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ORIGINAL ARTICLE

Relationship between serum sex hormones levels and degree of benign prostate hyperplasia in Chinese aging men

Qin-Song Zeng[1,2,*], Chuan-Liang Xu[1,*], Zhi-Yong Liu[1,*], Hui-Qing Wang[1], Bo Yang[1], Wei-Dong Xu[1], Tai-Le Jin[1], Cheng-Yao Wu[1], Gang Huang[1], Zheng Li[3], Bo Wang[4] and Ying-Hao Sun[1]

Benign prostatic hyperplasia (BPH) is one of the most common medical conditions in middle aged and older men. This study investigated the relationship between serum levels of sex hormones and measures of BPH in the aging male population of China. Prostate symptoms were assessed as part of a free health screening program for men ⩾40 years of age. The examination included digital rectal examination, determination of serum prostate-specific antigen levels, International Prostate Symptom Score (IPSS) and transrectal ultrasonography. Serum levels of total testosterone (TT), sex hormone binding globulin (SHBG), free testosterone (FT), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL) and estradiol (E_2) were evaluated. The men also completed a health and demographics questionnaire and received a detailed physical examination. The final study population consisted of 949 men with a mean age of 58.9 years. Pearson correlation analysis indicated that there were significant correlations between age and levels of all sex hormones except TT, and between age and prostate volume (PV; $r=0.243$; $P<0.01$) or IPSS ($r=0.263$; $P<0.01$). Additional significant correlations were found between IPSS and serum levels of LH ($r=0.112$; $P<0.01$) and FSH ($r=0.074$; $P<0.05$), but there were no significant correlations between sex hormone levels and PV. Multivariate linear regression analysis showed significant correlations between age and body mass index (BMI) with PV ($P<0.0001$). In addition, there was a significant correlation between age and PV with IPSS ($P<0.0001$). Serum sex hormone levels did not correlate with PV or IPSS. The effects of endocrine changes on measures of BPH in aging men require further investigation in longitudinal and multicenter studies that include patients with all severities of BPH.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histologic condition affecting >50% of men over 60 years and nearly all men aged over 80 years, frequently resulting in bladder outlet obstruction and lower urinary tract symptoms (LUTS).[1,2] The sixth national census of China in 2010 showed that 13.26% of the Chinese population were older than 60 years.[3] The predicted increase in the proportion of elderly people in future years means that the prevalence of BPH and costs of treatment will continue to increase.[4]

Age-related changes in androgens are widely accepted as the main factors involved in the pathogenesis of BPH.[1,2,5] Previous studies have shown a positive correlation between BPH and changes in free testosterone (FT), estradiol (E_2) and estriol levels.[5] BPH does not occur in androgen-deficient men with impaired sexual development.[6]

It has been suggested that the prevalence of BPH and LUTS varies in subjects from different racial or ethnic backgrounds.[7–10] A study in Australia reported that prostate volume (PV) and International Prostate Symptom Scores (IPSS) were significantly lower in Chinese men residing in China than in either Australian non-Chinese or Chinese migrants.[7] Likewise, a large cohort study of American male health professionals found that African-American men were not at as high risk of developing BPH as Caucasian-American men, and Asian men were less likely to have undergone BPH surgery than Caucasian-American men.[8] A study of Asian men aged 50–80 years reported that the prevalence of LUTS varied from 14% in Singapore to 59% in the Philippines.[9]

As previous studies have suggested a link between sex hormones and prostate growth,[2,5] we investigated the possible association between serum hormone levels and measures of BPH in a Chinese population in an attempt to further define ethnic differences in the prevalence of BPH and LUTS.

MATERIALS AND METHODS

Subjects

One thousand males subjects (>40 years) who participated in a free epidemiologic study for aging men at Changhai Hospital and Renji Hospital between November 2009 and June 2010 were eligible for

[1]Department of Urology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China; [2]Department of Urology, General Hospital of Guangzhou Military Command of PLA, Guangzhou 510010, China; [3]Department of Urology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200127, China and [4]Family Planning Research Institute of Shanghai City, Shanghai 200032, China
* These authors contributed equally to this work.
Correspondence: Professor YH Sun (sunyh@medmail.com.cn)
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enrollment in the study. The men were all volunteers from the Chinese Han population. Each provided written informed consent for participation in the study. The study was approved by the hospital ethical committee.

Subjects with malignancy, liver cirrhosis, acute illness, depression, hypothyroidism or chronic alcoholism, as well as those who were taking hormones, antiandrogen agents, antifungal agents, or steroidal agents or those who had undergone surgical or medical therapy for BPH were excluded from the study.

Hormone measurements

Blood samples were obtained before undertaking digital rectal examination or transrectal ultrasonography (TRUS). All samples were collected between 9 a.m. and 11 a.m. to minimize the effects of diurnal variation. Serum levels of prostate-specific antigen (PSA), free PSA (fPSA), total testosterone (TT), sex hormone-binding globulin (SHBG), FT, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL) and E_2 were measured using chemical or luminescent methods. Instruments and test agents were manufactured by the Beckmann Co. (Bremen, Germany). The intra- and inter-assay coefficients of variation were less than 8.5%.

Subject questionnaires

Demographic information and detailed medical history, particularly about chronic systemic diseases such as diabetes mellitus and hypertension, were obtained from all patients. Blood pressure, body weight, height and waist circumference were measured. Body mass index (BMI) was calculated as body weight divided by the square of height.

All participants completed the IPSS questionnaire. Urinary retention symptoms were evaluated by the sum score of question 2 (frequency), 4 (urgency) and 7 (nocturia) of the IPSS while voiding symptoms were evaluated as the sum score of question 3 (intermittency), 5 (weak stream) and 6 (straining) of the IPSS.

Prostate evaluation

In all subjects, the length, width and height of the prostate were measured by TRUS. The PV was calculated using the formula for a prolate ellipsoid ($(\pi/6)\times$(width in maximal transverse dimension)$\times$(length in maximal anteroposterior dimension)$\times$(height in maximal superoinferior dimension)).[11] Men with abnormal findings by TRUS or an elevated serum PSA level (>4.0 ng ml^{-1}) were referred for prostate biopsy to exclude the possibility of prostate cancer.

Statistical analysis

Statistical analysis was performed using SAS software (SAS Institute, Cary, NC, USA). Correlations between different variables were first estimated using Pearson's correlation coefficients. Factors that were associated ($P<0.01$) with PV or IPSS (total or subscores) were further evaluated using multivariate linear regression models after adjusting for age, BMI and/or LH.

Values of $P<0.05$ were considered statistically significant.

RESULTS

Among the original 1000 subjects who were screened, 51 subjects were excluded from the study population, including 13 who had undergone surgical or medical therapy for BPH, four who had malignancy, two who were taking antiandrogen agents and a further 32 who provided incomplete data for evaluation.

The final study population consisted of 949 men with a mean age of 58.9 years (range: 40–78 years). The respective endocrine variables and clinical characteristics of the study population are given in **Table 1**. The mean IPSS (s.d.) was 4.73 (5.92) and the mean PV was 31.49 (13.01) cm^3. The distribution of sex hormone levels by age group is shown in **Table 2**.

Analysis using Pearson's correlation statistics indicated that there was a positive correlation between PV and age ($r=0.243$; $P<0.01$), BMI ($r=0.302$; $P<0.01$) and IPSS ($r=0.224$; $P<0.01$). However, no significant correlations were found between PV and serum hormone levels or between PV and PSA (**Table 3**).

There was a significant correlation between IPSS and age ($r=0.263$; $P<0.01$), PV ($r=0.224$; $P<0.01$), LH ($r=0.112$; $P<0.01$) and FSH ($r=0.074$; $P<0.05$). This parameter was not significantly correlated with any of the other hormone levels or with PSA. The IPSS retention symptom subscore was correlated significantly with age ($r=0.289$), BMI ($r=0.097$), PV ($r=0.209$), LH ($r=0.105$) and FSH ($r=0.093$) (all $P<0.01$). Voiding symptoms were significantly associated with age ($r=0.208$), PV ($r=0.215$) and LH ($r=0.102$)(all $P<0.01$) (**Table 3**).

There was a positive correlation between age and PV ($r=0.243$), IPSS ($r=0.263$), SHBG ($r=0.275$), LH ($r=0.314$), FSH ($r=0.344$)(all $P<0.01$) and also with E_2 ($r=0.066$; $P<0.05$). There were negative correlations between age and FT ($r=-0.201$; $P<0.01$) and PRL ($r=-0.074$; $P<0.05$) (**Table 3**).

FT concentrations were lower with aging ($r=-0.201$; $P<0.01$), but there was no significant association between age and TT ($P=0.31$). Increasing age was also associated with higher SHBG, LH and FSH levels (**Table 3**). Due to the variability within each of the age groups assessed, the correlation coefficients were not significant. In addition, there was no correlation between age and BMI, waist circumference, PSA or fPSA levels (**Table 3**).

Table 1 Principal clinical and endocrinologic data ($n=949$)

Variable	n *(%)*	*Mean*	*s.d.*	*CV*	*Min.*	*Max.*
Clinical						
Age (year)		58.91	7.42	12.59	40.00	78.00
BMI (kg m^{-2})		24.92	3.33	13.37	15.32	64.13
Waistline (cm)		86.85	14.12	16.26	20.00	184.00
PV (cm^3)		31.49	13.01	41.30	12.89	192.12
Total IPSS		4.73	5.92	125.30	0.00	35.00
Retention symptoms subscore		2.55	2.85	112.09	0.00	15.00
Voiding symptoms subscore		1.48	2.62	176.90	0.00	15.00
Hypertension	225 (23.7)					
Diabetes mellitus	118 (12.4)					
Smoking	506 (53.3)					
Alcohol	448(47.2)					
Endocrinologic						
PSA (ng ml^{-1})		1.45	3.57	246.32	0.17	99.90
fPSA (ng ml^{-1})		0.27	0.42	155.27	0.01	10.41
TT (ug l^{-1})		4.44	1.37	30.99	1.36	13.24
SHBG (nmol l^{-1})		44.93	23.83	53.03	8.80	329.00
FT (ng dl^{-1})		13.43	3.82	28.45	1.02	27.95
LH (IU l^{-1})		5.64	3.02	53.47	1.02	34.61
FSH (IU l^{-1})		11.14	7.22	64.80	1.98	80.77
PRL (ug l^{-1})		10.83	7.68	70.99	0.22	150.43
E_2 (pg ml^{-1})		34.68	14.70	42.38	0.00	93.00

Abbreviations: BMI, body mass index; CV, coefficient of variation; E_2, estradiol; fPSA, free prostate-specific antigen; FSH, follicle-stimulating hormone; FT, free testosterone; IPSS, International Prostate Symptom Score; LH, luteinizing hormone; PRL, prolactin; PSA, prostate-specific antigen; PV, prostate volume; SHBG, sex hormone-binding globulin; TT, total testosterone.

Table 2 Mean (s.d.) values of different sex hormonal test results of different age groups

Age group (year)	*TT (μg l^{-1})*	*SHBG (nmol l^{-1})*	*FT (ng dl^{-1})*	*LH (IU l^{-1})*	*FSH (IU l^{-1})*	*PRL (μg l^{-1})*	*E_2 (pg ml^{-1})*
40–50	4.28 (1.17)	31.90 (14.00)	14.40 (3.62)	4.52 (1.91)	7.72 (3.76)	12.45 (13.72)	31.82 (14.27)
51–60	4.53 (1.39)	44.07 (23.85)	13.84 (3.94)	5.10 (2.46)	10.14 (6.14)	10.77 (6.14)	34.83 (14.79)
61–70	4.39 (1.43)	49.89 (24.23)	12.66 (3.60)	6.56 (3.49)	13.23 (7.89)	10.37 (6.27)	35.43 (14.90)
71–80	4.25 (1.30)	56.45 (28.96)	12.02 (3.57)	7.93 (4.29)	16.63 (13.17)	9.86 (5.31)	36.33 (11.66)

Abbreviations: E_2, estradiol; FSH, follicle-stimulating hormone; FT, free testosterone; LH, luteinizing hormone; PRL, prolactin; SHBG, sex hormone-binding globulin; TT, total testosterone.

Multivariate linear regression models showed that age and BMI were significantly associated with PV (**Table 4**). It is also shown that age and PV were significantly associated with the total IPSS and the IPSS subscores for retention and voiding symptoms (**Table 5**).

DISCUSSION

BPH is a common disease of the prostate that is associated with considerable morbidity in aging men. The two etiologic factors that are largely accepted to play a role in the pathogenesis of the disease are aging and alterations in androgen levels.[2,5] Previous studies have established that racial and ethnic differences in genetic make-up, cellular composition of the prostate and hormonal changes may account for the differences in the incidence of BPH in different demographic populations.[10]

Serum androgen levels steadily decrease after the age of 40 years at the time when PV increases.[12] FT levels decrease with advancing age in all men. A cross-sectional study to assess sex steroid levels in a cohort of 2623 older men found that age was inversely associated with FT levels ($r=-0.17$; $P<0.001$), but there was no significant association between age and TT ($r=-0.03$; $P=0.27$).[13] Likewise, in the Chinese population in our study, we demonstrated that age was inversely associated with FT but was not associated with TT levels. Therefore, the proportion of older men with FT levels falling below the normal range for younger men would be expected to be greater than the proportion with TT levels below the normal range.[13]

It has been well established that androgens are essential for prostate development and play a major role in the pathophysiology of BPH.[14] Androgen withdrawal therapy is therefore widely used to manage BPH in clinical practice. PV in patients with BPH has been shown to markedly decrease following either orchiectomy[15] or administration of the antiandrogen flutamide.[16] However, it remains unclear why the state of BPH is prevalent during the stage of life when serum androgen levels are undergoing age-related decline. Relationships between the risk of BPH and serum androgens have yet to be established despite many studies have investigated this issue. Joseph *et al.*[17] found that large PV was marginally associated with increased TT levels in African-American men, while results of the prostate cancer prevention trial suggested that higher total and bioavailable testosterone levels were associated with reduced BPH risk.[18] Other studies found no difference in serum TT between control subjects and men with BPH or LUTS.[19,20]

Our findings in Chinese men suggest that serum SHBG and FT levels are significantly correlated with age, and that the circulating levels of the three androgens are significantly correlated with PV or IPSS. We also demonstrated a positive correlation between PV and BMI, but there was no statistical correlation between PV and waist circumference according to Pearson's correlation analysis. However, the multivariate linear regression analysis, age and BMI were significant predisposing factors for PV. These findings support published data showing BMI to be directly associated with PV in men without prostate cancer.[21] Furthermore, a study in men who had undergone radical prostatectomy showed a positive association between BMI and PV in men <63 years old.[22] In our study, both age and PV (but not TT) were significantly associated with total IPSS and with IPSS retention and voiding components (**Tables 4** and **5**).

The male reproductive system can be viewed as an interactive homeostatic network in which changes at different levels may occur during the course of aging.[23] The prostate, as the target organ of the hypothalamic–pituitary–testicular axis, is closely connected to the endocrine network.[23] Besides androgens, a growing body of evidence implicates the relationship between plasma estrogen levels and the risk of BPH. In the Physicians' Health study,[24] multivariate analyses indicated a strong trend for increasing risk of BPH with increasing E_2

Table 3 Pearson's correlations of endocrinologic parameters with age, PV and IPSS

Variable	*Age*	*PV*	*IPSS*	*Retention symptoms subscore*	*Voiding symptoms subscore*
TT	−0.002	−0.021	0.029	0.02	0.041
SHBG	0.275**	0.0264	0.034	0.027	0.029
FT	−0.201**	0.024	−0.02	−0.012	−0.007
LH	0.314**	0.025	0.112**	0.105**	0.102**
FSH	0.344**	0.016	0.074*	0.093**	0.029
PRL	−0.074*	0.031	0.021	0.013	0.039
E_2	0.066*	0.0192	−0.018	−0.05	0.017
Age	—	0.243**	0.263**	0.289**	0.208**
BMI	−0.002	0.302**	0.058	0.097**	0.006
Waistline	0.033	0.022	0.042	0.053	0.015
PV	0.243**	—	0.224**	0.209**	0.215**
PSA	0.048	−0.015	0.009	0.011	0.013
fPSA	0.025	0.018	−0.004	−0.003	0.008

Abbreviations: BMI, body mass index; E_2, estradiol; fPSA, free PSA; FSH, follicle-stimulating hormone; FT, free testosterone; IPSS, International Prostate Symptom Score; LH, luteinizing hormone; PRL, prolactin; PSA, prostate-specific antigen; PV, prostate volume; SHBG, sex hormone-binding globulin; TT, total testosterone.
Data presented as Spearman's rank correlations; $n=949$. *$P<0.05$. **$P<0.01$.

Table 4 Multivariate linear regression model-derived β coefficients and *P* values for factors significantly associated with PV

Factor	*β coefficient*	P *value*
Age	0.233	<0.0001
BMI	0.295	<0.0001

Abbreviations: BMI, body mass index; PV, prostate volume.

levels. Other groups have shown that increased PV was associated with E_2 levels in men with bioavailable testosterone levels above the study sample median, whereas no association between E_2 level and PV was detected in those with bioavailable testosterone levels below the median.[20] These findings suggest that there may be a synergistic effect between testosterone and E_2 in the pathogenesis of BPH. However, in our study, we were unable to show a significant correlation between E_2 and either PV or IPSS (total and subsocres) using either form of correlation analysis.

It is well known that primary age-related testicular dysfunction with decreased androgen production might be reflected by a rise in serum gonadotropin levels, similar to the female menopause. The prevalence of this condition appears to increase with age and may contribute to the statistically significant increases in serum FSH and LH reported in aging men.[25,26] Our study supports this possibility showing that serum LH and FSH levels were significantly correlated with age as well as with IPSS scores. In fact, LH and FSH were the only two hormones that were found to be correlated with IPSS in our study.

It is increasingly recognized that PRL, the cognate molecule of growth hormone, stimulates proliferation and differentiation of prostatic epithelial cells.[27,28] For example, transgenic mice overexpressing PRL have been found to have a 20-fold increase of prostatic weight.[29] In our study, however, we found no significant relationships between PRL and measures of BPH, such as PV or IPSS. Thus, although involvement of growth hormone and PRL in the physiology of the rodent prostate has recently been demonstrated, their roles in the pathology of human BPH are still debatable.[30]

To our knowledge, the present study is the largest available evaluation of sex hormone levels and measures of the prostate disease in Chinese men. We focused on the associations between age, sex hormone levels and measures of BPH in Chinese Han population, and identified age as the most important risk factor, adding support to the findings of many large-scale epidemiologic studies.[31–33] The major limitation of our study is that it lacks information on subjects with moderate to severe pathologic BPH. Patients who had undergone surgery or who were receiving medical treatment for BPH were excluded from our evaluation. Further studies in a population including subjects with moderate to severe BPH who have not yet commenced treatment would provide a broader population base to evaluate the relationship between sex hormones and BPH or IPSS.

Table 5 Multivariate linear regression model-derived β coefficients and *P* values for factors significantly associated with IPSSs

Factor	*β coefficient*	P *value*
IPSS		
Age	0.272	<0.0001
PV	0.177	<0.0001
Retention symptoms		
Age	0.289	<0.0001
PV	0.169	<0.0001
Voiding symptoms		
Age	0.221	<0.0001
PV	0.166	<0.0001

Abbreviations: IPSS, International Prostate Symptom Score; PV, prostate volume.

CONCLUSIONS

Our analysis of hormonal and other factors associated with BPH in Chinese men indicated that age was the strongest predictor of increased PV and IPSS scores. Age, PV and the serum levels of LH and FSH all showed significant correlations with IPSS scores based on univariate analysis. Multivariate analysis showed that significant correlations of age and BMI with PV and PV were strongly correlated with total IPSS scores and with IPSS retention and voiding subscores. The links between measures of BPH and endocrine changes in aging men merit further study in longitudinal and multicenter studies.

AUTHOR CONTRIBUTIONS

YHS designed the experiments. QSZ, CLX, ZYL, ZL, HQW, BY, WDX, TLJ, GH and CYW carried out the survey and lab testing work. BW carried out statistical analysis. QSZ and CLX participated in drafting, interpreting the data and critically revising the paper for key intellectual content. All authors read and approved the final manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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