Introduction

The prostate is an exocrine gland in the male reproductive system, which is approximately of the size of a walnut, located below the bladder and just in front of the rectum. Prostate tumours constitute a major health problem across the globe. Prostate cancer accounts for the second most common cancer and ranks fifth among the leading causes of cancer mortality in men worldwide. There is a rapid rise in its incidence worldwide, including the Asian countries. It is estimated that 80% of males are associated with this tumour by the age of 80 years.[1] Males in their 30s and 40s have an occurrence of small foci of cancer, whereas older men have larger lesions, implying that there occurs a stepwise progression. According to epidemiological studies, nearly 83% of prostatic cancers are associated with Benign Prostatic Hyperplasia elsewhere in prostate and approximately 3–20% of patients who have undergone transurethral prostatectomy (TURP) or open prostatectomy for Benign Prostatic Hyperplasia subsequently develop prostate cancer.[2]

The exact etiology of prostate cancer is vague, although the evidence suggests that prostate cancer is multifactorial. Age, ethnicity, genetics, environment, hormones and dietary factors do contribute.[10] Recently, vitamin D deficiency is believed to be

ABSTRACT

Introduction: Prostate cancer incidence is rising rapidly worldwide, which includes Asian countries too. There are a lot of controversies regarding the link between endogenous testosterone levels and prostate disorders. This study was conducted to understand the value of serum testosterone in predicting the risk and occurrence of prostate carcinoma. Material and Methods: Eighty males in the age group of 50–80 years, out of which forty were diagnosed as Prostate cancer patients and forty were healthy controls matched with respect to age and sex, were recruited in the study. Serum testosterone and serum prostate-specific antigen levels were estimated in both groups. Results: Serum testosterone levels were low in 67.5% and normal in 32.5% of the patients of prostate cancer. In comparison with the controls, serum PSA levels were observed to be higher in prostate cancer patients ($P < 0.001$). Analysis of the data was done with the help of an unpaired t-test, and $P < 0.05$ was considered to be statistically significant. Discussion: Androgens promote cellular differentiation and proliferation of prostate epithelial cells via the genetic alterations in the TMPRSS2 gene and ETS (E26 transforming sequences) transcription factor genes involved in cell proliferation and tumor cell invasion. These genes are found to be over-expressed in prostate carcinomas. Suppression of testosterone by prostate cancer-induced production of inhibin that initiates the hypothalamic-pituitary axis negative feedback mechanism might be the reason for lower levels of serum testosterone in prostate carcinoma patients. Hence, screening of elderly men above 60 years of age for serum testosterone levels should be done for early identification of prostate carcinoma as well as a better prognosis in the management of the disease.

Keywords: Prostate carcinoma, PSA (prostate-specific antigen), testosterone

Introduction

The prostate is an exocrine gland in the male reproductive system, which is approximately of the size of a walnut, located below the bladder and just in front of the rectum. Prostate tumours constitute a major health problem across the globe. Prostate cancer accounts for the second most common cancer and ranks fifth among the leading causes of cancer mortality in men worldwide. There is a rapid rise in its incidence worldwide,
related to the abnormal growth of the prostate. However, the available data is inconclusive.

Throughout the life of a man, the prostate gland has the plasticity to respond to androgenic signalling; the maximal volume, however, is reached as the man ages. Prostate cancer develops due to the uncontrollable growth of cells in the prostate. This leads to symptoms such as difficulty while urinating, pelvic pain and difficulty in ejaculation. A majority of patients with early-stage prostate carcinomas do not present with symptoms. A locally advanced or metastatic disease is often suspected in patients who are symptomatic.

Testosterone is the primary male reproductive hormone produced mainly by the Leydig cells of the testis (95%) and to a small extent (≈5%) by the peripheral conversion from the precursors dehydroepiandrosterone (DHEA) and androstenedione (4-dione). Both of these are produced in the zona reticularis of adrenal glands. Testosterone production by the Leydig cells is regulated by luteinizing hormone (LH), which is further under the regulation of gonadotropin-releasing hormone (GnRH). Testosterone enters the prostate cells by the process of passive diffusion. In the prostate, it is converted to the more potent form of androgen, i.e., dihydrotestosterone (DHT), with the help of an enzyme, 5-α reductase. DHT is beneficial in the developing prostate, but in the adult prostate, it might cause pathological growth of the prostate and produce a detrimental effect. What is the role of DHT in other adult tissues? This is yet not certain. The effects of DHT are in no way more unique and beneficial as compared to testosterone. However, it is believed to have a significant role in amplifying the weaker hormonal signal of testosterone.

Testosterone production starts to increase significantly during the pubertal age and declines with increasing age. Circulating androgens, particularly testosterone, is critically vital for normal function and growth of the prostate, in addition to prostate carcinoma progression and initiation. On the contrary, it was found that patients with high-grade metastatic prostate carcinoma who were deprived of androgen therapy showed a reduction in the symptoms as well as the progression of the disease. There is ample evidence suggesting testosterone as a contributory factor promoting prostate carcinoma in the experimental studies. However, there is no clear confirmation for the part of endogenous testosterone in inducing the development of prostate cancer in humans. In vivo, the induction of prostate carcinogenesis by androgens is still debatable.

Although PSA levels are a marker for prostate pathology, it lacks sensitivity and does not rule out other non-prostatic causes of elevations in serum PSA levels. Hence, there is a need for a potential endogenous biomarker that can further aid in the screening of patients with prostate cancers in addition to the PSA weighted criteria for diagnosis of prostate carcinoma. Keeping these facts in mind, this work is designed to assess the causative link of endogenous testosterone with prostate cancer in addition to other parameters that are routinely done to diagnose prostate diseases. The results of this study might ensure that physicians screen elderly men above 60 years of age for serum testosterone levels so as to consider it as a prognostic biomarker in prostate cancer, especially in those with a positive family history.

**Material and Methods**

The serum samples were collected from the Department of Urology and Urosurgery and processed in the Central laboratory and Special investigation laboratory under the Biochemistry Department of a tertiary care hospital. This study was conducted on Forty Prostate cancer patients and forty age and sex-matched healthy controls. A brief introduction to the study protocol was given to all the participants, and their informed consent was taken. Ethical committee clearance from the institution was taken before the conduct of the work.

Male patients between 50 to 80 years of age presenting with the signs and symptoms of difficulty in urination, pelvic pain, difficulty in ejaculation, with a positive family history of prostate carcinoma, having increased levels of PSA and USG or any other investigations indicative of carcinoma prostate were included in the study. PSA is a serine protease that is produced by benign and malignant prostate tissues.

Patients in the age group <50 or >80 years, those taking drugs like finasteride, dutasteride or any other inhibitors of testosterone reductase, and those with hypogonadism were not included in the study.

**Estimation of the biochemical parameters**

Blood samples (5 ml) were collected in a vacutainer serum separating vial, and serum was separated within one hour of collection for the analysis of serum testosterone and PSA stored in a deep freezer at –40°C till further analysis. Testosterone levels were estimated using Testosterone Reagent Kit (7K73) with the help of Chemiluminescent Microparticle Immunoassay (CMIA) technology with flexible assays. Serum prostate-specific antigen levels were estimated using the Total PSA Reagent Kit (7K70).

**Results**

Forty diagnosed patients of prostate cancer were taken from the in-patient department of Urology, from a tertiary care hospital. Their age range was 50 to 80 years. The patients’ mean age was 68.02 years. Forty healthy volunteers matched with respect to age and sex were included in the control group. Their mean age was 66.15 years. Serum PSA and testosterone levels of both the controls and patients were measured.

Age distribution of the cases and control group showed that the maximum number of patients with prostate cancer (65.0%) were in the age range of 61–70 years [Table 1]. Serum testosterone levels were low (198 ± 238 ng/dl) as compared to the controls (345 ± 210 ng/dl) as depicted in Table 2, Figure 1. Serum
testosterone levels were low in 67.5% of the patients and normal in 32.5% of the patients with prostate carcinoma [Table 3]. Testosterone levels were low in 10% and normal in 90% of healthy controls, as shown in Table 3. In comparison with the controls, serum PSA levels were observed to be higher in prostate cancer patients, as shown in Table 2, Figure 1.

**Statistical analysis**

Data were analysed with the help of SPSS software 27.0 version and GraphPad Prism 7.0 version software. The analysis of continuous data was done using an unpaired t-test, and the results were found to be statistically significant (P < 0.05).

**Discussion**

Prostate cancer incidence, as well as benign prostatic hyperplasia, is rising worldwide. In India, the majority of prostate carcinoma patients are diagnosed in the advanced stage, and hence, morbidity remains high. The exact causes of prostate carcinogenesis and its progression are unidentified. Considerable evidence suggests that both genetics and environmental factors play a role in the origin and evolution of this disease. Epidemiologic evidence reveals that prostate cancers have both a genetic and familial component. Age, race, diet and some genetic associations are the factors that pose a risk for prostate cancer.

The pre-pubertal concentration of testosterone is low (<50 nanograms/dL). At the time of puberty, the concentration of testosterone increases to around 500 to 700 ng/dL. Testosterone remains high throughout adulthood, i.e., during the third and fourth decade. Men above 30–40 years of age show an age-related decrease in testosterone concentrations circulating in the blood. This has been consistently observed in both cross-sectional and longitudinal analytical studies. Altogether, these studies demonstrate a 0.5 to 2% drop in total serum testosterone concentration per year from about the fourth decade onwards. This decline in testosterone might be due to (1) a decrease in Leydig cell numbers, (2) decreased GnRH pulse amplitude and (3) increase in sex hormone-binding globulin. In general, testosterone is known to produce both anabolic and virilizing effects. Virilizing effects comprise mostly of secondary sexual characteristics like the growth of the penis, voice deepening, as well as appearance beard and hair over the torso and formation of the scrotum. An increase in muscle mass and strength, increase in bone density and accelerated maturation of bones, the pubertal spurt of increase in height are the anabolic effects of testosterone.

Does serum testosterone have a vital role in prostate carcinogenesis? This is a controversial and widely-discussed question. Various studies documented the association between low serum testosterone levels and metastasis in carcinoma prostate as well as high-grade prostate cancer. George AM et al. demonstrated that low testosterone level is an independent biomarker for high-grade prostate cancers in Black men. According to this study, in localised prostate Ca, higher grade carcinoma was observed in patients with hypogonadism. This suggests serum testosterone levels could be a potential biomarker for prognosis in high-grade carcinoma prostate. Other studies by Michaud J E et al. reported no association between serum testosterone and the risk for prostate cancer. Some of the previous studies documented concerns regarding a higher risk of prostate cancer in men with low serum testosterone levels. However, few longitudinal studies reported a higher risk of prostate cancer with increased concentrations of testosterone. Smaller, well-designed studies demonstrated increased prostate cancer risk in patients with lower testosterone concentrations. A placebo arm study was conducted on 3242 patients in the age group of 50–75 years with at least one earlier biopsy report that was negative for prostate carcinoma. Men were tested for their baseline serum testosterone levels, increase in PSA,
abnormal digital rectal exam (DRE) and prostate biopsy at two and four years was undertaken. Researchers observed that there was no association of testosterone or DHT with Prostate Ca occurrence or Gleason grade. There are several studies showing positive correlation, no correlation as well as a null hypothesis with relation to testosterone levels. No correlation was found in the longitudinal studies with large sample sizes, while small-sized sample studies showed a positive correlation. The present study also shows that the risk of prostate cancer increases in men with lower levels of testosterone. The present study shows low testosterone levels <142.39 in 67.5% of the patients with prostate cancer. The association between low serum testosterone levels and high-risk prostate cancer may be due to hormonal changes induced by the chronic disease. In the present study, many patients with low serum testosterone exhibited an increased serum PSA level. 72.5% of the patients showed serum PSA value >30 ng/ml, while 67.5% of the patients showed low testosterone levels <142.39 ng/dl.

Whether an increased serum testosterone level promotes prostate cancer or low serum testosterone is a predictor for prostate carcinoma is still under debate. Although previous data suggest that androgens alone may not sufficiently contribute to promoting prostate carcinogenesis, many studies have identified that androgens promote the proliferation of prostate cancer cells. The development, maturation and maintenance of the prostate are influenced by the androgens. They affect both luminal epithelial proliferation and differentiation. When prostate is exposed to the androgens at key developmental times, the risk for prostate carcinogenesis increases. Androgens contribute to the induction of prostate epithelial cell proliferation in many direct or indirect ways. The most common form is via means of genetic alterations by fusion between two genes, i.e., TMPRSS2 gene and ETS transcription factor genes, ERG or ETV1. ETS transcription factors are responsible for cell proliferation and cancer cell invasion. TMPRSS2-ETS translocation is observed in 72% of all prostate cancers as per the current research. TMPRSS2 is a serine protease bound to the cell membrane. It is overexpressed in prostate cancers and is under regulation by the androgens. Moreover, its expression is more specifically limited to the prostate luminal epithelial cells. The most commonly overexpressed proto-oncogene in prostate cancer is the ERG gene, but the underlying mechanism for ERG overexpression is unclear. TMPRSS2-ETS translocations suggest that androgens may induce the expression of ETV1 and ERG, leading to the genesis of prostate carcinoma.

One more growth factor which is androgen-regulated is FGF8. Its carcinogenic effect has been demonstrated in both genetically engineered mice and cell culture. This protein is found to have overexpressed in human prostate carcinomas. The level of expression of this protein positively correlates with the stage of cancer, its grade and disease-specific survival rate.

The first work to document that low testosterone levels do not offer protection to prostate cancer development was conducted by Morgentaler et al. This study reported that asymptomatic men with low free and total serum testosterone levels had a high prevalence rate of carcinoma prostate. Hence, further interest aroused amongst researchers to demonstrate the relationship between endogenous testosterone levels and the risk for development and progression of carcinoma prostate.

The exact cause for the link between low testosterone concentration and high-risk prostate carcinoma is still not clear. One of the reasons might be the suppression of the release of testosterone by prostate cancer via the hypothalamic-pituitary-gonadal axis. Miller et al. concluded that prostate cancer suppresses testosterone production by producing inhibin locally. Inhibin, in turn, initiates negative feedback on the hypothalamic-pituitary-gonadal axis. Also, it has been found that testosterone concentrations rise drastically after radical prostatectomy.

Zhang et al. reported lower testosterone levels in patients with high-grade tumors than in those with moderate grade prostate tumors. Schatzl G et al. also reported lower testosterone as well as serum estradiol levels in patients with high Gleason score prostate cancers. The explanation for this also goes in favour of the tumor-mediated suppression of gonadotrophins, particularly in men with high-grade prostate carcinoma. They also observed that in prostate cancer patients with low testosterone, the androgen receptor expression was higher. However, the biologically active form of testosterone is free testosterone. Hence, it is advisable to consider free testosterone more valuable for the prediction of prostate cancer prognosis rather than total serum testosterone. Hence, further studies with serum-free testosterone levels and its correlation with the staging of prostate carcinoma are warranted, which remains the limitation of our study. Moreover, the true relation between low testosterone and prostate carcinoma needs to be validated in larger prospective study designs. Thus, to conclude, pre-operative total and, more specifically, free testosterone should be tested as a routine investigation along with serum PSA levels to improve the prognosis and for better management of patients with prostate carcinoma.

There are controversial results regarding the role of testosterone in the progression of prostate carcinoma. Epidemiological studies favour the findings that androgens promote prostate carcinoma growth in animal models, and hence, androgen deprivation therapy might benefit in Ca prostate. In order to come to a consensus regarding this controversy, a saturation model was proposed, which says that there is a biologic saturation point for the maximal stimulation of prostate tissues by androgens. This point falls in the lower testosterone level range, i.e., around 8.7 nmol/L or 250 ng/dl. If testosterone levels are above this saturation point, further stimulation of the tissues will not occur. Hence, in such cases, TRT will not induce the growth of prostate tissues. This model provides the basis for understanding the effects of testosterone in the context of androgen receptor responsiveness and highlights differences in offering TRT in hypogonadal and eugonadal men.
From the physician’s point of view, though there is limited clinical data suggesting that there is no increase in growth of prostate tumour in men on testosterone replacement therapy (TRT), it can be given to selected patients after careful monitoring outweighing potential risks and benefits of the treatment to the patient.

Conclusion

Screening of elderly men above 60 years of age for serum testosterone levels should be done for the early identification of prognosis in prostate cancer, especially in those with a positive family history.

Key points

1. Screening of elderly men above 60 years for serum testosterone levels should be considered as a prognostic biomarker in prostate cancer, especially in those with a positive family history.
2. Pre-operative total testosterone should be routinely added to serum prostate-specific antigen estimation in patients with prostate carcinoma to improve prostate cancer management.
3. TRT in prostate carcinoma patients should be given judiciously in hypogonadal men.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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