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Significance of Androgen/Estrogen ratio in Prostate Cancer and Benign Prostatic Hyperplasia: An Eclipsed Truth

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Abstract

The International Agency for Cancer Research (IARC) has shown a low incidence of prostate cancer in East Asian countries as compared to western counterparts although its incidence in India is rising as well. As endogenous testosterone production physiologically declines with increasing age while life expectancy continues to rise; recognition of testosterone deficiency syndrome (TDS) is currently increasing. The hormonal regulation of prostate cancer is not limited to a role for androgens and we propose that androgens in combination with estrogens are required for PCa. So this is the primary approach to find the significance of Androgen and Estrogen ratio in Prostate cancer and benign prostatic hyperplasia that is being eclipsed for years by an androgen dominated interest.

Material and Methods- A cross-sectional study was conducted to test the association of Testosterone, Estrogen and its ratio with histological Gleason grade in patients of prostate cancer. Serum samples of men with suspicion of prostate cancer on the basis of high prostate specific antigen (PSA) and/or abnormal DRE were withdrawn before biopsy between 8am and 11am serum PSA, testosterone, and estrogen levels were estimated using ELISA on the same day.

Results- A total of 190 patients were included in the study. Out of these, 95 patients were in BPH and 95 in PCa group. The age of the patients was almost similar in both BPH (65.66±10.66) and PCa (66.54±7.11) groups. The level of BMI was significantly ($p<0.001$) higher in the patients of PCa (26.58±4.76) as compared to BPH (22.15±2.90). Similarly, the waist hip ratio was also significantly ($p<0.0001$) higher in the patients of PCa (1.08±0.37) as compared to BPH (0.86±0.15). The free testosterone was significantly ($p<0.0001$) higher in PCa (Median=6.67) patients as compared to BPH patients (Median=3.32). Similarly, the total testosterone was significantly ($p<0.0001$) higher in PCa patients (Median=8.66) as compared to BPH patients (Median=5.22). However, dihydrotestosterone was significantly higher in BPH patients (Median=535.71) as compared to PCa patients (Median=7.60). The estrogen level was significantly ($p<0.0001$) lower in PCa (Median=13.0) patients as compared to BPH patients (Median=22.93). Similarly, E ratio T level was significantly lower ($p<0.0001$) in PCa patients (Median=2.84) as compared to BPH patients (Median=4.79).

Conclusion- The comparative levels or ratio of these hormones are very imperative in the progression of prostate cancer. Once the cancerous state has set in, age of the patient not seems to be strongly related with these changes. Future studies with a larger sample size are needed to establish its association.

Keywords: Testosterone, Estrogen, Prostate cancer, BPH patients.

Introduction

The International Agency for Cancer Research (IARC) has shown a low incidence of prostate cancer in East Asian countries as compared to western counterparts [1] although its incidence in India is rising as well [2]. Benign and malignant disorders of the prostate are amongst the most common diseases affecting males, particularly in industrialized countries. Prostate cancer is ranked as sixth most commonly diagnosed cancer in India. Its incidence rate is 4.6 men per 100.000 of population (Sinha et al., 2003)[3] which may be an underestimate as most cases of the prostate cancer are only detected at later stages and many cases in rural areas are not even reported since there is no well structured screening programmes for the diagnosis of prostate cancer in India. However, according to a recent study on cancer registries in five Indian cities (Mumbai, Chennai, Bangalore, Delhi & Bhopal) incidence of cancer may have increased (Yeole., 2008)[4]. Still, in India the age adjusted incident rates of prostate cancer is only one tenth of that seen in the western world.

As endogenous testosterone production physiologically declines with increasing age while life expectancy continues to rise; recognition of testosterone deficiency syndrome (TDS) is currently increasing. The prevalence of symptomatic biochemical hypogonadism was 26.1% in India. Androgens and increasing age are established risk factors associated with prostate cancer, paradoxically, testosterone levels gradually decline with increasing age as the incidence of prostate cancer (PCa) rises in older men. Estrogens have been implicated in PCa as estrogen levels in older men remain relatively unchanged resulting in a decline in the ratio of androgens: estrogens with age. Thus the hormonal regulation of prostate cancer is not limited to a role for androgens and we propose that androgens in combination with estrogens are required for PCa. Our hypothesis is based on the following evidence, the serum estrogens are known to increase and androgens decrease upon aging, which changes precede or coincide with the increasing incidence of prostate cancer. The altered ratio of serum androgens to estrogens and progression of prostate cancer have been suggested to have a causal relationship with each other. However, despite extensive studies, there is no conclusive clinical evidence of a strong correlation between elevated serum estrogen or estrogen/androgen ratio[5], so this is the primary approach to find the significance of Androgen and Estrogen ratio in Prostate cancer and benign prostatic hyperplasia that is being eclipsed for years by an androgen dominated interest**.**

Material and Methods

A cross-sectional study was conducted to test the association of Testosterone, Estrogen and its ratio with histological Gleason grade in patients of prostate cancer. Between January 2013 and December 2013, 95 men diagnosed with prostate cancer and 95 men with BPH, were evaluated and the following assessments were done.

Anthropometric examination and blood sampling: All men underwent physical examination to measure the height, weight and body mass index (BMI). WHR was calculated from waist circumference at umbilicus divided by hip circumference at greater trochanter and a cut off of 0.9 was taken to categorize central obesity.

Hormonal and biochemical Assessment: Serum samples of men with suspicion of prostate cancer on the basis of high prostate specific antigen (PSA) and/or abnormal DRE were withdrawn before biopsy between 8 am and 11am Serum PSA, testosterone, and estrogen

levels were estimated using ELISA on the same day. The serum was separated, aliquoted and kept frozen at -80ºC for analysis. The serum androgen and estrogen levels were measured using commercial ELISA kit of calbiotech (Linco Research, St. Charles, Missouri, USA).The study protocol was approved by the Institutional Review Board for ethical clearance. All participating subjects were informed about the purpose of the study and provided written informed consent.

Staging and grading: Tissue biopsies and resected prostatic specimen were fixed in 10% buffered formalin and processed for histopathological examination as per standard histological protocol: 3-5 micron thick sections were cut and stained with haematoxylin and eosin. The histological diagnosis of BPH and PC was done by one histo-pathologist (MMG). The Gleason grading was done on biopsy tissue and on the basis of score patients were divided into Group 2A: Gleason score ≥ 6, Group 2B: Gleason score <6.

Statistics: Descriptive statistics was used to characterize the study population in terms of frequency and percent, or median and inter-quartile range. The software used was SPSS (version 16), independent t-test used, if data meet normally assumption, and Mann-Whitney U test, if data not normally distributed data were presented as mean $\pm$ SD, median (IQR) and p value <0.05 was considered as significant. Binary logistic regression analysis is used to find out the potential risk factor. The odds ratio (OR) and its 95% confidence interval (CI) was calculated.

Exclusion Criteria: Patients suffering from diabetes, chronic liver, kidney, heart disease those taking lipid-lowering drugs or 5-alpha reductase inhibitors were excluded from the study leaving only 50 patients who were included.

Results

A total of 190 patients were included in the study. Out of these, 95 patients were in BPH and 95 in PCa group. The age of the patients was almost similar in both BPH (65.66±10.66) and PCa (66.54±7.11) groups. The level of BMI was significantly ($p<0.001$) higher in the patients of PCa (26.58±4.76) as compared to BPH (22.15±2.90). Similarly, the waist hip ratio was also significantly ($p<0.0001$) higher in the patients of PCa (1.08±0.37) as compared to BPH (0.86±0.15). The free testosterone was significantly ($p<0.0001$) higher in PCa (Median=6.67) patients as compared to BPH patients (Median=3.32). Similarly, the total testosterone was significantly ($p<0.0001$) higher in PCa patients (Median=8.66) as compared to BPH patients (Median=5.22). However, dihydrotestosterone was significantly higher in BPH patients (Median=535.71) as compared to PCa patients (Median=7.60). The estrogen level was significantly ($p<0.0001$) lower in PCa (Median=13.0) patients as compared to BPH patients (Median=22.93). Similarly, E ratio T level was significantly lower ($p<0.0001$) in PCa patients (Median=2.84) as compared to BPH patients (Median=4.79). (Table 1)

Table 1 (Comparison of parameters between BPH and PCa patients)

	BPH (n=95) Mean ± SD	PCa (n=95) Mean ± SD	p-value*
Anthropometric measurements			
Age	65.66±10.66	66.54±7.11	0.51
BMI	22.15±2.90	26.58±4.76	<0.001**
WHR	0.86±0.15	1.08±0.37	<0.0001**
Androgen			
Free testosterone	3.78±2.99 (3.32)	6.82±4.42 (6.67)	<0.0001**
Total testosterone	5.67±3.14 (5.22)	8.60±4.74 (8.66)	<0.0001**
Dihydrotestosterone	575.32±202.42 (535.71)	8.51±5.44 (7.60)	<0.0001**
Estrogen			
Estrogen	28.61±21.64 (22.93)	18.19±16.31 (13.0)	<0.0001*
T ratio E[1]	0.30±0.26 (0.20)	0.63±0.66 (0.50)	<0.0001*

[1]Mann-Whitneu U test

The age of the patients was almost similar in both Lower (66.58±7.28) and Higher (66.52±7.08) grades. The level of BMI was significantly (p=0.008) higher in the patients of Higher grade (27.52±5.03) as compared to Lower grade (24.82±3.67).The higher grade patients had more risk of being overweight than the lower grade patients (Unadjusted OR=1.14, 95%CI=1.03-1.16).Similarly, the waist hip ratio was also significantly (p=0.03) higher in the patients of Higher grade (1.14±0.39) as compared to Lower grade (0.97±0.29). The Higher grade patients had almost 4 times more risk of having high WHR level than the lower grade patients (Unadjusted OR=1.14, 95%CI=1.03-1.16).The free testosterone level of the patients was significantly (p<0.0001) lower in High grade patients (Median=4.95) as compared to Low grade patients (Median=10.51). The Low grade patients had 24% higher risk of having high level of free testosterone level than the High grade patients (Unadjusted OR=0.76, 95%CI=0.67-0.86). The total testosterone level was significantly lower (p<0.0001) in High grade (Median=6.94) PCa patients as compared to Low grade patients (Median=12.50) (Table-2).The risk of having higher level of total testosterone was 22% in Low grade patients than the High grade (Unadjusted OR=0.78, 95%CI=0.67-0.88).The DHT level was significantly Higher (p=0.02) in High grade (Median=8.67) PCa patients as compared to Low grade patients (Median=6.60). The risk of having higher level of DHT was higher in High grade patients than the Low grade (Unadjusted OR=1.17, 95%CI=1.04-1.32). The estrogen level of the patients was significantly (p<0.0001) lower in High grade patients (Median=12.22) as compared to Low grade patients (Median=19.67). The Low grade patients had 6% higher risk of having high level of estrogen level than the High grade patients (Unadjusted OR=0.94, 95%CI=0.90-0.98). However, the E ratio T level was insignificantly lower (p=0.25) in High grade (Median=2.82) PCa patients as compared to Low grade patients (Median=2.90).

Table 2 (Comparison of parameters between Low grade and High grade patients)

	Low grade (n=33) Mean ± SD (Median)	High grade (n=62) Mean ± SD (Median)	p-value*	Unadjusted OR (95%CI)
Anthropometric parameters				
Age	66.58±7.28	66.52±7.08	0.97	0.99 (0.94-1.06)
BMI	24.82±3.67	27.52±5.03	0.008**	1.14 (1.03-1.16)
WHR	0.97±0.29	1.14±0.39	0.03**	4.32 (1.08-17.33)
Androgen				
Free testosterone	9.73±4.36 (10.51)	5.27±3.62 (4.95)	<0.0001**	0.76 (0.67-0.86)
Total testosterone	11.62±4.61 (12.50)	7.00±4.00 (6.94)	<0.0001**	0.78 (0.67-0.88)
Dihydrotestosterone	6.37±2.33 (6.60)	9.66±6.24 (8.67)	0.02**	1.17 (1.04-1.32)
Correlation of Estrogen and Eratio T levels with Grade of Prostate Cancer patients				
Estrogen	24.47±24.61 (19.67)	14.85±7.71 (12.22)	<0.0001*	0.94 (0.90-0.98)
T ratio E	0.66±0.44 (0.55)	0.62±0.75 (0.50)	0.22	0.91 (0.48-1.70)

The age of the patients was almost similar in both Stage-III (66.66±7.53) and Stage-IV (66.29±6.28) patients. The level of BMI was insignificantly (p=0.10) higher in the patients of Stage-III (27.15±4.44) as compared to Stage-IV (25.42±5.30) patients. The Stage-III patients had 8% higher risk of being overweight than the Stage-IV patients (Unadjusted OR=0.92, 95%CI=0.84-1.02). However, the waist hip ratio was significantly (p<0.0001) higher in the patients of Stage-IV (1.39±0.44) as compared to Stage-III (0.93±0.20) patients. The Stage-IV patients had almost 4 times higher risk of having high WHR level than the Stage-III patients (Unadjusted OR=3.74, 95%CI=2.68-15.67). The free testosterone level of the patients was insignificantly (p=0.17) lower in Stage-IV patients (Median=5.59) as compared to Stage-III patients (Median=7.06). The risk of higher level of free testosterone was 7% higher in the patients of Stage-III as compared to Stage-IV patients (Unadjusted OR=0.93, 95%CI=0.84-1.03). Similarly, the level of total testosterone was insignificantly lower (p=0.17) in the patients of Stage-IV (Median=7.58) as compared to Stage-III (Median=9.05) patients. The risk of higher level of total testosterone was 6% higher in the Stage-III patients as compared to Stage-IV patients (Unadjusted OR=0.94, 95%CI=0.86-1.03). The DHT level was insignificantly lower (p=0.51) in the patients of Stage-IV (Median=6.70) as compared to Stage-III (Median=7.80) patients. The risk of higher level of DHT was almost equal in the patients of Stage-III and Stage-IV (Unadjusted OR=0.99, 95%CI=0.91-1.07). The estrogen level of the patients was insignificantly (p=0.48) lower in Stage-IV patients (Median=12.33) as compared to Stage-III patients (Median=13.80). The risk of higher level of estrogen was almost equal in the patients of Stage-III and Stage-IV patients (Unadjusted OR=0.99, 95%CI=0.95-1.02). Similarly, the level of T ratio E was insignificantly lower (p=0.30) in the patients of Stage-IV (Median=0.49) as compared to Stage-III (Median=0.53) patients (Table -3). The risk of higher level of estrogen was almost equal in the patients of Stage-III and Stage-IV patients (Unadjusted OR=0.99, 95%CI=0.94-1.05).

Table 3 (Comparison of parameters between stage III and stage IV patients)

	Stage III (n=64) Mean ± SD (Median)	Stage IV (n=31) Mean ± SD (Median)	p-value*	Unadjusted OR (95%CI)!
Anthropometric parameters				
Age	66.66±7.53	66.29±6.28	0.82	0.99 (0.93-1.06)
BMI	27.15±4.44	25.42±5.30	0.10	0.92 (0.84-1.02)
WHR	0.93±0.20	1.39±0.44	<0.0001**	3.74 (2.68-15.67)
Androgen				
Free testosterone	7.25±4.71 (7.06)	5.94±3.67 (5.59)	0.17	0.93 (0.84-1.03)
Total testosterone	9.03±5.03 (9.05)	7.71±4.04 (7.58)	0.17	0.94 (0.86-1.03)
Dihydrotestosterone	8.63±5.16 (7.80)	8.28±6.06 (6.70)	0.51	0.99 (0.91-1.07)
Correlation of Estrogen and T ratio E levels with Stage of Prostate Cancer patients				
Estrogen	19.10±18.64 (13.80)	16.31±9.92 (12.33)	0.48	0.99 (0.95-1.02)
T ratio E	0.58±0.40 (0.53)	0.74±1.01 (0.49)	0.30	1.39 (0.73-2.62)

Discussion

Altered androgen levels - Androgens are necessary for the growth, maintenance, and functional activity of the prostate gland. Androgens and estrogens play significant roles in the prostate, their specific balance seems to be critically important in maintaining prostate health and tissue homeostasis in adulthood. Accordingly, it appears likely that these hormones also play some role in the development of hypertrophy and hyperplasia of the prostate gland. However, this does not necessarily mean that variation in hormone levels within the normal endogenous range would be reflected in prostate cancer risk, although this is a reasonable possibility. Studies comparing circulating male sex hormone levels in subjects with and without prostate carcinoma have produced widely varying results. Gann et al. found a statistically significant increasing risk of prostate carcinoma with increasing levels of testosterone and an inverse trend in prostate carcinoma risk with increasing levels of SHBG.

Several studies have focused on the relationship between serum androgen concentrations and clinical BPH in elderly men, but the results have not been consistent. **Joseph *et al*. *(2002)*[6]** found that large prostate volume was marginally associated with increased Total Testosterone (TT) level in African-American men, but **Meikle *et al*. *(1997)*[7]** found an inverse correlation between prostate volume and TT level in 214 male twins based on white populations. Others have not found a significant association between TT level and prostate volume.[6,7]

However, studies done by **Schatzl G. et al (2000)[8]** and **Roberts R.O. et al (2004)[9]** found that prostate volume was not associated with FT level or TT level after adjustment for age.

Beutel *et al (2005)*[10] also found that TT and FT levels decreased significantly with age in aging urologic outpatients. Ethnic differences exists in the prevalence of LUTS / BPH[11,12,13], Ca Prostate and in serum androgen levels. Moreover, most of the available data describing the associations between androgen status and BPH has been based on white and African-American populations[14]. The impact of androgen status on the prostate condition could be different in Asian populations.

Therefore, the purpose of this study was to evaluate the association of serum androgen levels and measures of BPH in aging men in Indian population.

Comparison of Androgens levels in BPH and PCa patients- Androgens are considered to play a substantial role in pathogenesis of both benign prostatic hyperplasia (BPH) and prostate cancer. The importance of determination of androgen levels in tissue and serum for cancer progression and prognosis has been poorly understood. Intraprostatic androgen levels might be used in the future assessment and management of prostate cancer. Since the data on the significance of intraprostatic and serum androgen determination in subjects with and without prostate cancer are still insufficient and often controversial.

The prostate, like other accessory sex organs, is stimulated in its growth, maintenance and secretory function by the continued presence of certain hormones and growth factors. Foremost among these is testosterone, which is converted within the prostate into a more potent androgen, dihydrotestosterone (DHT). Testosterone is synthesized in the Leydig cells of the testes from pregnenolone by a series of reversible reactions. Despite strong circumstantial evidence indicating that androgens play a part in the etiology of prostate cancer; data from previously published epidemiologic studies have shown inconsistent and often conflicting results (Nomura et al, 1991; Anderson et al, 1993; Terrence et al, 2000)[15,16,17.]

Though the association of androgen levels with BPH or CaP risk is still controversial, it would be interesting to see if obesity or adipose tissue affects androgens synthesis, metabolism or bioavailability. Adiposity with its associated hyperinsulinism suppresses the synthesis of sex hormone binding globulin (SHBG) synthesis and therewith the levels of circulating testosterone (Farid et al, 2011)[18]. SHBG is a carrier protein that specifically binds circulating testosterone and Dihydrotestosterone (DHT) and reduces their availability to tissues. In obese men, however, not only are total testosterone, SHBG and diurnal luteinizing hormone levels reduced, but bioavailable testosterone levels also are reduced (Kaaks et al, 2010)[19].These various observations collectively argue against a role for total or bioavailable serum androgen levels in mediating the contribution of excess weight /adipose tissue to BPH or CaP risk.

In the present study, the free testosterone was significantly ($p<0.0001$) higher in PCa (Median=6.67) patients as compared to BPH patients (Median=3.32). Similarly, the total testosterone was significantly ($p<0.0001$) higher in PCa patients (Median=8.66) as compared to BPH patients (Median=5.22).However, dihydrotestosterone was significantly higher in BPH patients (Median=535.71) as compared to PCa patients (Median=7.60).Hsing in 1993, conducted a population-based nested case-control study to determine the relation of prediagnostic serum levels of testosterone, dihydrotestosterone, prolactin, follicle-stimulating hormone, luteinizing hormone, estrone and estradiol to the risk of subsequent PCa finding no significant differences in levels of these hormones between cases and controls, although elevated levels of luteinizing hormone and of testosterone: dihydrotestosterone ratios were associated with mild increase in the risk of PCa. Gann observed in 1996, a prospective nested case-control study that high levels of circulating testosterone and low levels of SHBG, both within normal endogenous ranges, are associated with increased risk of PCa and that low levels of circulating estradiol may represent an additional risk factor. Androgens have now been well accepted as a risk factor for BPH, although BPH presents clinically when testicular activity is declining (Schatzl et al, 2000). Men castrated before puberty (eunuchs) did not develop BPH and those with an inherited deficiency of 5-alpha-reductase type 2 have only a vestigial prostate gland, further supporting the relation between androgens and prostate anomalies.

Comparison of Estrogens & T:E levels in BPH and PCa patients- The prostate, like other sex accessory tissues, is stimulated in its growth, maintenance, and secretory function by the continued presence of certain hormones and growth factors. Foremost among these is testosterone, which is converted within the

prostate into the more active androgen dihydrotestosterone (DHT). Testosterone is synthesized in the Leydig cells of the testes from pregnenolone by a series of reversible reactions. However, once testosterone is converted by 5α-reductase into DHT or converted by aromatase into estrogens, the process is irreversible; testosterone can be converted to DHT or estrogens, but estrogens and DHT cannot be converted to testosterone**.** Androgens, estrogens, and adrenal steroids are believed to have strong effects on different cells and tissues in the body that can vary with development and age. In addition to testosterone, the adrenal secretes a weak androgen, androstenedione; however, this is not a major pathway since, in both animals and humans, castration leads to almost complete involution of the prostate, meaning that insufficient adrenal androgens are present to stimulate any meaningful growth of the normal prostate. Similar to serum testosterone, androstenedione can undergo aromatization to estrone. Overproduction of androstenedione, such as occurs in certain forms of congenital adrenal hyperplasia, may stimulate prostate growth; however, again, the role of adrenal androgens in regulating prostate growth is minor. The presence of a nontesticular minor androgen source has led to the concept of total androgen blockade for the treatment of advanced prostate cancer, whereby both a luteinizing hormone–releasing hormone agonist and a nonsteroidal auto antigen are combined to eliminate testosterone production and block any residual androgen stimulation of the prostate from the adrenal gland. This strategy remains controversial and is discussed at length elsewhere. In the present study, the estrogen level was significantly ($p<0.0001$) lower in PCa (Median=13.0) patients as compared to BPH patients (Median=22.93). Similarly, E ratio T level was significantly lower ($p<0.0001$) in PCa patients (Median=2.84) as compared to BPH patients (Median=4.79). There are few limitations in the study that is a single assessment of circulating sex steroid concentrations may not be completely reliable clinically however, a single fasting morning venous blood sample makes the assessment of the hormone milieu more user-friendly in everyday clinical practice. However, because it is almost impossible clinically to follow the circulating hormone milieu in a sufficient number of men throughout their entire life span to assess the role of sex steroids as independent predictors of the eventual biology of PCa.

Conclusion

Our study indicates that the altered ratio of serum androgens to estrogens and progression of prostate cancer have been suggested to have a causal relationship with each other. The comparative levels or ratio of these hormones are very imperative in the progression of prostate cancer. Once the cancerous state has set in, age of the patient not seems to be strongly related with these changes. Future studies with a larger sample size are needed to establish its association.

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