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Original research article

A Study of Serum Testosterone Levels in Prostate Cancer

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Abstract

Background: Prostate cancer (PCa) diagnoses have been linked to low testosterone levels. Hormonal levels in PCa-affected men, particularly those who underwent radical prostatectomy, have been linked to poor prognostic variables. The current study aimed to establish a link between hormone levels and PCa prognostic elements in PCa-affected men before starting treatment.

Methods: The study sample was obtained from the patients referred to the Department of Urology based on the inclusion and exclusion criteria. All prostate cancer participants in this study were evaluated at the time of admission using a thorough clinical examination, baseline blood tests, serum PSA, serum testosterone, and Gleason grading (TRUS biopsy), which includes the primary, secondary, and total Gleason scores or sum Imaging studies (bone scan, CECT/MRI abdomen and pelvis, and chest x-ray). Radical prostatectomy (RP) was recommended for patients with localized prostate cancer, including those with clinical stage T1 and T2 disease without regional pelvic nodal involvement and metastasis.

Results: The patients in the low testosterone group I had a higher overall tumor stage on clinical evaluation compared to the normal testosterone group. The p-value is found statistically significant. The overall pathological T staging is not statistically significant the patients in low testosterone (group I) had higher T_3 disease than group II patients. The p-value is not statistically significant. The Postoperative pathological nodal status between the two groups was compared. The Patients in the low testosterone group I had more proportion of pathological lymph nodal involvement than patients in the normal testosterone group. P value was found to be statistically significant ($p = 0.0121$).

Conclusion: The higher percentage of predominant Gleason pattern 4, a sign of aggressive prostate cancer, is linked to low total serum testosterone. When compared to patients with normal blood testosterone levels, patients with low serum testosterone levels had higher serum PSA values. Patients who underwent radical prostatectomy and had low testosterone levels had a higher percentage of positive surgical margins, extracapsular extension, and seminal venous invasion, all of which are possible signs of aggressive prostate cancer behavior.

Keywords: Carcinoma Prostate, Prostatectomy, Low Testosterone Levels

Introduction

One of the most prevalent medical conditions afflicting senior men is prostate cancer. The most frequent non-cutaneous cancer among American males is prostate cancer or carcinoma. In the United States, males have a lifetime risk of prostatic carcinoma of 16.7% and a lifetime risk of mortality of about 2.6 percent, however, the lifetime risk of death from prostate cancer is far lower than the lifetime risk of diagnosis. When compared to younger men, older men in industrialized nations have a higher prevalence of prostate cancer. Approximately 15% of men in affluent countries have been diagnosed with prostate cancer, compared to only 4% of those in developing countries. Since a few decades ago, the relationship between serum testosterone and prostate cancer has been understood. Since the early 1940s, when Huggins et al., [1, 2] published their research on how prostate cancer (PCa) responded to testosterone deprivation, testosterone has been viewed as "fuel to the fire" of PCa. They had previously shown the therapeutic advantages of androgen suppression in the treatment of metastatic (advanced) prostate cancer. This association, however, is complicated by the fact that while prostate cancer detection rates rise with age, testosterone serum levels decline. [3] No research has connected elevated testosterone levels to an increased risk of PCa development as of yet. However, some research suggests that PCa may manifest at lower bioavailable testosterone levels. [4–6] The benefits of androgen suppression are now being used to manage patients with prostate cancer who do not yet have the metastatic disease as well as recurrent prostate cancer.

The research is inconsistent and the link between testosterone and prostate cancer (PCa) is debatable. Low serum testosterone levels have also been linked to PCa patients' worse prognoses and aggression traits after radical prostatectomy (RP), according to research. [7–13] The majority of the information that is currently known about PCa and testosterone comes from investigations of RP patients. Before the treatment, there are scant data on the hormonal pattern and factors influencing PCa diagnosis and prognosis at prostate needle biopsies. [14–17] Before receiving treatment and having access to final pathology results, the PCa prognosis can be predicted using clinical data and information from the *Transrectal ultrasound*-guided *prostate biopsy (*TRUS) prostatic biopsy using the D'Amico risk of progression classification and other methods. The present study is to find out the role of low serum testosterone levels in predicting prostate cancer behavior in comparison with normal serum testosterone levels in patients and to find out the relationship between low serum testosterone levels and serum Prostate Specific Antigen (PSA) levels in TRUS biopsy-proven cancer prostate patients.

Material and Methods

This cross-sectional study was done in the Department of Urology, Chalmeda Anand Rao Institute of Medical Sciences [CAIMS], Bommakal, Karimnagar, Telangana State. Institutional Ethical committee approval was obtained for the study. Written consent was obtained from all the participants of the study after explaining the nature of the study in the local language. The study sample was obtained from the patients referred to the Department of Urology based on the inclusion and exclusion criteria.

Inclusion criteria

1. All newly diagnosed prostate cancer (TRUS guided biopsy proven) patients
2. Aged 40 years and above
3. voluntarily willing to participate in the study

Exclusion criteria

1. Patients already on testosterone replacement therapy
2. Patients on other hormonal therapy
3. Men taking medications known to lower serum PSA levels (Finasteride or
4. Dutasteride)

Based on the inclusion and exclusion criteria n=50 patients with prostate cancer were enrolled in the study. Blood tests were done to determine the levels of testosterone, PSA, and other baseline tests. Testosterone serum measurements were made between 7 and 9.30 am. The relevant standard protocol was used to measure the serum levels of testosterone. Based on the amounts of serum testosterone, the patients were split into two groups. Group I (serum testosterone levels (<250 ng/dl) and Group II serum testosterone levels (> 250 ng/dl). Based on the results of the bone scan, contrast-enhanced CT scan, or MRI of the abdomen and pelvis, the clinical staging was performed for all patients. After one month from surgery, all patients underwent surgery and were then monitored. All prostate cancer participants in this study were evaluated at the time of admission using a thorough clinical examination, baseline blood tests, serum PSA, serum testosterone, and Gleason grading (TRUS biopsy), which includes the primary, secondary, and total Gleason scores or sum Imaging studies (bone scan, CECT/MRI abdomen and pelvis, and chest x-ray). Radical prostatectomy (RP) was recommended for patients with localized prostate cancer, including those with clinical stage T1 and T2 disease without regional pelvic nodal involvement and metastasis. Patients with advanced prostate cancer, including those with clinical stage T3 and T4 disease and metastatic prostate cancer, were treated with hormonal therapy in the form of surgical castration followed by anti-androgen therapy.

A comparison was made between prostate cancer patients with low serum testosterone (group I) and those with normal testosterone in the postoperative period for patients who underwent radical prostatectomy (RP). The parameters included post-operative Gleason grade, pathological tumor (PT) status, pathological node (PN) status, surgical margin status (SMS), extracapsular extension (ECE) of the tumor, and seminal vesical invasion (SVI) (group II). Following radical prostatectomy (RP), patients had histopathological specimen analysis performed, and parameters such as post-operative Gleason grade, pathological tumor (PT) status, pathological node (PN) status, surgical margin status (SMS), extracapsular extension (ECE) of the tumor, and seminal vesical invasion (SVI) were compared between prostate cancer patients with low serum testosterone (group I) and normal testosterone levels (group II). *Statistical analysis*: Data was evaluated statistically using MS Excel spreadsheet and SPSS 22.0. Categorical variables were analyzed using the Chi-square test. The significance of variations in continuous variables of the study population before and after the surgical operations was examined using ANOVA and the paired Student's t-test. P values of 0.05 or higher were regarded as significant, and P values of 0.001 or higher as very significant.

Results

A total of n=50 patients were enrolled in our study of which patients with low testosterone levels (<250 ng/dl) were categorized as group I and the remaining patients with normal testosterone levels (> 250 ng/dl) were categorized as group II and is found not statistically significant between the two groups. The youngest age of the patient was 44 years and the oldest recorded age was 81 years. The mean age of the cohort in the study was 63.25 ± 10.5 years. The patient demographics between the two groups are presented in table 1.

Table 1: Demographic profile of the cases included in the study

Age group (years)	*Group I N (%)*	*Group II N (%)*	*Total N (%)*
40 – 50	1 (9.09)	3 (7.69)	4 (8.0)
51 – 60	3 (27.27)	11 (28.20)	14 (28.0)
61 – 70	4 (36.36)	16 (41.02)	20 (40.0)
71 – 80	2 (18.18)	5 (12.82)	7 (14.0)
> 80	1 (9.09)	4 (10.25)	5 (10.0)
Total	11 (100)	39 (100)	50 (100)

All of our study participants had their serum PSA levels checked, and we compared the PSA levels across patients in groups I and II. The results are shown in table 2 below. Compared to only 25% of patients in the matching group, the majority (60%) of patients in the low testosterone group have serum PSA readings higher than 20. It is discovered that the P value is statistically significant.

Table 2: Estimation of a prostate-specific antigen in both groups

Prostate-specific antigen (PSA) levels	*Group I N (%)*	*Group II N (%)*	*Total N (%)*
< 10	1 (10.0)	13 (32.5)	14 (28.0)
10 – 20	3 (30.0)	17 (42.5)	20 (40.0)
> 20	6 (60.0)	10 (25.0)	16 (32.0)
Total	10 (100)	40 (100)	50 (100)

The comparison between two groups of the total Gleason score (low <7, intermediate 7, and high 8-10) is shown in table 3. Most of the patients (81.81%) in the low testosterone group had a higher Gleason grade (8-10) compared to the normal testosterone group II. The p-values were found to be statistically significant (<005). This shows that patients in low testosterone group I had a higher proportion of high Gleason score compared to the normal testosterone group II.

Table 3: Total Gleason Score in both groups

Total Gleason Score	*Group I N (%)*	*Group II N (%)*	*Total N (%)*
< 7	0 (0.0)	17 (43.59)	17 (34.0)
7 – 8	2 (18.18)	19 (48.17)	21 (42.0)
8 – 10	9 (81.81)	3 (7.69)	12 (24.0)
Total	11(100)	39(100)	50 (100)

The preoperative clinical tumor (T) status, Nodal status (N), and metastasis (M) status were analyzed and the results between the two groups were represented in table 4. A critical analysis of table 4 reveals that patients in the low testosterone group I had a higher overall tumor stage on clinical evaluation compared to the normal testosterone group. The p-value is found statistically significant.

Table 4: Clinical tumor status in both the groups of patients in the study

Clinical Stage of Tumor	*Group I N (%)*	*Group II N (%)*	*Total N (%)*
T2A	1 (8.33)	3 (7.89)	4 (8.0)
T2B	2 (16.67)	6 (15.79)	8 (16.0)
T2C	1 (8.33)	1 (2.63)	2 (4.0)
T3A	2 (16.67)	12 (31.57)	14 (28.0)
T3B	4 (33.33)	16 (42.10)	20 (40.0)
T4A	1 (8.33)	0 (0.00)	1 (4.0)
T4B	1 (8.33)	0 (0.00)	1 (4.0)
Total	12 (100)	38 (100)	50 (100)

Patients' clinical Nodal status (N) was analyzed and the results between the two groups were represented in figure 1. Group I patients had a higher nodal involvement than group 2 patients. The p-value is found statistically significant. Patients in the low serum testosterone group had more proportion of people with nodal metastasis (N1 group) than in the normal testosterone group as shown in figure 2. Patients' clinical metastasis status (M) was analyzed and the results were between the two groups. The p- values were (<0.05) found statistically significant. 3 Out of n=50 cases n=6(12%) underwent radical prostatectomy and n=44(88%) cases were given hormonal therapy details depicted in figure 3.

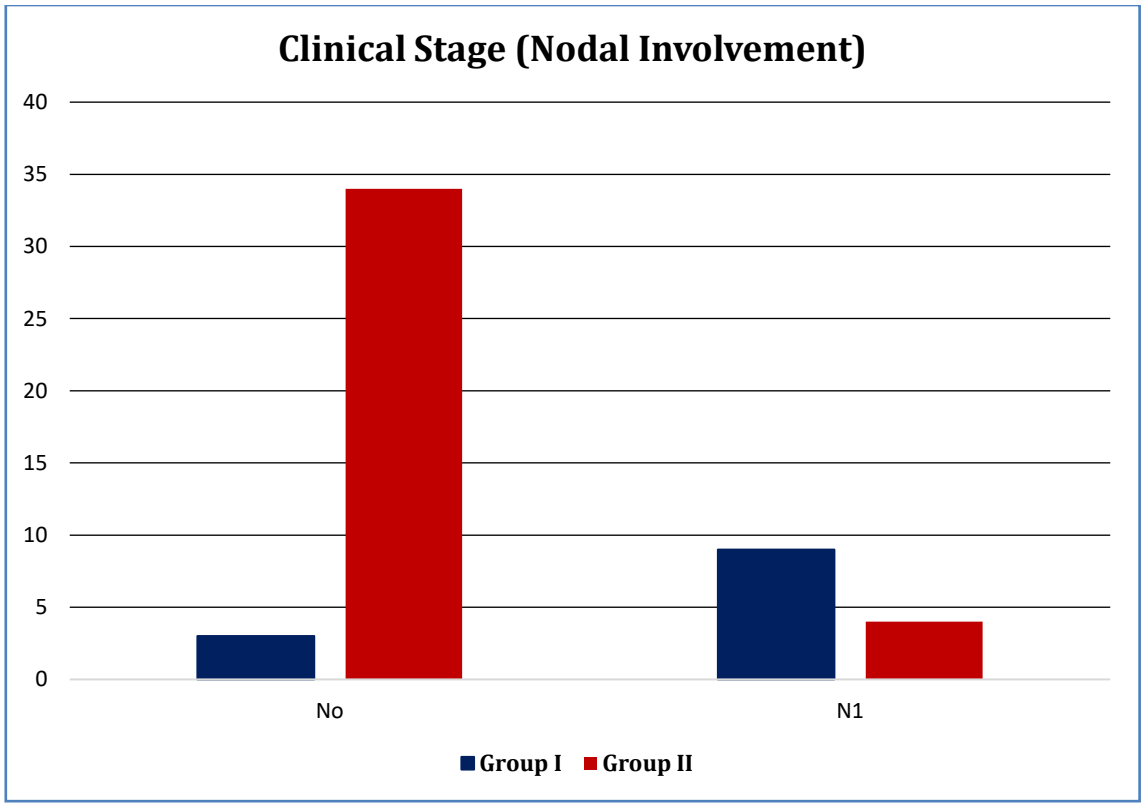

Figure 2: Clinical stage of nodal involvement in both groups of cases

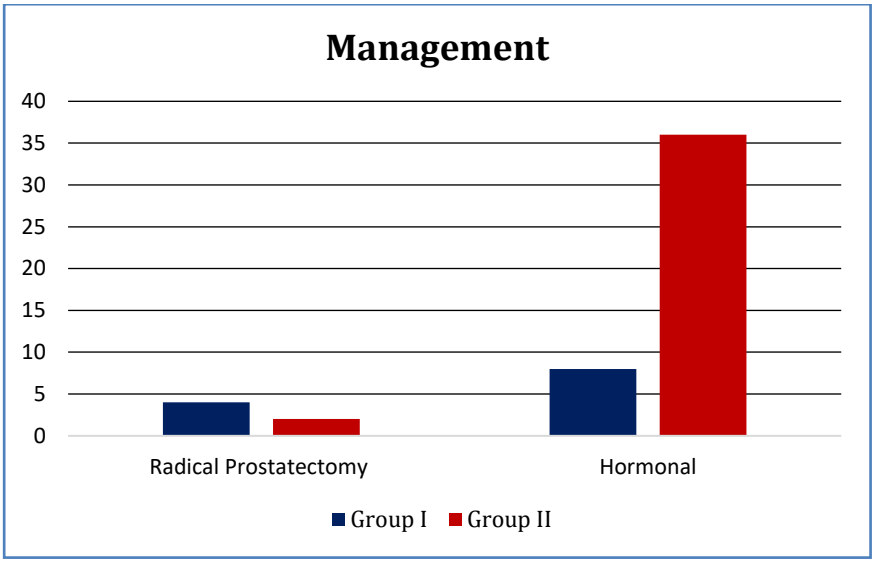

Figure 3: Management of the cases included in the study

The pathological tumor characteristics were compared between the two groups and are represented in the following table 5. Although overall pathological T staging is not statistically significant the patients in low testosterone (group I) had higher T_3 disease than group II patients. The Overall p-value is not statistically significant. The Postoperative pathological nodal status between the two groups was compared as shown below in Figure 4. Patients in the low testosterone group had more proportion of pathological lymph nodal involvement than patients in the normal testosterone group. P value was found to be statistically significant (p = 0.0121).

Table 5: Histopathological characteristics of tumors

Pathological Stage of Tumor	*Group I N (%)*	*Group II N (%)*
PT2A	0	2
PT3A	0	1
PT3B	1	0
PT2B	1	1
Total	2	4

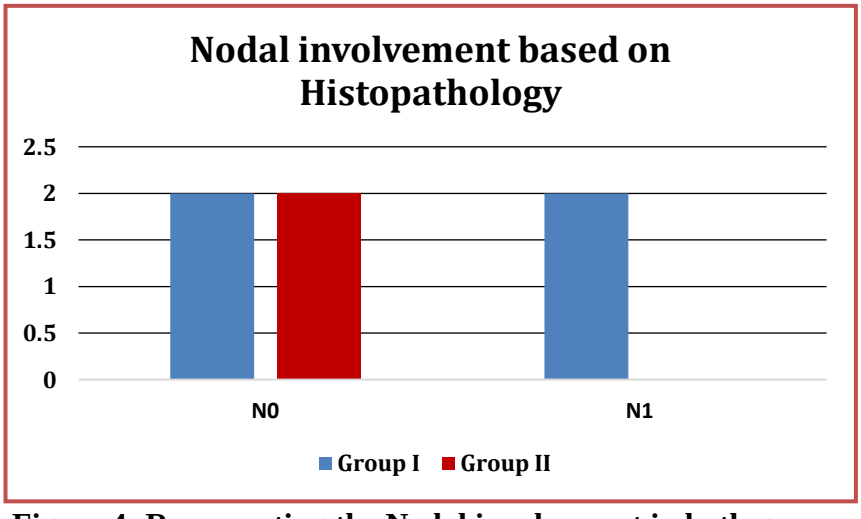

Figure 4: Representing the Nodal involvement in both groups

Post prostatectomy histopathological specimen total Gleason scores between the two groups were analyzed and shown in Figure 5, below. The p-value was found statistically significant.

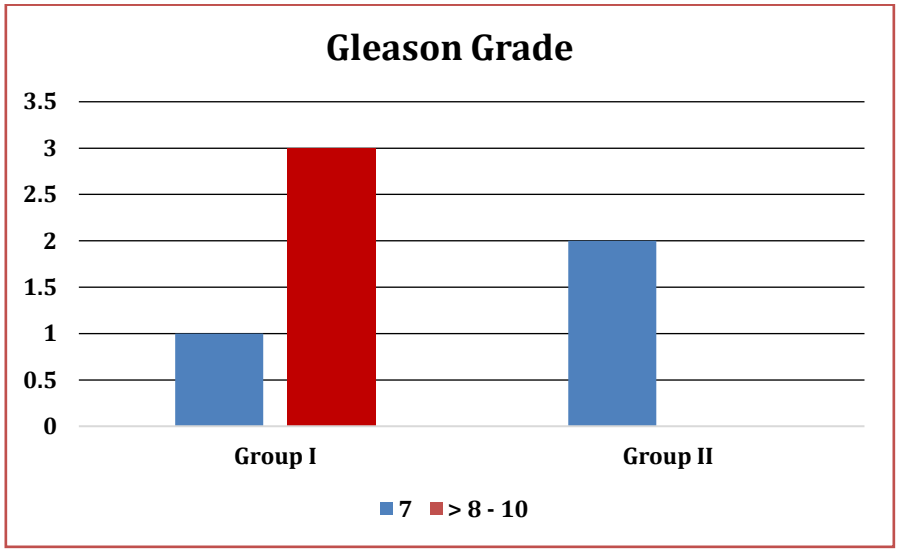

Figure 5: Post prostatectomy histopathological specimen total Gleason score

Post radical prostatectomy histopathological specimen Surgical Margin Status (SMS) between the two groups was analyzed. It was found that most (> 60%) of the patients in the low serum testosterone group had positive surgical margins when compared to none in the normal testosterone group. P value was found statistically significant (P = 0.026). The surgical margin status between the low (Group I) and normal serum testosterone (group II) was analyzed. Post prostatectomy histopathological specimen Extra Capsular Extension (ECE) status between the two groups was analyzed. The Patients in the low serum testosterone group had a greater number of extracapsular extensions than the normal serum testosterone group as shown below. The p-value were found statistically significant (p = 0.0212). Post prostatectomy histopathological specimen Seminal Vesical Invasion (SVI) status between the two groups was analyzed the postoperative seminal Vesical invasion was more in the low serum testosterone group (Group I) than in the normal serum testosterone group (Group II). The p-value was found statistically significant (p = 0.0147).

Discussion

The idea that low levels of serum testosterone are associated with metastatic disease and high-grade prostate cancer is debatable and frequently disputed. Various research has examined and confirmed the relationship between low levels of serum testosterone and these conditions. According to research by A Morgentaler et al., [18] men with low serum testosterone have a greater incidence of prostate cancer. There is no correlation between the risk of prostate cancer and androgens, including blood testosterone, according to other investigations from the Massachusetts Aging Study. [19] Concerns concerning the increased risk of prostate cancer in men with reduced testosterone levels have been raised in some earlier research. A TRUS-guided prostate biopsy has revealed cancer in 15% of individuals with hypogonadal clinical status and a PSA of 4.0 ng/ml; the risk of cancer doubles with bigger reductions in blood testosterone levels. [20, 21] Prostate cancer and serum testosterone have not yet been linked with strong evidence. The negative feedback impact of serum testosterone on the hypothalamo-pituitary axis may be the cause of the association between low testosterone levels and prostate cancer. According to research by Miller et al., [22] the hormone inhibin decreases the generation of serum testosterone in prostate cancer patients. Patients with low serum testosterone and their

associations with TRUS biopsy Gleason grade, serum PSA, clinical tumor (T) and pathological nodal (PN) status, postoperative histopathological specimens Gleason total score, surgical margins status, extracapsular extension, and seminal vesicle invasion were examined in our current study in comparison to patients with normal serum testosterone levels. Zhang et al., [23] have shown a correlation between low serum testosterone levels and high Gleason grade prostate cancer. A higher percentage of individuals in our study who had low serum total testosterone had high Gleason total scores. Our study's findings were corroborated by research by Schatzl et al., [24] who discovered that patients with low serum testosterone levels had higher Gleason total scores when compared to people with normal serum testosterone levels. In contrast to patients with normal levels of serum testosterone, our study also revealed that patients with low total testosterone levels had advanced clinical stages of the disease, including clinical tumor status, nodal status, and metastasis to bone and other viscera. The findings of our study were consistent with earlier research by Perez Marquez et al., [25] who discovered that men with low testosterone levels have a higher chance of developing metastatic disease and tumor growth. According to Hoffman et al., [11] patients with low serum testosterone are a sign of the aggressiveness of prostate cancer. Serum testosterone levels have also been found in another study to be a significant and independent marker in determining prostate biopsy positive. An increased risk of aggressive prostate cancer is linked to the Gleason score, pathological tumor stage, and baseline serum PSA in post-prostatectomy histo-pathology tissues.

Conclusion

Within the limitations of the current, it can be concluded that a higher percentage of predominant Gleason pattern 4, a sign of aggressive prostate cancer, is linked to low total serum testosterone. When compared to patients with normal blood testosterone levels, patients with low serum testosterone levels had higher serum PSA values. Patients who underwent radical prostatectomy and had low testosterone levels had a higher percentage of positive surgical margins, extracapsular extension, and seminal venous invasion, all of which are possible signs of aggressive prostate cancer behavior.

References

1. Huggins C, Stevens RE, Hodges CV. Studies on prostatic cancer. II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 1941; 43: 209 – 23.
2. Huggins C. Effect of orchiectomy and irradiation on cancer of the prostate. Ann Surg 1942; 115: 1192 – 200.
3. Isbarn H, Pinthus JH, Marks LS, et al. Testosterone and prostate cancer: revisiting old paradigms. Eur Urol 2009; 56:48 – 56.
4. Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA 1996; 276: 1904 – 06
5. García-Cruz E, Huguet J, Piqueras M, Márquez MP, Peri L, Izquierdo L, Franco A, Alvarez-Vijande R, Ribal MJ, Alcaraz A. Low testosterone bioavailability is related to prostate cancer diagnose in patients submitted to prostate biopsy. World J Urol. 2012; 30(3):361-65.
6. Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 ng/mL or less. Urology 2006; 68: 1263 – 67.
7. Isom-Batz G, Bianco FJ, Kattan MW, Mulhall JP, Lilja H, Eastham JA. Testosterone as a predictor of pathological stage in clinically localized prostate cancer. J Urol 2005; 173: 1935 – 57.
8. Imamoto T, Suzuki H, Fukasawa S, et al. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with

radical prostatectomy. Eur Urol 2005; 47: 308 – 12
9. Massengill JC, Sun L Moul JW et al. Pre-treatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. J Urol 2003; 169: 1670 – 75.
10. Lane BR, Stephenson AJ, Magi Galluzzi C, Lakin MM, Klein EA. Low testosterone and risk of biochemical recurrence and poorly differentiated prostate cancer at radical prostatectomy. Urology 2008; 72: 1240 – 45
11. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum-free testosterone a marker for high-grade prostate cancer? J Urol 2000; 163: 824 – 27.
12. Schatzl G, Madersbacher S, Thurridl T, et al. High-grade prostate cancer is associated with low serum testosterone levels. Prostate 2001; 47: 52 – 58.
13. Yamamoto S, Yonese J, Kawakami S, et al. Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy. Eur Urol 2007; 52: 696 – 701.
14. Stattin P, Lumme S, Tenkanen L et al. High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. Int J Cancer 2004; 108: 418 – 24.
15. Morote J, Ramirez C, Gómez E et al. The relationship between total and free serum testosterone and the risk of prostate cancer and tumor aggressiveness. BJU Int 2009; 104: 486 – 89
16. Sofikerim M, Eskicorapci S, Oruç O, Ozen H. Hormonal predictors of prostate cancer. Urol Int 2007; 79: 13 –18.
17. Yano M, Imamoto T, Suzuki H et al. The clinical potential of pre-treatment serum testosterone level to improve the efficiency of prostate cancer screening. Eur Urol 2007; 51: 375 – 805.
18. Morgentaler A, Bruning CO, 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA. 1996; 276:1904–1906.
19. Watts EL, Appleby PN, Perez-Cornago A, Bueno-de-Mesquita HB, et al. Low Free Testosterone and Prostate Cancer Risk: A Collaborative Analysis of 20 Prospective Studies. Eur Urol. 2018 Nov;74(5):585-594.
20. Morgentaler A., Rhoden E. (2006) Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen levels of 4.0 Ng/Ml or less. Urology 68: 1263–1267.
21. Shin B., Hwang E., Im C., Kim S., Jung S., Kang T., et al. (2010) Is a decreased serum testosterone level a risk factor for prostate cancer? A cohort study of Korean men. Korean J Urol 51: 819–823.
22. Miller LR, Partin AW, Chan DW, Bruzek DJ, Dobs AS, Epstein JI, et al. Influence of radical prostatectomy on serum hormone levels. J Urol. 1998; 160:449–453.
23. Zhang PL, Rosen S, Veeramachaneni R, Kao J, DeWolf WC, Bubley G. Association between prostate cancer and serum testosterone levels. Prostate 2002; 53:179-82.
24. Schatzl G, Madersbacher S, Thurridl T, Waldmüller J, Kramer G, Haitel A, et al. High-grade prostate cancer is associated with lower serum testosterone levels. Prostate 2001; 47:52-58.
25. Perez Marquez M, Garcia-Cruz E, Piqueras Bartolome M, et al. Low testosterone levels are associated with poor prognosis risk factors on needle prostate cancer biopsies. J Men's Health 2009; 3:252.