Effect of Testosterone and Estrogen Ratio - An indicator of Benign Prostatic Hyperplasia (BPH)

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Abstract

Background: Benign prostatic hyperplasia (BPH) is one of the most common disease and major cause of morbidity in elderly men. Prostatomegaly often used interchangeably with BPH, is a prominent feature of the disease. Although sex steroid hormones play a vital role in prostate growth, their clinical significance is not completely clear. The phenomenon may be correlated with changes of sex hormone in serum of elderly population. Hence, the objective of this study was to study the roles of serum hormones levels – Testosterone (T) and Estradiol (E_2) in elderly patients aged 60-75 years who are diagnosed with benign prostatic hyperplasia (BPH) and to understand the correlation between T/E_2 ratio over age as markers of prostate disease.
Methods: To conduct this case control study, a population of 30 patients with benign prostatic hyperplasia (BPH) had been selected and 30 well-matched males without BPH as a control group.
Result: Testosterone level declined with age, but serum estrogens level remains unaltered so estrogen may be involved in the development of BPH.
Conclusion: The present study suggests that testosterone estrogen ratio can be an indicator of BPH in patients above 45 years of age.

Keywords: Benign prostatic hyperplasia (BPH), Testosterone T and Estradiol (E2).

Access this article online	
Quick Response Code:	**Website:** www.innovativepublication.com
	DOI: 10.5958/2394-2126.2016.00030.X

Introduction

The prostate is small at birth (1.5 g) and remains so until early puberty when it increases in size via an androgen dependent pubescent growth phase from 10 g to an average of 20 g in young adults.[8] After this initial growth and remodelling phase, which involves the entire prostate gland (peripheral, central and transitional zones), there is a second selective growth phase of the transitional zone that occurs in approximately 50% of men by age 50, and 90% of men older than 80 years. This growth is pathologically recognized as BPH and clinically noted as benign prostatic enlargement (BPE) or Benign Prostatic Obstruction/BOO. It is thought that the normal interactions between the epithelial and fibro-muscular stromal components of the transitional zone prostate tissue are altered leading to a reduced epithelial/stroma ratio and thus micro-nodular re-modelling that characterizes BPH.

Relationship of metabolic syndrome, lower urinary tract symptoms (LUTS) and testosterone replacement therapy (TRT) has been discussed. There is an increased understanding of links between metabolic syndrome and LUTS. A group of 1224 otherwise healthy police officers, 29% of whom were diagnosed with metabolic syndrome has been investigated.[4] When compared with those without metabolic syndrome (and corrected for age and serum testosterone), they had a worse IPSS, larger TPV, and larger PVR volume. Risk factors associated with BPH progression (TPV of > 31 cm3, PSA level of > 1.6 ng ml−1, Qmax < 10.6 ml s−1, or PVR of > 39 ml) in men with moderate to severe LUTS has been studied and demonstrated a significant association with the increasing number of components of metabolic syndrome.[5] These concepts are reinforced by other studies that demonstrate that in obese men (body mass index [BMI] >25), only their age, increasing total testosterone and sex score were related to their worsening LUTS.[6]

As BPH is associated with elevations in plasma Estradiol/Testosterone ratio, insulin, and insulin-like growth factor-I, daily aerobic exercise can reduce all of these plasma factors, particularly when combined with a low-fat, high-fiber diet consisting of whole grains, fruits, and vegetables. In cell culture studies, this type of lifestyle regimen has recently been shown to reduce the growth of serum-stimulated prostate epithelial cells and the growth of androgen-dependent prostate cancer cell lines.[7]

Serum testosterone has been shown to decrease in men with age by approximately 2%–3% annually.[9] The prevalence of hypogonadism (often defined as serum testosterone < 300 ng dl−1) ranges from 6% to as high as 38% in some primary practice settings.[10,11] The

process of BPH, however, continues as men age and despite the fact their serum testosterone decreases.

Though BPH typically manifests in later stage of life when androgen levels are declining, androgens are thought to be pre-requisites for the development of BPH.[12]

It is observed from the previous studies that the testosterone concentrations were significantly lower in patients with BPH than control group ($p \leq 0.05$), while the Estradiol and PSA concentrations were significantly higher in patients with BPH than control group ($p \leq 0.05$).[13] The net result is a significant decrease in the T/E2 ratio allowing the imbalance between androgens and estrogen regulation of prostate growth to shift towards estrogen dominance. It has been proposed that increased estrogenic stimulation of the prostate in the aging male may lead to reactivation of growth and subsequent hyperplasia transformation.

In the present study the relationship between Testosterone, Estrogen and T/E ratio with BPH has been investigated.

Materials and Methods

To conduct this case control study, a population of 30 patients with benign prostatic hyperplasia (BPH) had been selected and 30 well-matched males without BPH as a control group. The subjects were selected from the urology outpatient of Princess Esra Hospital located in the city of Hyderabad, India. They were free to join or leave the study at any time during the phase of the study. Prior to recruitment informed consent was obtained from all the subjects and the study was approved by the ethics committee of Deccan College of Medical Sciences.

Detailed medical and urological examinations using ultrasonic scans and digital rectal examinations were done on each subject. Diagnosis of patients was dependent on the following criteria:

a) Male subjects aged between 60-75 years with prostrated volume more than 33 cubic centimetres were included in the study.
b) Digital Rectal Examination showing enlarged prostate
c) **Symptoms:** Frequent urination, nocturia and dribbling of urine.

An age matched group of 30 healthy volunteers with no known co morbidity were also included as a control group. Hormonal estimation of Total Testosterone and Estradiol were carried out by a solid phase enzyme-linked immunosorbent assay (ELISA) method, based on the principle of competitive binding.

Serum samples were assayed for **Testosterone** (T) using DRG Testosterone kit and **Estradiol** (E2) using DRG Estradiol kit. Kit was supplied with instruction for hormone assay by ELISA. (USA)

Specimen Collection: The blood samples were collected by venous-puncture and allowed to clot. Whole samples were centrifuged immediately after collection into tubes containing anti-coagulant and then the serum separated by centrifugation at room temperature. Specimens are capped and stored for up to 5 days at 8°C prior to assaying.

Results

It is a case control study with a sample size of (N=30)male patients between the ages of 60-75 years selected at random from a list of patients identified with benign prostatic hyperplasia (BPH). Patients were confirmed to have BPH by earlier clinical examination using ultrasonic scan, digital rectal examination and other symptoms such as frequent urination, nocturia and dribbling of urine. Patients were free to join or leave the study at any time during the study and informed consent was obtained from all the subjects prior to their recruitment. Another 30 well-matched healthy males without BPH and any known co morbidities between the ages of 60-75 years were taken as a control group. All the subjects were selected from the outpatient of Princess Esra Hospital located in the city of Hyderabad, India. The 95% confidence interval of both these group(patients with BPH and control groups) were in the range of 63.75 to 68.85 and 65.53 to 69.74 respectively (Fig. 1).

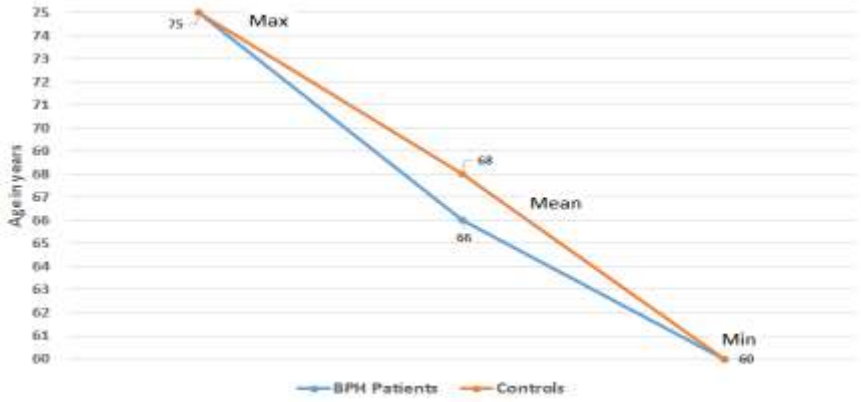

Fig. 1: Comparison of Age range between BPH patients & controls

The mean values of all the measured parameters are depicted in (Table 1). Among the measured parameters – Testosterone (ng/mL) and Estradiol (pg/mL), no significant difference was seen between the patients with BPH group and the control group. The mean testosterone value for the patients with BPH was observed to be (5.40±3.75 SD) which was not significantly different from the mean testosterone value for control group at (4.38±2.19 SD Fig. 2).

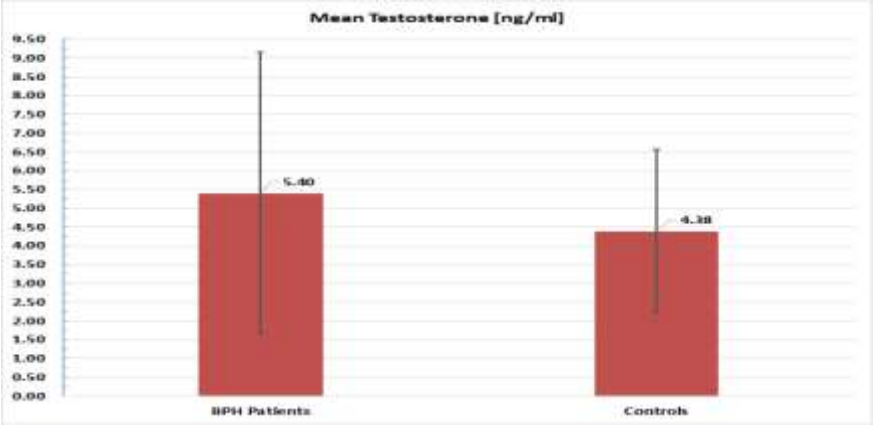

Fig. 2: Mean Testosterone (T) value – BPH patients vs controls

Similarly, there was no significant difference between the mean Estradiol values between the two groups. The mean value for patients with BPH was (31.93±16.41SD) and the mean value for control group was (25.49±11.25 SD). The confidence interval for both the group was in the range (23.6692 to 40.1835) for patients with BPH and (20.3364 to 31.3123) for the control group (Fig. 3).

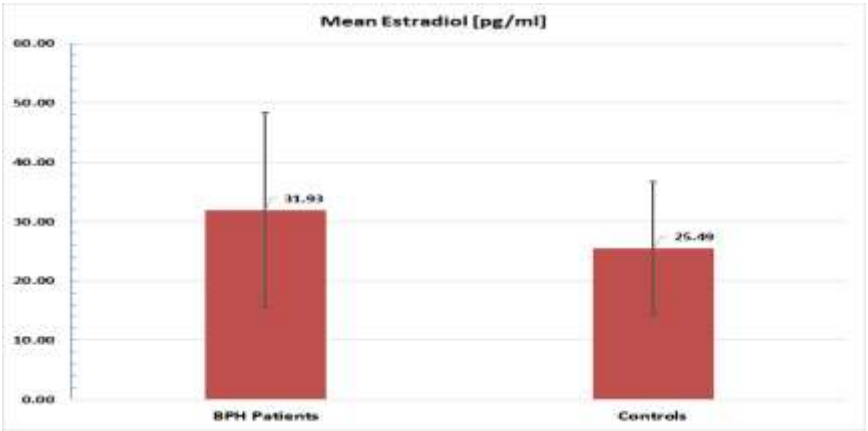

Fig. 3: Mean Estradiol (E2) value – BPH patients vs controls

For Patients:	Age Range: 60-75 Years
	Ultra Sound: Prostate volume >=30 cc
	Digital Rectal Examination: Enlarge Prostate
	Symptoms: Frequent Urination, Nocturia and Dribbling of urine
For Controls:	Age Range: 60-75 Years
	No prostrate enlargement reported
	No comorbidities known
#Total Number of Patients	60
#Patients with BPH	30
#Controls Group	30
Hormones Evaluated	Testosterone [ng/ml]
	Estradiol [pg/ml]

Table 1: Summarized Test Results including mean value, standard deviation, standard error of mean and confidence interval

Age (Years)	Range	Mean Value	SD	SEM	N	90% CI	95% CI	99% CI	Min	Median	Max
BPH Patients	60-75	66	5.07	0.93	30	64.73 to 67.87	64.41 to 68.19	63.75 to 68.85	60	65	75
Controls	60-75	68	4.19	0.76	30	66.33 to 68.93	66.07 to 69.20	65.53 to 69.74	60	67	75
Testosterone [ng/ml]	**Normal Value**	**Mean Value**	**SD**	**SEM**	**N**	**90% CI**	**95% CI**	**99% CI**	**Min**	**Median**	**Max**
BPH Patients	2.6-10.6	5.40	3.75	0.684	30	4.2395 to 6.5638	4.0028 to 6.8006	3.5163 to 7.2870	1.73	4.175	18.43
Controls		4.38	2.19	0.4005	30	3.7021 to 5.0632	3.5635 to 5.2018	3.2787 to 5.4867	1.4	3.5	9.6
Estradiol [pg/ml]	**Normal Value**	**Mean Value**	**SD**	**SEM**	**N**	**90% CI**	**95% CI**	**99% CI**	**Min**	**Median**	**Max**
BPH Patients	<52	31.93	16.41	2.9956	30	26.8364 to 37.0163	25.7996 to 38.0531	23.6692 to 40.1835	7	32.945	68.44
Controls		25.49	11.25	1.991	30	22.4414 to 29.2073	21.7523 to 29.8964	20.3364 to 31.3123	10.2	23.625	50.06

The level of testosterone and estradiol over age for the collected sample of 30 patients with BPH was linear i.e. both values increased with age. However, as can be seen from the slope of the graphs below, the level of estradiol increased more than the level of testosterone, thus affecting the T/E_2ratio.

Discussion

In this study population, age is an important factor that influences both urinary tract diseases and sex hormones. The incidence of urinary tract disease increases with age and the levels of sex hormones vary with age by Ansari M.A.J et al.[1] However, age is not the only factor that influences sex hormones. Abnormal metabolism can change the sex hormone levels in elderly men by Meigs, J.B. et al, 2001.[2] Subject were age matched but there was no significant difference in the level of hormones to suggest their influence on patients in developing BPH.

The mean testosterone level for patients with BPH was (5.40±3.75 SD) which is not significantly different from the mean testosterone level for control group at (4.38±2.19 SD). Both these values are within the normal range of testosterone which is 2.6 to 10.6 ng/mL. This implies that with age there is no significant difference in the level of testosterone at least in the same age range of elderly men. As can be seen in the Fig. 4, the testosterone level of patients with BPH compared with the testosterone level of control group is not significantly different. The plot is evenly distributed between patients with BPH and control group above and below the linear line.

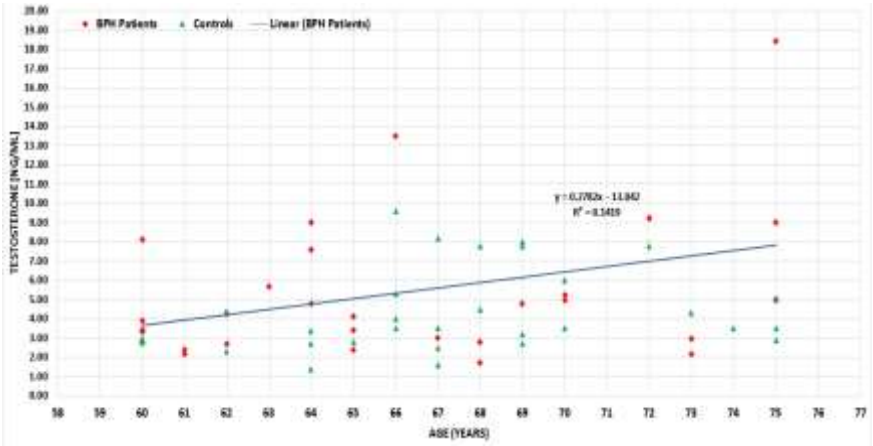

Fig. 4: Correlation of testosterone (T) between patients with BPH and controls over age

Similarly, the mean estradiol values between patients with BPH was at (31.93±16.41 SD) and was not significantly different from the mean estradiol values of the control group at (25.49±11.25 SD). Both these values are within the normal estradiol level 0-52 pg/mL suggesting there is no correlation between the levels of estradiol and the age of the patient. As can be seen from the graph below, the estradiol levels of patients with BPH and normal patients are equally distributed across the linear line. (Fig. 5)

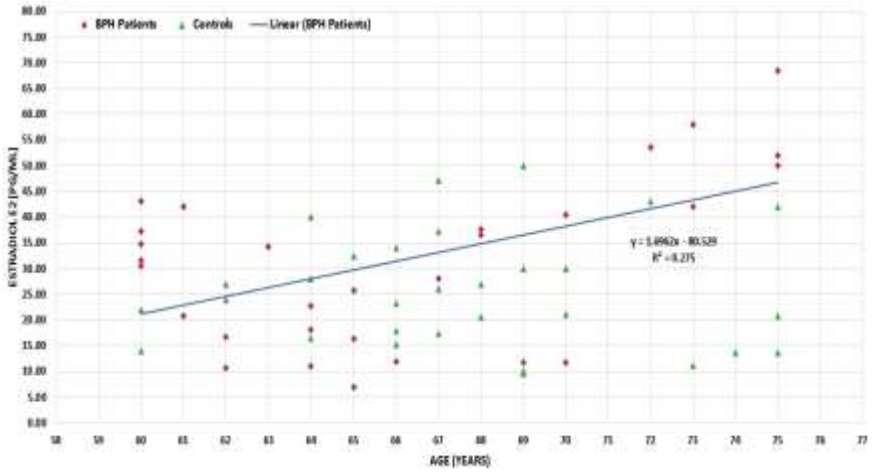

Fig. 5: Correlation of estradiol (E_2) between patients with BPH and controls over age

Conclusion

Hence, it was investigated to see if the variance in the levels of hormones has any significant impact on the T/E_2 ratio over age. As can be seen from the graph below, the T/E_2over age between patients with BPH is not significantly different from the control group. As can be seen from the Fig. 6, the ratio is generally within the range of 0.00 to 0.5 with few patients having the radio above 0.5.

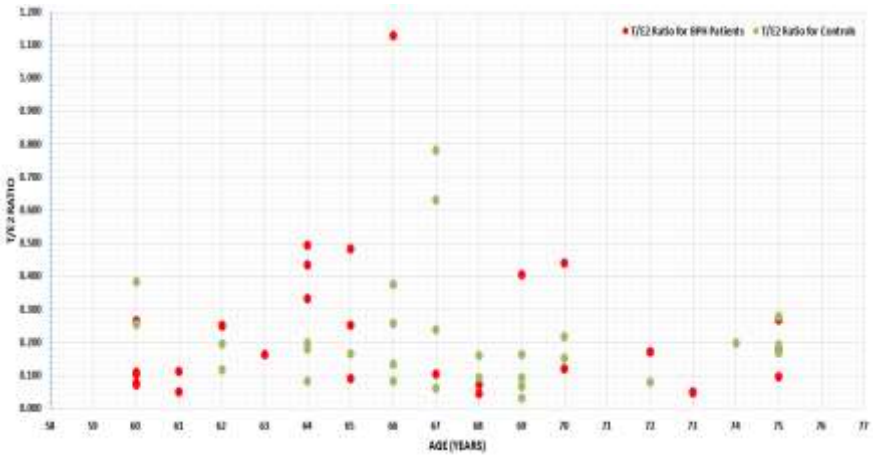

Fig. 6: Comparison of T/E2 ration over age- BPH patients vs controls

A statistical analysis of the T/E2 ratio over age between patients with BPH and control was done using unpaired t test with Welch correction. The t test assumes that the data are sampled from populations that follow Caucasian distributions.

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