Association between Low Serum Testosterone and Prostate Cancer Behaviour

K. Arunprasad[1], V. Chandramohan[1]

ABSTRACT

Introduction: Cancer is a leading cause of mortality and the burden of disease. Lifestyle constituents, such as smoking, poor diet, and physical inactivity account for a significant relationship of cases, but sex hormones are thought to have a role in the etiology of some cancers. Study aimed to determine the association of low serum testosterone and prostate cancer behaviour and with a Secondary objective to determine the relationship of serum PSA level in cancer prostate patients with low serum testosterone.

Material and Methods: Patients are divided into two groups based on the serum testosterone levels. Patients with low serum testosterone levels (<250ng/dl) were categorized as Group A, and patients with normal serum testosterone levels (>250 ng/dl) were classified as Group B, and the findings between two groups will be compared.

Results: The majority (74%) of patients in low testosterone group has got a serum PSA of more than 20 values compared with only 34% of patients in the corresponding group. Most of the patients (82.6%) in low testosterone group had a higher Gleason grade (8-10) compared to the normal testosterone group. patients in low testosterone group had higher overall tumour stage, higher nodal stage and extensive metastases on clinical evaluation compared to the normal testosterone group.

Conclusion: Patients with low serum testosterone levels were associated with an increased serum PSA levels compared with patients with normal serum testosterone levels. Preoperative total testosterone should be routinely added to serum prostate-specific antigen estimation to improve prostate cancer management.

Keywords: Prostate Cancer, Biopsy, Testosterone

INTRODUCTION

Prostate cancer is one amongst the most common medical diseases affecting senior men. Carcinoma of the prostate is the most common non-cutaneous cancer diagnosed in American male population. The lifetime risk of prostatic carcinoma is 16.7% and the risk of death during the entire lifetime is around 2.6% for men in the United States but the overall lifetime risk of death due to prostate malignancy is low about the lifetime risk of diagnosis. In developed countries, carcinoma of the prostate gland is more prevalent in the elderly male population compared with younger men. Around 15% of men diagnosed to have cancer of the prostate in the developed world when compared to only about 4% of men in emerging nations. The relationship of cancer prostate and serum testosterone is known for the past few decades. The benefits of surgical castration and the role of estrogen treatment in the management of metastatic cancer prostate was evaluated since olden days (Huggins and Hodges, 1941).[1,2] They earlier demonstrated the beneficial clinical effects of androgen suppression therapy in the management of metastatic (advanced) cancer prostate. The androgen suppression benefits are recently extended in the management of even in non-metastatic prostate cancer patients and recurrent prostate cancer after definitive management.[3] Again there is a role for hormonal therapy in neoadjuvant settings like before radical prostatectomy which resulted in the decrease in serum PSA, Shrinkage of prostate tumor volume and reduction in the rate of positive surgical margins. The reduction in prostate volume following neoadjuvant hormonal therapy is more in peripheral zone compared to the central zone.[4] Prostate cancer is hormone-dependent cancer, and the clinical course of prostate cancer varies with the individual, and again it varies within the individual in relationship to serum testosterone levels.[5-7] The present study is to find out the role of low serum testosterone level in predicting prostate cancer behavior in comparison with normal serum testosterone level patients and to find out the relationship between low serum testosterone level and serum PSA levels in TRUS biopsy-proven cancer prostate patients.

Study aimed to determine the association of low serum testosterone and prostate cancer behaviour and with a Secondary objective to determine the relationship of serum PSA level in cancer prostate patients with low serum testosterone.

MATERIAL AND METHODS

This prospective study was conducted in the Department of Urology, Madras Medical College, and Rajiv Gandhi Government General Hospital.

Inclusion criteria: All newly diagnosed prostate cancer (TRUS guided biopsy proven) patients with age more than 40 years in our institution were enrolled.

Exclusion Criteria: Patients already on testosterone replacement therapy, Patients on other hormonal therapy,

[1]Assistant Professor, Department of Urology, Government Vellore Medical College, Tamilnadu, India

Corresponding author: Dr. V. Chandramohan, Assistant Professor, Department of Urology, Government Vellore Medical College, Tamilnadu, India

How to cite this article: K. Arunprasad, V. Chandramohan. Association between low serum testosterone and prostate cancer behaviour. International Journal of Contemporary Medical Research 2018;5(8):H1-H4.

DOI: http://dx.doi.org/10.21276/ijcmr.2018.5.8.3

Men taking medications known to lower serum PSA level (Finasteride or Dutasteride)

Informed consent was obtained from all patients. All TRUS biopsy-proven cancer prostate patients were screened. Blood investigations like serum PSA, serum testosterone, and other baseline investigations were obtained. The serum determinations of Testosterone obtained between 7 – 9.30 am. The serum Testosterone levels measured by appropriate standard protocols.

Patients were divided into two groups based on the serum testosterone levels. Patients with low serum testosterone levels (<250ng/dl) were categorized as Group A, and patients with normal serum testosterone levels (>250 ng/dl) were classified as Group B, and the findings between two groups were compared.

Patients with localized prostate cancers which include patients with Clinical stage T1 and T2 without regional pelvic nodal involvement and metastasis were counseled and given the option of radical prostatectomy (RP) and other patients who were in advanced stage of the disease which includes clinical T3 and T4 disease and metastatic prostate cancer were managed with hormonal therapy in the form of surgical castration followed by anti-androgen therapy.

Patients who underwent radical prostatectomy (RP) were followed up postoperatively with histopathological specimen analysis and parameters like post-operative Gleason grade, pathological tumour (PT) status, pathological node (PN) status, surgical margin status (SMS), extracapsular extension (ECE) of a tumour and seminal Vesical invasion (SVI) were compared between the prostate cancer patients with low serum testosterone (group A) and normal testosterone (group B).

RESULTS

Total of 106 patients with cancer prostate were taken into our study of which 5 patients on 5 alpha reductase inhibitors and 1 patient on testosterone replacement therapy were excluded from our study and finally 100 patients were enrolled in our study.

The prostate cancer patients population demographics found not statistically significant between the two groups. The youngest age of the patient was 45 years, and oldest recorded age was 85 years.

The serum PSA levels were measured in all our study patients, and the PSA levels between patients with group A and group B were analyzed. The majority (74%) of patients in low testosterone group has got a serum PSA of more than 20 values compared with only 34% of patients in the corresponding group (table 1,2). P value was found to be statistically significant.

Most of the patients (82.6%) in low testosterone group had a higher Gleason grade (8-10) compared to the normal testosterone group. P value was found statistically significant (<005).

The relation between total Gleason score (TGS) and prostate cancer patients serum testosterone levels between the two groups. Patients in low testosterone group had the higher proportion of high Gleason score compared to the normal testosterone group.

The preoperative clinical tumor (T) status, Nodal status (N), and metastasis (M) status were analyzed, patients in low testosterone group had higher overall tumor stage, higher nodal stage and extensive metastases on clinical evaluation compared to the normal testosterone group. P value is found statistically significant.

Serum PSA	Serum Testosterone		P value
	< 250	> 250	
< 10	1	16	0.003
10-20	5	35	
> 20	17	26	

Table-1: Cross tabulation of Serum PSA with Serum Testosterone

TGS	Serum Testosterone		P value
	< 250	> 250	
< 7	0	34	0.005
7	4	39	
8-10	19	4	

Table-2: Cross tabulation of TGS with Serum Testosterone

Clinical Stage - T	Serum Testosterone		P value
	< 250	> 250	
T2A	1	7	0.002
T2B	6	10	
T2C	2	3	
T3A	2	26	
T3B	8	31	
T4A	2	0	
T4B	2	0	

Table-3: Cross tabulation of Clinical Stage - T with Serum Testosterone

Clinical Stage - N	Serum Testosterone		P value
	< 250	> 250	
N0	7	68	0.05
N1	16	9	

Table-4: Cross tabulation of Clinical Stage - N with Serum Testosterone

Grade	Serum Testosterone		P value
	< 250	> 250	
7	0	4	0.022
8-10	5	2	

Table-5: Cross tabulation of Postprostatectomy TGS with Serum Testosterone

SMS	Serum Testosterone		P value
	< 250	> 250	
Positive	3	0	0.026
Negative	2	6	

Table-6: Cross tabulation of Postprostatectomy SMS with Serum Testosterone

Patients clinical Nodal status (N) was analyzed, group 1 patients had a higher nodal involvement than group 2 patients (table-3). P value was found statistically significant.

The pathological tumor characteristics were compared between the two groups, although overall pathological T staging is not statistically significant the patients in low testosterone group had higher T 3 disease than group B patients. Overall P value was not statistically significant.

Postoperative pathological nodal status between the two groups was compared; patients in low testosterone group had more proportion of pathological lymph nodal involvement than patients in normal testosterone group. P value was found to be statistically significant (p = .015) Table 4.

Postprostatectomy histopathological specimen total Gleason score between the two groups were analyzed and found statistically significant Table 5.

Post-radical prostatectomy histopathological specimen Surgical Margin Status (SMS) between the two groups was analyzed. Most (> 60%) of the patients in low serum testosterone group had positive surgical margin when compared to none in normal testosterone group (table-6). P value was found statistically significant (P = .026)

Postprostatectomy histopathological specimen Extra Capsular Extension (ECE) status between the two groups was analyzed, patients with the low serum testosterone group had more number of extracapsular extension than normal serum testosterone group as shown below. P value was found statistically significant.

Postprostatectomy histopathological specimen Seminal Vesical Invasion (SVI) status between the two groups was analyzed, the postoperative seminal Vesical invasion was more in low serum testosterone group than in normal serum testosterone group. P value was found statistically significant.

DISCUSSION

The view that Serum testosterone has got a crucial part in the development of cancer prostate is controversial and widely discussed, and various studies have analyzed and documented the association between low level of serum testosterone and metastatic disease and high-grade cancer prostate. Morgentaler et al. have shown a higher incidence of cancer prostate in patients with low serum testosterone.[8] Other studies by Michaud JE et al aging study have reported no association between androgens including serum testosterone and cancer prostate risk. Some of the previous studies have stated concerns about the increased risk of prostate cancer in men with lower levels of testosterone. In patients with hypogonadal clinical status and with a PSA < 4.0 ng/ml, TRUS guided prostate biopsy has shown cancer in around 15%, with the risk of the tumor increases twice when met with the greater reduction in the serum testosterone levels.[9]

The association between serum testosterone and cancer prostate is not yet well established. The possible explanation for the link between low serum testosterone and cancer prostate is due to the negative feedback effect of serum testosterone on hypothalamic-pituitary axis. Miller et al. have shown that cancer prostate inhibits serum testosterone production by the hormone inhibin.[10] The association between low serum testosterone level and high-risk cancer prostate may be due to chronic disease induced hormonal change. In our present study, patients with low serum testosterone and its association with TRUS biopsy Gleason grade, serum PSA, Clinical Tumour (T) status, Clinical nodal (N) status, Clinical metastasis (M) status, Pathological tumour (PT) and Pathological nodal (PN) status, postoperative histopathological specimens Gleason total score, Surgical margins status, extracapsular extension and Seminal vesical invasion were analyzed in comparison with normal serum testosterone patients. The association between low level of serum testosterone and high Gleason grade prostate cancer have been demonstrated by Zhang et al.[11] In our study greater percentage of patients with low serum total testosterone were presented with high Gleason total scores (≥ 8). Our study report was supported by similar to the study by Schatzl et al have shown that patients with low level of serum testosterone were found to have higher Gleason total score when plotted against normal serum testosterone.[12] Our study also demonstrated that patients with low total testosterone level were associated with advanced clinical stage of the disease including clinical tumor status, nodal status and metastasis to bone and other viscera compared to patients with the normal level of serum testosterone. The results of our study were similar to the previous study done by Perez Marquez et al. who found that patients with low testosterone levels are at an increased risk of metastatic disease and the higher risk of tumor progression.[13] The study by Hoffman et al. reported that patients with low serum testosterone is a marker of aggressive nature of cancer prostate.[14] Another study also shown that serum testosterone values are an important and independent marker in assessing prostate biopsy positivity. The post prostatectomy histo-pathological specimens Gleason score, pathological tumour stage and baseline serum PSA are associated with an increased risk of aggressive prostate cancer. In our study patients with low serum total testosterone were associated with higher Gleason score and less favorable pathological stage and an increased incidence of positive surgical margins in the resected specimen, extracapsular extension of tumor either unilateral or bilateral and finally positive Seminal Vesical invasion. There are few limitations in our study which has to be taken care in future prospective studies of similar population groups. One of the limitation is small prostate cancer population size and again the number of patients who presented with low serum levels of testosterone were only 23. Second limitation of our present study is number of patients who were fit under the criteria for radical prostatectomy was only 11. Finally, the follow-up period up is short, and it is recommended that in the future long-duration studies involving a larger group of patients will be helpful in confirming our current study report and also throw more light on this ever debated prostate cancer study.

CONCLUSION

Low total serum testosterone is correlated with a higher proportion of predominant Gleason pattern 4, an indicator

of aggressive prostate cancer. Patients with low serum testosterone levels were correlated with an increased serum PSA levels compared with patients with normal serum testosterone levels. Patients with low testosterone who were managed by radical prostatectomy had a higher proportion of positive surgical margin, extracapsular extension and seminal Vesical invasion suggesting an aggressive prostate cancer behavior. Preoperative total testosterone should be routinely added to serum prostate-specific antigen estimation to improve prostate cancer management.

REFERENCES

1. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin 1972;22: 232 40.
2. Huggins C, Stevens RE Jr, Hodges CV. Studies on prostatic cancer. II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 1941;43:209–23.
3. Daniell HW. A worse prognosis for men with testicular atrophy at therapeutic orchiectomy for prostate carcinoma. Cancer 1998;83:1170–3.
4. 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.
5. Hoffman MA, DeWolf WC, Morgentaler A.Is low serum free testosterone a marker for high grade prostate cancer? J Urol2000; 163: 824–7.
6. Schatzl G, Madersbacher S, Thurridl T et al. High-grade prostate cancer is associated with low serum testosterone levels.Prostate 2001;47: 52–8.
7. Massengill JC, Sun L, Moul JW et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy.J Urol 2003; 169: 1670–5.
8. Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA 1996;276:1904-6.
9. Michaud JE, Billups KL, Partin AW. Testosterone and prostate cancer: an evidence-based review of pathogenesis and oncologic risk. Therapeutic Advances in Urology. 2015;7(6):378-387. doi:10.1177/1756287215597633.
10. Miller LR, Partin AW, Chan DW et al. Influence of radical prostatectomy on serum hormone levels. J Urol 1998; 160:449–53.
11. Zhang PL, Rosen S, Veerramachaneni R, Kao J, DeWolf WC, Bubley G. Association between prostate canc Vergho DC, Heine K, Wolff JM. The role of PSA in diagnosis of prostate cancer and its recurrence. Pathologe2005;26:473-868.
12. Schatzl G, Madersbacher S, Haitel A, et al. Associations of serum testosterone with micro vessel density, androgen receptor density and androgen receptor gene polymorphism in prostate cancer. J Urol 2003;169:1312-1315.
13. 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.
14. Hoffman MA, DeWolf WC, Morgentaler A.Is low serum free testosterone a marker for high grade prostate cancer? J Urol2000; 163: 824–7.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 25-06-2018; **Accepted:** 27-07-2018; **Published:** 19-08-2018