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Correlation of Age, Prostate Volume, Serum Prostate-Specific Antigen, and Serum Testosterone in Indian, Benign Prostatic Hyperplasia Patients

Sasanka K Baruah, Simanta Jyoti Nath, Rajeev T Puthenveetil, Saumar J Baruah, Phanindra Mohan Deka, Bikash Bawri

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ABSTRACT

Introduction and Objective: Benign prostatic hyperplasia is the most common neoplastic disorder affecting the aging male population worldwide. Various factors such as age, prostate volume, serum prostate-specific antigen, and testicular androgens determine the natural history and its progression. The objective of the study is to correlate the relationship between these factors in men with benign prostatic hyperplasia.

Methods: A total of 121 men aged above 50 years with benign prostatic hyperplasia were enrolled in this study. Patients were evaluated by history, digital rectal examination, focused neurological evaluation, uroflowmetry, transrectal ultrasonography of the prostate, serum prostate-specific antigen, serum testosterone (free and total), and prostate biopsy done in patients with prostate-specific antigen > 4 ng/ml to exclude prostatic carcinoma. Patients were divided by age, and a Spearman rank correlation test was done to compare variables.

Results: There was a positive correlation within age, prostate volume, and serum prostate-specific antigen level. Age negatively correlated with serum total and free testosterone level. A comparison among serum PSA, prostate volume, and serum testosterone level did not reveal any statistically significant relationship.

Conclusion: We observed statistically significant correlations within age, prostate volume, and serum prostate-specific antigen level. These variables bear no significant relationship with serum testosterone levels. Considering the contradictory data on the inter-relationship of various variables, further evaluation in a large cohort of the aging population with benign enlargement of the prostate is needed to establish the influence of one over the other.

INTRODUCTION

Benign prostatic hyperplasia (BPH) in the most common neoplastic disorder affecting the aging male population worldwide. Various factors such as age, prostate volume, serum prostate-specific antigen (PSA), and testicular androgens determine the natural history and its progression. However, these parameters are subject to racial and ethnic variations [1] and may be influenced by other associated health-related events.

The objective of the study is to correlate the relationship within age, prostate volume, serum prostate-specific antigen, and serum testosterone level in previously untreated men with lower urinary tract symptoms due to benign prostatic hyperplasia who are racially different from their western counterpart with divergent ethnicity.

MATERIAL AND METHODS

A total of 121 consecutive men aged over 50 years with

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CORRESPONDENCE: Sasanka K Baruah, Assistant Professor, Department of Urology, Gauhati Medical College Hospital, Guwahati, Assam, India (sasankagmch@gmail.com)

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Figure 1. Correlation between age and prostate volume.

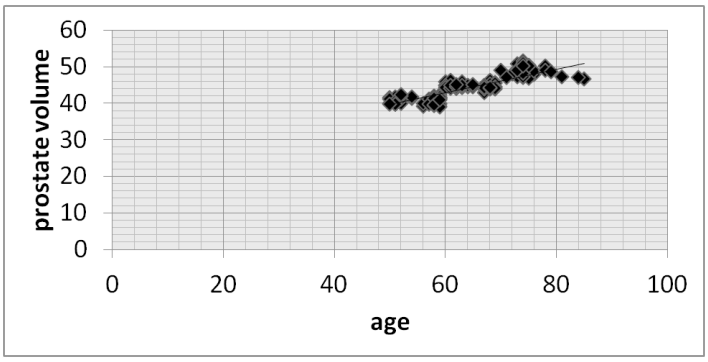


Table 1. Clinical, biochemical, and endocrinologic variables

Parameter	Geometric Mean ± SD	Range
Age	62.84 ± 7.57	51-81 years
Prostate volume	44.11 ± 19.57	20-155 gm
S PSA	3.08 ± 1.26	0.29-7.94 ngm/ml
S total testosterone (2.80 to 8.0 ngm/ml)*	8.47 ± 5.29	1.07-33.2 ngm/ml
S free testosterone (10.8 to 24.6 pgm/ml)**	12.66 ± 5.81	3.98-27.5 pgm/ml

* Normal total serum testosterone level
** Normal free serum testosterone level

lower urinary tract symptoms suggestive of benign prostatic hyperplasia were enrolled in this study. Informed consent was obtained from all patients who then underwent systematic evaluation, including clinical history, digital rectal examination, focused neurological evaluation, uroflowmetry, and transrectal ultrasonography of the prostate to estimate prostate volume using the formula Π/6 x height x width x length. The estimation of serum PSA and serum testosterone (free and total) were done, and those with serum PSA > 4 ngm/ml were subjected to prostate biopsy to exclude prostatic carcinoma. Those patients with suspected neurovesical dysfunction, vesical calculus, previous surgery or medications, diabetes mellitus, and renal insufficiency were excluded from the study. The patients were divided into 4 groups according to age: 50 to 59 years, 60 to 69 years, 70 to 79 years, and over 80 years.

A Spearman rank correlation test was done to compare age with other variables such as prostate volume, serum PSA, and serum-free and total testosterone levels. A minus 1 indicated a perfect negative correlation while a plus 1 indicated a perfect positive correlation. A correlation coefficient of zero meant there was no correlation between 2 variables. The results of all variables were then expressed as a geometric mean ± the standard deviation. Statistical power is 90 in the clinical data analysis.

RESULTS

The statistics of 4 different age groups and the average values of the clinical, biochemical, and endocrinal variables are depicted in Table 1.

Ages ranged from 51 to 81 years (geometric mean: 62.84 ± 8.22), prostate volume ranged from 20 to 155 cm³ (geometric mean: 43.9 ± 3.117), serum PSA ranged from 0.29 to 7.94 ngm/ml (geometric mean: 2.55 ± 0.555 ngm/ml), serum total testosterone ranged from 1.07 to 33.2 ngm/ml (geometric mean: 7.95 ± 2.01), and free testosterone ranged from 3.89 to 27.5 pgm/ml (geometric mean: 13.68 ± 3.71 pgm/ml).

The percentage of patients with a PSA < 4 ngm/dl was 86.77% while 13.22% had a PSA > 4 ngm/ml. Of the men in the present study, 8.26% had subnormal serum total testosterone levels. The average values of different variables in the 4 subgroups are depicted in Table 2.

The maximum number of patients fell within the 50 to 59 years of age group with an average prostate volume of 40.8 cm³ while there were only 3 patients above 80 years with an average prostate volume of 47 cm³. The Spearman rank correlation test analyzing age and other variables is depicted graphically in Figure 1, Figure 2, and Figure 3. The correlation among variables is depicted in Table 3

There was a positive correlation among age, prostate volume ($r = 0.84$, $p = 0.001$) (Figure 1), and serum PSA level ($r = 0.7717$, $p = 0.001$] (Figure 2). A positive correlation was observed (Figure 3) between prostate volume and serum PSA level ($r = 0.777$, $p = 0.001$). Age negatively correlated with the serum total and free testosterone level ($r = 0.144$, $p = 0.11$ and $r = 0.148$, $p = 0.100$), respectively. Prostate volume was found to bear a negligible correlation with serum total and free testosterone level. A comparison between serum PSA and serum testosterone level did not reveal any statistically significant relationship.

DISCUSSION

Several epidemiological studies have revealed that age is the most important risk factor for developing benign prostatic hyperplasia [2]. This occurs in an environment of declining testicular function with a simultaneous rise in intraprostatic

Table 2. The average values of different variables

Age Group	No of Patients	Prostate Volume	S PSA 0-4 ngm/ml	Total Testosterone 2.80-8.0 ngm/m	Free Testosterone 10.8-24.6 pgm/ml
50-59 years	48	40.8	2.1	10.53	13.54
60-69 years	47	44.7	2.9	7.19	12.06
70-79 years	23	48.8	3.7	6.69	10.92
> 80 years	3	47	2.33	9	21.53

Table 3. Correlation among variables.

Correlation	P Value	R Value
Age with prostate volume	0.0001	0.84
Age with PSA	0.0001	0.7717
Prostate volume with PSA	0.001	0.777
Age with total testosterone	0.11	0.144
Age with free testosterone	0.10	0.148

Figure 2. Correlation between age and serum PSA.

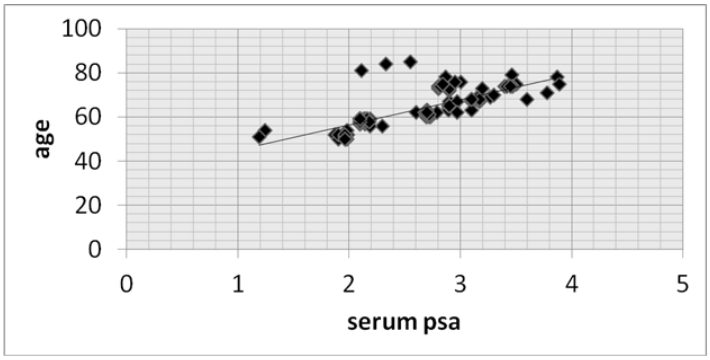
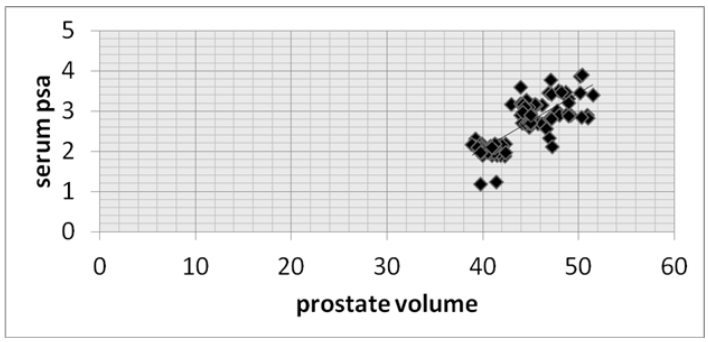


Figure 3. Correlation between serum PSA and prostate volume.



androgen level [3]. In the current study, the maximum number of patients with symptomatic benign prostatic hyperplasia was identified within patients aged 50 to 69 years, and there was a positive correlation observed between age and prostate volume (r = 0.84, p = 0.001), which was in accordance with other published literature [4-9] .However, some studies did not find any correlation between age and prostate volume in men with benign prostatic hypertrophy. Multiple linear regression also didn't demonstrate any significant influence on age and prostate volume [10-12].

Although the majority of cross-sectional and longitudinal studies documented increase in prostate volume with advancing age, it is not well known which factor is primarily responsible for the age-related growth of the prostate. In a study among 43 men with spinal cord injuries, Benaim et al. had opined that factors other than an intact pituitary gonadal axis and male steroid hormone may be responsible for normal age-related growth of the prostate [13]. Epithelial cells of the prostate are the source of PSA, and it was reported to be associated with the age of the individual as observed in the current study (r = 0.7717, p = 0.001). Park et al. have also reported a positive correlation between age and serum PSA in patients with benign prostatic hyperplasia [4], and similar observations were made by other investigators [5-7].

In a study population of 112 men with benign prostatic

hypertrophy, Dutkiewicz and colleagues did not observe any correlation between age and serum PSA level [10]. Morote et al. [11] and Chang et al. [12] had also observed a negative correlation between age and serum PSA concentration. The probable reason for the reported differences in the relationship between age and serum PSA is not well understood and may be influenced by some intrinsic or extrinsic factors that need further evaluation.

Although intraprostatic androgen is a prerequisite for the development of benign prostatic hyperplasia, a gradual decline in serum testosterone seems to occur with aging. In the current study, 8.26% of men are found to be hypoandrogenic and have serum total testosterone less than 3 ng/ml/ml. There was a negative correlation between age and serum testosterone ($r = 0.11$, $p = 0.144$). Mearini has recently reported a 9% incidence of subnormal testosterone level in patients with BPH [14]. The clinical impact of low testosterone levels among aging males is still a matter of debate, and there is a lack of unanimity for testosterone supplementation for such partial androgen deficiency in aging males [15]. In a study of 526 men, Schatzl and colleagues had observed that aging is associated with a gradual decline in serum testosterone levels, but the degree of decline depends on the health status of the individuals, associated comorbidity, the intake of medications, and lifestyle factors [16]. Their data analysis further emphasized that the lower cut-off value of testosterone (3 ng/ml) is only appropriate for men younger than 40 years of age and is clearly too high for older individuals. Hence, it is still inconclusive whether a decline in serum testosterone levels among the aging male population is due to the aging process or due to associated comorbid conditions.

The prostate study group of the Austrian Society of Urology failed to demonstrate a clear age-related decrease in serum testosterone levels despite more than 20% of the study population being hypoandrogenic among 312 men with lower urinary tract symptoms due to BPH [17]. Park et al. has also reported a negative correlation between age and serum testosterone levels among Korean men with BPH [4] while Tan et al. reported a higher total testosterone level in patients older than 70 years of age. They further opined that serum concentration of sex hormones has little impact on the severity of BPH symptoms [18]. Age-related changes might occur in serum follicle-stimulating hormone levels without any significant change in testosterone levels [13].

Since the prostatic epithelial cells are responsible for determining the serum PSA, it has been observed that prostate volume has a strong correlation with serum PSA levels [4-6, 9]. The mean PSA and prostate volume increased with each advancing cohort for age, and the correlation of PSA and prostate volume was found to be statistically significant in a cohort of 2 270 men with lower urinary tract symptoms suggestive of BPH [19]. The PSA production by prostate may have racial differences as Japanese men with BPH were found to release more PSA per unit of prostate volume than white men [8]. On the other hand, Korean men were found to produce slightly lower PSA levels than Caucasians [20] and produce more PSA per unit of prostate volume than white men [21].

Our study failed to demonstrate a significant, positive correlation between prostate volume and serum total testosterone levels ($r = 0.035$, $p = 0.700$). Serum testosterone level negatively correlated with prostate volume among 312 men with previously untreated BPH [16]. When adjusted for age, no correlation was established between prostate volume and serum testosterone levels in obese individuals. The obese men had lower testosterone concentrations and greater prostate volume [22]. Among 4 254 men with BPH participating in a placebo-controlled dutasteride trial, Merberger and colleagues had observed no decrease in prostate volume even at low baseline-serum testosterone levels [23]. Even the 3 different fractions of testosterone—namely total, free, and bioavailable testosterone concentration—did not correlate significantly with prostatic volume [24]. It is also suggested that there exists a complex relationship between sex steroids and prostate volume in aging males, rather than a simple independent effect [25].

Serum PSA and serum testosterone are independently produced from 2 different sources, and although prostate growth is androgen dependent, these 2 variables negatively correlated in the present study ($r = 0.135$, $p = 0.139$). Such negative correlation was also observed by other investigators [16,22]. In prostate cancer patients, there was a close relationship between the diurnal fluctuation of serum PSA and testosterone levels, and such fluctuations were not uniform [26]. PSA expression was not found to be testosterone dependent in hypogonadal men [27]. A recent study has shown that serum PSA level is influenced by the interrelationship between the individuals' lipid profile and testosterone concentration [28].

CONCLUSION

There is inconsistency in the current literature regarding the relationship within the various clinical and biochemical variables with that of serum androgen concentration in men with symptomatic benign prostatic hyperplasia. We observed statistically significant correlations among age, prostate volume, and serum PSA level. The prostate volume also showed strong correlations with serum PSA concentration. However, these clinical and biochemical variables bear no significant relationship with serum testosterone levels in symptomatic BPH patients. Only 8.26% of the studied individuals were hypoandrogenic.

Considering the contradictory data on the inter-relationship of various BPH-related variables, further evaluation in a large

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cohort of the aging population with BPH is needed to establish reliably the influence of one over the other.

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