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**Original Research Article**

# Correlation between Serum Testosterone and Prostate Cancer Aggressiveness

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## Abstract

Prostate cancer is a major public health issue in men in their advancing years. Huggins and colleagues demonstrated the relationship between testicular androgen (testosterone) and prostate cancer growth. Since then, a lot more had been done in this area of study. Recently, low serum level of testosterone had been linked to aggressive prostate cancer (Pca). We set out to investigate the relationship between low serum testosterone and parameters related to Pca aggressiveness. ***Materials and Methods*:** We retrospectively studied fifty-one (51) men diagnosed with Pca who also met the inclusion criteria. Case-notes of these men were retrieved and relevant information for the study were extracted and entered into a spread-sheet and analyzed using the Statistical Package for Social Sciences (SPSS) version 20.0 software. ***Results*:** The mean age and standard deviation for all men was 68.51±7.179 years ranging from 52 to 88 years. Men with low serum testosterone were older. Mean prostate specific antigen (PSA) and Gleason score (GS) were 45.90±30.95 ng/ml and 8.04 ±1.038 respectively; both indicating features of aggressive Pca. Mean serum testosterone was 3.741±1.938 and this correlated inversely with serum PSA and GS. ***Conclusion***: Serum testosterone correlated inversely with notable parameters of aggressive Pca.

**Keywords:** Correlation, Serum Testosterone, Prostate Cancer Aggressiveness.



## INTRODUCTION

Pca is becoming a global phenomenon and a public health issue. It afflicts men in their advancing years. Testosterone has been implicated in the growth of prostate cells in both benign and malignant conditions. The pioneer work is credited to Huggins and colleagues who demonstrated regression of metastatic Pca after androgen deprivation therapy (ADT), but not in localized Pca [2]. On this premise, it is expected that high serum level of testosterone should increase the risk of developing high grade Pca. In contrast, cumulative data from epidemiological studies had failed to correlate with this assumption [3]. In this subject, there are definitely mixed and contrary reports. Most authors report a strong correlation between low serum testosterone and prostate parameters that portray aggressive nature of the disease including high GS [4], higher pathological stage [5], higher risk of positive surgical margin in radical prostatectomy specimens, risk of progression and poorer prognosis [6]. Others on the other hand conclusively differ, inferring that cancers in low testosterone environment do not demonstrate aggressive nature [7, 8]. These differences may not have a ready explanation but could be due to the population studied that may not collaborate different demographics including race and age. Again, study design and methodological standards may differ as well as different cut-off values for hypogonadism.

Morgentaler and Traish in an attempt to push further in support of the link between low testosterone and Pca aggressiveness proposed the "**saturation model theory**" of serum testosterone and prostate cancer which emphasized the fact that "Pca is testosterone sensitive at low testosterone level, but after the androgen receptors (AR) are fully occupied, further increments have modest or no effect on the prostate or Pca dynamics [9]. This theory is supported by hypogonadic men on testosterone replacement therapy (TRT) who have minimal or no PSA increase as well as Pca risk [10]. The saturation model theory further explains that patients with hypogonadism do not reach levels of testosterone necessary for normal or physiological proliferation of the epithelium instead leading to greater risk of abnormal proliferation and differentiation progressing to high grade disease [10]. In contrast, others argue that dihydrotestosterone (DHT), the most biologically active prostate cellular androgen does not reflect the serum total testosterone and so DHT estimation should be used instead of testosterone [11]. This assumption may lack clear evidence since intra-prostatic DHT depends on the serum pool of testosterone. However, the exact pathway and

mechanism of testosterone and Pca interactions that lead to high aggressive nature or lack of it, is still unknown. Based on these controversies, we set out to study our men diagnosed with Pca and attempted to correlate serum testosterone with Pca aggressiveness.

## MATERIALS AND METHODS

This was a retrospective study conducted in our facility between April 2023 and March 2024. A search was made in the health information department for case-notes of patients diagnosed with Pca and who also had documented serum testosterone prior to prostate biopsy. Other parameters retrieved included age of patients, pre-biopsy PSA, Gleason score, kidney function test results. Since it was a retrospective study, we could not report on the body mass index (BMI), diabetic and hypertensive status of the patients which could have affected our results in a way. Exclusion criteria were patients with other urinary tract cancers, medications that could decrease serum testosterone level such as cimetidine, digoxin, neuroleptics, opiates, cannabinoids etc. Indications for prostate biopsy were abnormal digital rectal examination (DRE) findings, elevated PSA (>4.0ng/ml), and symptoms and signs of Pca metastasis. Serum testosterone samples are routinely collected during the morning hours (between 8:00am and 11:00am). Results were graded according to the recommendations by the American society of clinical endocrinologists into hypogonadism when the serum level is < 3.0ng/ml and normal when levels are ≥ 3.0ng/ml [2]. Age of patients was categorized at intervals of 10 years (decades), PSA was also grouped based on values of >4-10.0 ng/ml in group I and >10ng/ml in group 2. GS was categorized as shown in table 2. Collated data were imputed into a spread sheet and analyzed using SPSS version 20.0 software.

### Statistical Analysis

Means and standard deviations were calculated for continuous variables and frequency table was constructed for categorical variables. Students' T-test statistics was used to compare means and standard deviations between serum testosterone and means of age, PSA and GS. Statistically significant level was set at P<0.05. Pearson correlation was used to find any direct or inverse relationship between serum testosterone and other variables (Table 4).

## RESULTS

A total of 51 patients met the inclusion criteria and were included in the study. Mean age of all patients was 68.51±7.179 years ranging from 52 to 88 years. Mean age of patients with low and normal serum testosterone levels were respectively 69.40±7.33 years and 67.94 ± 7.14 years and did not reach a statistical significant level (Pv > 0.05). Overall mean PSA was 45.90±30.95ng/ml and mean PSA for the 2 groups were 57.14±36.40 ng/ml and 38.65±24.87ng/ml for low and normal testosterone levels respectively with a significant mean difference (Pv< 0.05). Mean GS for all patients was 8.04±1.038. Within the 2 groups; group with low testosterone had a GS of 8.25±0.91 while those with normal testosterone level had GS of 7.90 ± 1.10 (Pv > 0.05). Table 2 shows the frequency table for categorical variables. Table 4 demonstrated correlation of variables: Serum testosterone correlated inversely with GS (r = -.284, Pv = 0.043) and PSA (r = - .313, Pv = 0.025) but not with age (r = - .171, Pv = 0.230).

**Table 1: Means and Standard Deviation of Variables**

| Variable | Means Std | Min. | Max |
|---|---|---|---|
| Age (years) | 68.51 ± 7.179 | 52 | 88 |
| PSA (ng/ml) | 45.90 ± 30.95 | 6.8 | 143.4 |
| Testosterone (ng/ml) | 3.741 ± 1.938 | 3 | 7.3 |
| Gleason Score | 8.04 ± 1.038 | 5 | 9 |

**Table 2: Frequency Table**

| Variable | Frequency (n) | Valid% | Cumulative % |
|---|---|---|---|
| **(a) Age Category:** | | | |
| 50 – 59 | 6 | 11.8 | 11.8 |
| 60 – 69 | 20 | 39.2 | 51.0 |
| 70 – 79 | 25 | 49.0 | 100.0 |
| Total | 51 | 100.0 | |
| **(b) PSA Category:** | | | |
| > 4–10ng/ml | 7 | 13.7 | 13.7 |
| > 10ng/ml | 44 | 86.3 | 100.0 |
| Total | 51 | 100.0 | |
| **(c) Testosterone category**: | | | |
| < 3 ng/ml | 20 | 39.2 | 39.2 |
| > 3 ng/ml | 31 | 60.8 | 100.0 |
| Total | 51 | 100.0 | |
| | | | |

| Variable | Frequency (n) | Valid% | Cumulative % |
|---|---|---|---|
| **(d) Gleason Score Category:** | | | |
| 5 | 1 | 2.0 | 2.0 |
| 6 | 1 | 2.0 | 4.0 |
| 7 | 17 | 33.3 | 37.3 |
| 8 | 8 | 15.7 | 52.7 |
| 9 | 24 | 47.1 | 100.0 |
| Total | 51 | 100.0 | |
| **(e) Aggressiveness Category:** | | | |
| Non – Aggressive | 11 | 21.6 | 21.6 |
| Aggressive | 40 | 78.4 | 100.0 |
| Total | 51 | 100.0 | |

**Table 3: Students' T–test statistics between serum testosterone and other variables**

| Serum testosterone (ng/ml) | Mean age±std(yrs) | Mean PSA(ng/ml) | Mean Gleason Score |
|---|---|---|---|
| <3.0 | 69.40 ± 7.33 | 57.14 ± 36.40 | 8.25 ± 0.91 |
| > 3.0 | 67. 94 ± 7.14 | 38.65 ± 24.87 | 7.90 ± 1.10 |
| T–test | t = .033, P>0.05 | t = 3.13, P<0.05* | t= 0.877, P>0.05 |
| **Statistically Significance set at P< 0.05*** | | | |

**Table 4: Correlation table Between Testosterone and other Variables**

| Testosterone / Gleason Score | r = – .284, | P = 0.043* |
|---|---|---|
| Testosterone / PSA | r = – .313, | P = 0.025* |
| Testosterone / Age | r = – .171, | P = 0.230 |
| **Statistically Significance set at P< 0.05*** | | |

## DISCUSSION

Prognostic indicators in oncology is central in selecting treatment modalities and developing targeted therapies. Prostate cancer is a heterogeneous disease with both indolent and aggressive phenotypes. Identification of each type is crucial in order to avoid unnecessary and over treatments. D'Amico in an attempt to overcome this scenario, considered only 3 major prognostic markers namely; clinical stage, Gleason score and serum PSA to guide treatments [7]. This however, is not without flaws and limitations for use [3]. Recently, serum testosterone had been added alongside tumor density in biopsy specimens, third Gleason grade, genetic mutations and tumor characteristics on magnetic resonance imaging (MRI) [12].

The aim of this study was to correlate serum testosterone and parameters of Pca aggressiveness. In our study, the mean age of all patients was 68.51±7.179 years, an age range peculiar to Pca patients in this locality [13], marginally older than men in a study in Brazil with similar diagnosis and tumor characteristics [14]. Most of the patients were in their 8$^{th}$ decade of life; a previous study in this centre captured same information [15]. Mean PSA was 45.90±30.95 ng/ml a range of PSA frequently recorded in Pca patients in older and recent studies in this centre [16,17]. This actually informs the aggressive nature of this disease peculiar to the black race compared to the Caucasian population [1,18]. Higher PSA being an indicator of aggressive disease. Mean serum testosterone was 3.74±1.938ng/ml, a similar mean testosterone was recorded in a South American study [19]. This same study reported almost a similar prevalence of hypogonadism in their population (37.8%) as ours (39.2%). Mean GS was 8.04±1.038 and majority of them recorded GS of 9 supporting an aggressive nature of most Pca typically encountered in this environment [15], again, the percentage (78.4%) of aggressive disease was on the high side (GS 4+3 = 7 to 9). These observations were made in older male population between 45 and 84 years versus 52 to 88years in our study. Our work also reported that men with hypogonadism were older than men with normal serum testosterone, although did not reach statistical significant level (PV>0.05). These and other studies cutting across racial boundaries concur with the fact that serum free and total testosterone decrease with advancing age [19, 20].

Of all the variables namely age, GS and PSA; only mean PSA showed a significant mean difference between men with hypogonadism and men with normal testosterone (Table 3). On Pearson correlation table; PSA also correlated negatively with serum testosterone (r = -.313, Pv = 0.025). This implies that the higher the PSA level the lower the serum testosterone level. It is a known fact that PSA is partly regulated by androgen receptor [21]. Serum testosterone drives prostate cellular growth and PSA on the other hand is produced by prostate cells in benign and malignant conditions. A possible negative feedback inhibition of PSA on testosterone production is possible leading to low levels of testosterone when PSA is elevated. In this thought direction, Zhang *et al*., [22], proposed a possible inhibition theory of testosterone production by PSA leading to low level of the hormone. This has been widely discussed in the field of prostate oncology. Gleason score also correlated inversely with

serum testosterone (r = -.284, PV = 0.043). Other studies also found high GS [≥ 7(4 ± 3)] in both prostate biopsy and radical prostatectomy specimens to be associated with low serum testosterone levels [23-25]. These conclusions had been drawn independently despite differences in setting thresholds for hypogonadism. However, other researchers differed in their conclusions and failed to associate hypogonadism with high risk Pca parameters [14,26]. Age of the patients failed to show a significant statistical relationship with serum testosterone, although inversely related (r = -.171, PV = 0.230). This may be due to a mix of extended age range of the population studied (52–88years).

This study was retrospective in nature and so did not lack peculiar limitations. Firstly, diabetics and body mass index (BMI) status of the patients were not captured due to lack of information. A previous study in this centre reported lower serum testosterone levels in diabetic than non-diabetic patients [17]. This could have influenced our results. Other studies also had same conclusion [27, 28]. Secondly, our sample size was small; this may have skewed our results in a way. The greatest strength of this study is in the fact that, upon the difficulties in extracting data coupled with strict inclusion criteria, we were able to produce a work with results that conform with global thoughts in this field of study.

## CONCLUSION

Hypogonadism defined as serum testosterone <3.0 ng/ml correlated with high risk Pca characteristics in our cohort of patients and this information had been reported in various works done globally. Those who differ may be due to varying demographic characteristics, different testosterone cut-off values, time of testosterone collection, methods of sample analysis and variable methods of prostate specimen histo-analysis.

**Authors Contribution:**

**EAU**: Substantial contributions to conception and design, Acquisition of data, Drafting the article, revising it critically for important intellectual content, data analysis and Final approval of the version to be published.

**PEO**: Substantial contributions to conception and design, revising it critically for important intellectual content and final approval of the version to be published.

**JPO:** Substantial contributions to conception and design, revising it critically for important intellectual content and final approval of the version to be published.

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