC pathology.

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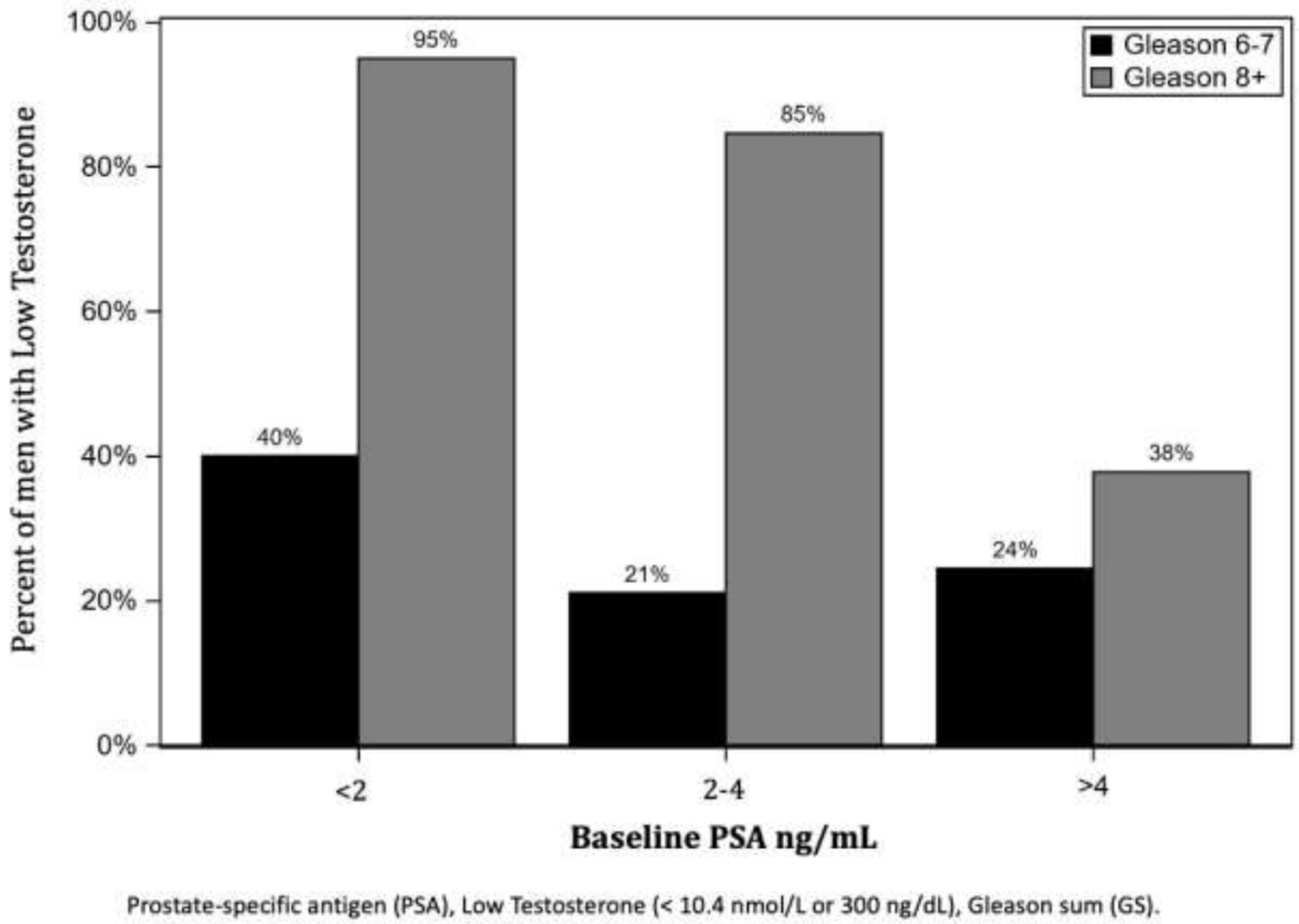

Figure 1.
Prevalence of low Testosterone among PSA Groups and According to Gleason Sum Pathology

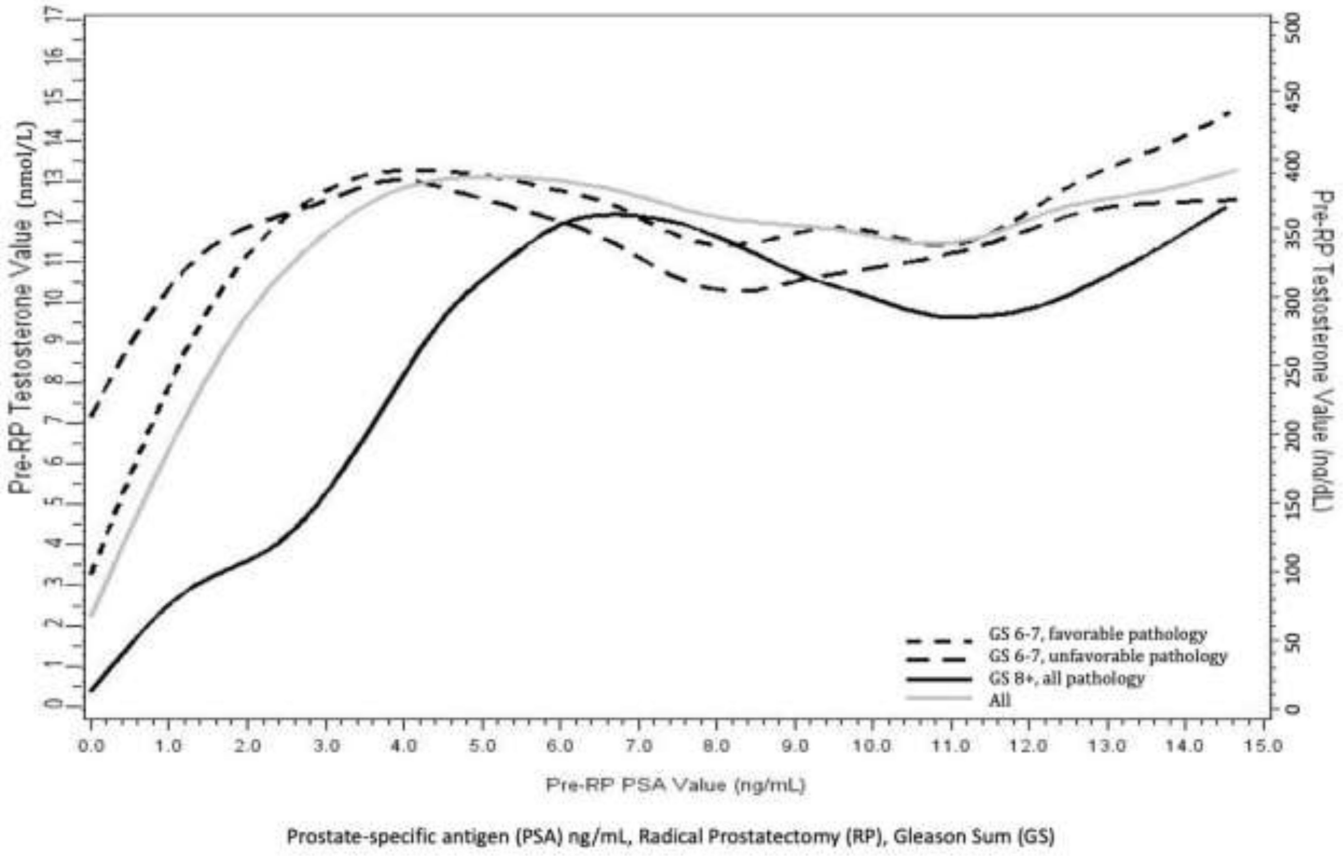

Figure 2:
Relationship between Testosterone levels, and PSA Stratified by Prostate Cancer Pathology

Table 1.

Sample Characteristics by Gleason group (N=646).

Variables	**Gleason Sum 6/7 n=523 (81.0%) Gleason 6 (8%) Gleason 7 (92%)**	**Gleason Sum 8+ n=123 (19.0%)**
Age, (media (IQR))	61.2 (55.8 – 66.4)	62.0 (56.3 – 67.8)
Diabetes (%)	10	12
Obstructive Sleep Apnea (%)	14	11
Coronary Artery Disease (%)	5	8
PSA ng/mL (median (IQR))	5.7 (4.1 – 8.4)	6.9 (3.5 – 11.3)
Prostate cancer stage		
Pathology T2 (%)	43	14
Pathology T3 (%)	56	72
Pathology T4 (%)	1	14
PSA group		
<2 ng/mL (%)	5.7	16
2–4 ng/mL (%)	18	11
>4 ng/mL (%)	76	73
Total testosterone (mean, SD) ng/dL nmol/L	 395 ± 158 13.7 ± 5.5	 284 ± 196 9.8 ± 6.8

Prostate-specific antigen (PSA), Coronary Artery Disease (CAD), Obstructive sleep apnea (OSA) standard deviation (SD).

Table 2.

Sample Characteristics by Testosterone levels (N=646)

Variable	Normal Testosterone (n=453)	Low Testosterone (n=121)	Very low testosterone (n=72)	P-value
Age, (mean, SD)	60.8 ± 7.7	61.1 ± 7.8	61.3 ± 7.6	0.8
Diabetes (%)	7.7	9.8	19.4	**0.01** *
Gleason Sum score				
Gleason Sum 6 (%)	78	15	8	**<0.001**
Gleason Sum 7 (3+4) (%)	77	19	4	
Gleason Sum 7 (4+3) (%)	72	16	12	
Gleason ≥8 (%)	48	24	29	
PSA group				
<2 ng/mL (%)	38	8.0	54	**<0.001** *
2–4 ng/mL (%)	71	19	10	
>4 ng/mL (%)	73	20	7.0	

(*)Prostate-specific antigen (PSA), standard deviation (SD). Low Testosterone (6.9 – 10.4 nmol/L or 200 – 300 ng/dL), very low Testosterone (< 6.9 nmol/L or 200 ng/dL), significant P-value.

Table 3:

Multivariable Analysis of Predictors of Low Testosterone. PSA levels Predicting Low Testosterone and Very Low Testosterone according to Prostate Cancer Pathology

Subset	Predictor	Low Testosterone OR (95% CI)	Very Low Testosterone OR (95% CI)
Gleason Sum 6/7, Favorable Path (n = 328)	PSA < 2 ng/mL	2.19 (0.8 – 6.2)	**9.08 (2.8 – 29)** *
	PSA 2–4 ng/mL	0.89 (0.5 – 1.7)	0.96 (0.3 – 3)
	PSA > 4 ng/mL	Ref	Ref
Gleason Sum 6/7 Unfavorable Path (n = 170)	PSA < 2 ng/mL	1.65 (0.4 – 6.9)	**6.36 (1.1 – 38)** *
	PSA 2–4 ng/mL	0.81 (0.3 – 2.4)	0.98 (0.1 – 8.7)
	PSA > 4 ng/mL	Ref	Ref
Gleason Sum ≥8 All Path (n = 123)	PSA < 2 ng/mL	**30.9 (3.9 – 241)** *	**37.6 (9.5 – 149)** *
	PSA 2–4 ng/mL	**8.49 (1.7 – 41)** *	**5.90 (1.6 – 22)** *
	PSA > 4 ng/mL	Ref	Ref

*(*)*Prostate-specific antigen (PSA) ng/mL, Low Testosterone (Under 10.4 nmol/L or 300 ng/dL), very low Testosterone (Under 6.9 nmol/L or 200 ng/dL), significant P-value.**(All 6 models are adjusted for Diabetes status)**