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Serum sex steroids, gonadotrophins and sex hormone-binding globulin in prostatic hyperplasia

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BACKGROUND: Benign prostatic hyperplasia (BPH) develops in elderly males when serum androgens are relatively lower than in healthy younger males, but it is not well understood whether and how sex steroids are altered in prostatic hyperplasia. It is also uncertain whether there is any change in sex steroid levels in males older than 40 years of age. The use of androgens in elderly males is often discouraged because of the probable worsening effect of androgens on prostatism. This study aimed to determine the relationship between prostatic hyperplasia and sex steroid levels and whether there is any significant change in these hormones after the age of 40 years.

SUBJECTS AND METHODS: We studied healthy males of age ≥40 years with (n=92) or without (n=93) clinical prostatic hyperplasia. Serum testosterone, estradiol, gonadotrophins and sex hormone-binding globulin (SHBG) were compared. The hormones and SHBG were also correlated with age.

RESULTS: No significant difference was found in any hormone in cases with prostatic hyperplasia as compared with the controls. There was no significant age-related change in any hormone except estradiol where as a negative correlation ($P<.003$) with age was found.

CONCLUSIONS: Serum sex steroids and SHBG remained unchanged in symptomatic prostatic hyperplasia and except for estradiol there was no significant age-related change in serum testosterone, gonadotrophins and SHBG in healthy males after the fourth decade. More studies are needed to confirm the age-related decline of estrogens in males.

The growth and development of the prostate gland is strongly influenced by androgens and their metabolites.[1-2] Prostatic hyperplasia is the commonest disorder of the prostate in elderly males. Only minor ethnic or racial variation in its prevalence has been found. Though males start to have prostatic hyperplasia after the fourth decade of life, it is not known why some develop it earlier and some males do not develop it at all. However, the overall incidence increases with age[3,4] and its prevalence reaches about 90% in men in their 80s, of whom only a proportion suffer from urinary symptoms. Medical and conservative treatments are used in management, but most patients eventually need surgery to get rid of the troublesome symptoms of prostatism. Until recently little has been known about the etiopathology and risk factors for this disease.[5,6] Studies on the etiopathology and risk factors seem insufficient and are derived mainly from animal rather than human studies. Age is the only unmodifiable and established factor known so far, although androgens, estrogens and several intraprostatic factors are believed to be responsible for its development.[1,7,8]

Serum androgens in elderly males are significantly lower than in young males. Following a relatively sharp pubertal surge, androgens in males rise steadily followed by a slow decline in the mid-30s.[9] After the 40s, the levels of androgens either remain constant or there is a slow decline with age. Though androgens, estrogens and their relative concentrations in the peripheral circulation are related to prostatic hyperplasia,[10,11] it is not understood why prostatic hyperplasia develops in that period of life when serum androgens and probably estrogens in the peripheral circulation are relatively lower. Whether there is any change in androgens and other sex steroid concentrations in those who develop prostatic hyperplasia is also not clear. A few early studies report-

ed increased androgens in prostatic hyperplasia but this was not reproduced in subsequent studies. For a long time it was commonly believed that androgens in the peripheral circulation can produce or worsen prostatic hyperplasia. Based on this assumption, use of androgens in elderly males is not encouraged despite clinical conditions where androgens are indicated, like partial androgen deficiency in aged males (PADAM).[12,13]

Recent studies on the etiopathology and risk factors of BPH have focused mainly on intraprostatic factors and have concluded that increased conversion of androgens to dihydrotestosterone (DHT) is mainly responsible for the development of BPH.[7] As the main source of androgens to be converted to DHT comes from the peripheral circulation, it is important to find out whether there is any change in the sex steroid levels in prostatic hyperplasia. In addition, the age-related changes in those hormones after 40 years of age need to be examined. We conducted this study to determine whether there is any change in the concentration of sex steroids, sex hormone binding globulins and gonadotrophins in prostatic hyperplasia and also to determine to what extent these hormones change with age.

SUBJECTS AND METHODS

For this study, we selected 103 BPH cases and 102 well-matched healthy males without BPH as controls from the inpatient and outpatient departments of Bangabandhu Sheikh Mujib Medical University, Dhaka Medical College Hospital and Bangladesh Medical College, all located in the city of Dhaka, Bangladesh during 2003-2004. The study was completed by 92 cases and 93 control subjects aged 40 to 90 years. Voluntary consent was taken from each participant. The ethical clearance for this study was obtained from the ethical committee of the Bangladesh Medical Research Committee. The participants were without any major systemic illness and had not taken any drug within 6 weeks before collection of serum samples. Detailed medical and urological examinations were done on each subject before inclusion. The cases and controls were different only in having and not having BPH. The BPH cases had a prostatic volume ≥30 mL and the controls had a volume ≤25 mL as determined by abdominal ultrasonography. The International Prostate Symptom Score (IPSS) was >8 for the cases and 0 for the controls. The IPSS was determined from the results of the standard questionnaire on incomplete voiding, frequency, intermittency, urgency, weak stream, straining and nocturia under supervision of a urologist. All the questionnaires were converted to the local language.[14] The clinical and laboratory characteristics of the cases and controls are shown in Table 1.

Venous blood samples were collected from each subject at 8:30 to 9:30 AM, the serum separated and preserved at -40°C until laboratory analysis. Laboratory assays were done within 3 months of collection. Serum samples were assayed for total testosterone, estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and sex hormone-binding globulin (SHBG) in the laboratory of the Popular Diagnostic Center, Dhaka. The reagents used were supplied by Diagnostic Products Corporation, 5700 West 96th Street, Los Angeles, USA. Each kit was supplied with instructions for hormone assay by IMMULITE 2000 Analyzer.

The means of the different variables were compared between the cases and the controls by the unpaired t test and P value<.05 was considered significant. Correlations between the variables were determined by the Pearson's correlation test. Data entry and statistical analyses were done by the software FOXPRO, SPSS release 6.0 and Excel.

RESULTS

No significant difference was found in the mean serum concentrations of total testosterone, estradiol, LH, FSH and SHBG between BPH cases and controls (Table 2). Combining the cases and controls, no significant correlation was found in testosterone, estradiol and SHBG with age. A significant negative correlation in serum estrogen concentration with age was found (P<.05) (Table 3).

DISCUSSION

We found no change in serum testosterone level in prostatic hyperplasia. This differs from earlier studies where raised androgen levels were reported in prostatic

Table 1. Clinical and laboratory profile of cases and controls.

	BPH cases (n=103)	Controls (n=102)
Age (year)	65.39±0.86	63.28±0.80
BMI (kg/m^2)	22.38±0.38	23.23±0.316
Prostatic symptom score 14	28.11±0.53	-
Volume of prostate (mL)	48.24±1.78	21.43±0.246
Pulse (rate/min)	80.53±0.83	78.00±0.673
Systolic blood pressure (mm Hg)	127.36±1.35	127.11±0.10
Diastolic blood pressure (mm Hg)	75.17±0.88	76.95±0.92
Serum creatinine (mg/dL)	1.100±0.02	1.13±0.015

Values are mean.

Table 2. Serum gonadal hormones, gonadotrophins and sex hormone-binding globulin concentrations for BPH cases and controls.

Hormonal/ biochemical parameters	BPH cases (n=92)	Controls (n= 93)	*P* value
Total testosterone (nmol/L)	14.96±.51	14.23±0.69	.392
Estradiol (ng/L)	34.72±1.29	31.84±1.16	.100
SHBG (nmol/L)	58.06±2.54	54.95±2.75	.406
LH (mIU/mL)	6.61±0.38	6.67±0.38	.911
FSH (mIU/mL)	7.59±0.47	8.23±0.63	.419
Estradiol/testosterone ratio	2.75±0.24	3.13±0.38	.395

Values are mean±SEM

hyperplasia.[10,11,15,16] This discrepancy is mainly due to differences in subject selection, laboratory analyses and methods of comparison adopted in those studies as compared to the present study. In one of these earlier studies by Vermeulen et al,[11] where raised androgens were reported in prostatic hyperplasia, comparisons between the cases and controls were done by dividing the subjects into several small subgroups by age rather than comparing all the cases and controls together. Even in those subgroups, raised androgens were found only in the 70- to 80-year age group. In other age groups, from 40 to 70 years, no significant difference in androgen concentration was found that conforms well with our findings. The number of subjects in the age group where raised androgen was reported also seems too small.

In other studies, the method of subject selection was such that asymptomatic BPH cases could not be excluded from the controls due to the unavailability of modern imaging techniques. For example, selecting cases and controls based on the presence or absence of lower urinary tract symptoms (LUTS) and digital rectal examination without measuring prostatic size by imaging technique seems insufficient to exclude or include prostatic hyperplasia. The laboratory methods for hormone assays were also less sensitive than those available now.

Because of the fact that the presence or absence of LUTS cannot include or exclude prostatic hyperplasia with certainty, it is possible that there could be a few asymptomatic prostatic hyperplasia cases included within the control group in our study and this might have confounded our results. However, we considered that cases of LUTS with enlarged prostate, excluding prostatic carcinoma, are practically cases of prostatic hyperplasia. With this limitation in mind our comparisons were between symptomatic BPH cases to age-matched males without LUTS and a normal-sized prostate.

In a recent study by Tan et al,[17] it was concluded that the concentration of sex hormones plays little role in the clinical severity of BPH. In Tan et al, though free testosterone was found to be lower in clinical BPH than in controls, the estrogen to bioavailable testosterone ratio was found to be higher in clinical BPH. Total testosterone was found to be higher in clinical BPH only in those of age >70 years and there was no change in males of age <70 years. Vermeulen et al[11] also found raised testosterone in BPH cases only in men 70 to 80 years of age. In the present study, comparisons were made taking all the cases and controls of all ages together as the number of subjects were not sufficient for age grouping. In addition, no obvious reason was found as to why the testosterone level in BPH cases was different only in the males within a particular age range i.e., >70 years. Liu et al[18] and Rohrmann et al[19] found no significantcorrelation of prostate volume or IPSS with circulating testosterone level in studies of different design. However, LUTS or BPH was related to other hormonal factors that appear complex. That the occurrence of clinical BPH is indifferent to circulating testosterone level was also found in a recent study by Marberger et al where clinical BPH was found to occur in elderly males with different baseline serum testosterone, ranging from low to high normal levels.[20] Hammond et al[21] reported the same results for androgen concentration as in our study. In fact most of the recent studies found no or only a weak change in serum testosterone concentration in prostatic hyperpla-

Table 3. Correlations of sex hormones, gonadotrophins and sex hormone-binding globulin with age (n=185).

	Correlation coefficient	*P* value
Total testosterone	-.0619	.403
Estradiol	-.1544	.036
Luteinizing hormone	.0250	.735
Follicle-stimulating hormone	-.0429	.562
Sex hormone-binding globulin	-.0867	.241

sia. However, there could be other hormonal changes that have not been addressed in our study. Though a few studies reported an altered androgen-estrogen ratio in prostatic hyperplasia,[22-24] we found no change either in absolute concentration of estradiol nor in androgen-estrogen ratio in prostatic hyperplasia, for which more studies are needed. The fact that no change in SHBG and gonadotrophins in prostatic hyperplasia was found in our study suggest that binding of the hormones and their pituitary regulations are also unchanged in prostatic hyperplasia. We also studied the correlations of different hormones and SHBG levels with age by combining both the cases and controls together. A significant negative correlation with age was found in estradiol concentration. For all other hormones and SHBG, no age-related change was found.

There are few studies that support our finding of no change in serum testosterone and gonadotrophins with age. Most studies report a slow decline of androgens in aging males.[25,26] In contrast to those studies where an age-related decline of androgens were reported,[27-29] our subjects were healthy except that half had prostatic hyperplasia. Therefore, age-related declines in serum androgens are insignificant in healthy males older than 40 years according to our study. The probable explanation for this difference is that the studies reporting an age-related decline in androgens included males with associated chronic diseases that might have confounded the results. Diminished gonadotrophins and sex steroids due to chronic diseases are also reported in some studies.[30,31]

Despite a few reports indicating a slow decline of estrogen with age,[32-34] a significant age-related decline in serum estradiol level as found in our study needs further study for confirmation. In our study, aged males were found to have a lower body mass index (BMI) (correlation of BMI with age -.15, P=.03 in our study). As peripheral conversion of androgens to estrogens depends on body fat content, a low BMI in aged males in our subjects could be the reason for the low estradiol concentration.

In conclusion, from our study and most of the recent studies in this field, it seems there is no significant change in serum levels of testosterone, estradiol, SHBG and gonadotrophins in clinical prostatic hyperplasia as compared with age-matched asymptomatic males with a normal-sized prostate. In addition, after 40 years of age there is no significant age-related change in serum testosterone, SHBG and gonadotrophins in the males without any systemic disease. Age-related declines in serum estradiol need further study for confirmation.

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