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EFFECTS OF SEX HORMONES ON PROSTATE VOLUME IN PATIENTS WITH LOWER URINARY TRACT SYMPTOMS

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Abstract

The objective of this study is to investigate the relationship between sex hormone levels and prostate volume in patients with lower urinary tract symptoms (LUTS).

This study involved 66 patients suffering from LUTS for more than one month, with age ranged from 36 to 85 years who attended Basrah General Hospital outpatient clinic of urological surgery seeking management, eleven of them were suffering from non-insulin dependent diabetes mellitus (NIDDM). The medical and surgical history were taken through special questionnaire and the severity of LUTS was assessed by International Prostate Symptom Score (IPSS). General and urological examinations were done to them. Four ml of venous blood was drawn from each patient to measure luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone (TT), free testosterone (fT), estradiol (E2) and prostate specific antigen (PSA) and the results were used to assess the presence of any association with IPSS or prostate volume. Also fasting blood sugar, blood urea, serum creatinine and thyroid stimulating hormone (TSH) were measured to identify unknown diabetic patients and exclude those with renal failure or dysthyroidism.

Mean±SD of age and prostate volume of the patients were (63.8±9.5) years and (45.5±24.8) ml, respectively. The IPSS and bother scores were (17.3±6.5) and (3.8±1.4), respectively. Mean serum FSH, LH, TT, fT and E2 were (11.5±13.0) mIU/ml, (6.7±5.9) mIU/ml, (4.6±2.4) ng/ml, (6.5±4.8) pg/ml and (47.9±24.4), respectively. Patients with larger prostate volume (>40 ml) had significantly higher mean age and also had higher mean estradiol level after age adjustment (p value <0.05). Prostate volume showed significant correlations with age, PSA and with E2 after age adjustment, but not with IPSS or any of the other sex hormones. The most important other correlation is the negative correlation between total testosterone and IPSS. Diabetes mellitus, hypertension and family history of BPH didn't seem to have significant effect on prostate volume.

In conclusion, age is the main determiner of prostate volume. Sex hormone doesn't affect prostate volume significantly apart from estradiol, and their contribution to severity of LUTS may have other mechanisms.

Introduction

In the past, several terms such as prostatism, clinical BPH and symptomatic benign prostatic hyperplasia (BPH) have been used to describe symptoms related to micturition in older men[1].

Paul Abrams developed the term lower urinary tract symptoms (LUTS) to replace the old and inappropriate term prostatism[2]. The LUTS complex affects 15–60% of men aged more than 40 years. Prevalence rises markedly with age[3,4]. The prevalence of LUTS increases to more than 70% in the seventh decade of life, in comparison to about 8% in the fourth decade and benign prostatic hyperplasia is the most common cause of LUTS in all age groups[5]. LUTS result in an increase of risk of falls, diminishes health-related quality of life, and associated with sadness, depression, impairment in instrumental activities of daily living and loss of work time[6,7].

The two factors that are generally accepted to have a role in the etiopathogenesis of BPH are aging and

androgens[8,9]. Androgens are considered to have permissive role in development of BPH. For example, anti-androgen therapy with Flutamide or 5α-reductase inhibitors and surgical castration causes rapid reduction in prostate size emphasizing androgen necessity[10].

On the other hand, the role of estrogens in BPH is not fully explained Serum estrogen levels increase in men with age, absolutely or relative to testosterone levels. Evidence indicates that estrogen action mediated through the separate receptors may contribute to the etiology and progression of multiple prostate diseased states[11].

Both BPH and LUTS have important genetic components. The age of onset of BPH is younger in men with inherited forms of BPH and they tend to have larger prostates than men with sporadic BPH[12].

Hypertension has also been suggested to be involved in the pathophysiology of BPH. Arterial hypertension occurs in about 25% of patients with BPH and those patients would have lower sexual function[13,14].

Disruptions in glucose homeostasis at multiple different levels - from alterations in serum insulin growth factor concentrations to diagnosis of clinical diabetes are associated with higher likelihoods of prostate enlargement, BPH, and LUTS[15].

These, in addition to other factors as stromal-epithelial interactions, growth Factors, oxidoreductase, inflammation, and neurotransmitters may play a role, either singly or in combination, in the etiology of the hyperplastic process[10,11].

Patients and Methods

Seventy four (74) total patients initially were included in this study which was carried out from the first of November 2011 to the end of January 2013. Eight patients were excluded, seven of them because of proven to have prostatic cancer and one because of hyperthyroidism. Sixty six (66) men represented the final population of the study, their ages ranged from 36 to 85 years, they have different residence all around Basrah and they were examined by the urologists.

Any patient known to have prostatic cancer or taking antiandrogen was excluded. Also we exclude all patients with psychological disorders.

The medical history was taken from the patients including an assessment of their LUTS severity by the use of IPSS questionnaire with total score of 35, in addition a quality of life question (Qol) was used to obtain a bother score ranging from 1-6. Any history of diabetes mellitus, hypertension or family history of BPH was recorded.

General and urological examinations were done to the patients; also an ultrasound was done to them to check the renal system and measure prostate volume using the ellipsoid formula ($\pi/6 \times$ transverse diameter $\times$ AP diameter $\times$ longitudinal diameter) which was found to have a correlation coefficient of 0.9 with prostate volume[16].

Four ml of venous blood was drawn from each patient to measure LH, FSH, TT (ELISA Kit, Monobind Inc, USA), free testosterone (ELISA Kit, DiaMetra Inc, Italy), estradiol and PSA (ELISA Kit, BioCheck Inc, USA). Also fasting blood sugar, serum creatinine (BIOLABO SA, France), blood urea (bioMerieux sa, France) and TSH (ELISA Kit, Monobind inc, USA) were measured to identify unknown diabetic patients and exclude those with renal failure or dysthyroidism.

The results were expressed in form of mean ± standard deviation. The difference between the means of any parameter in study in different groups was assessed by the use of independent sample t-test. The correlation between two different parameters was assessed by Pearson's correlation coefficients and the significantly associated factors with IPSS on Pearson's rank correlation. $P<0.05$ was considered the lowest limit of significance.

Results

The final study population consisted of men with a mean (range) age and prostate volume of 63.8 (36–85) years and 45.5 (10– 52) ml, respectively. Mean (range) IPSS and bother scores were 17.3 (8 to 33) and 3.8 (0 to 6), respectively. Mean ± SD of prostate volume was 45.5±24.8 ml. Mean ± SD of serum FSH, LH, TT, fT, E2 and PSA were (11.5±13.0) mIU/ml, (6.7±5.9) mIU/ml, (4.6±2.4) ng/ml, (6.5±4.8) pg/ml, (47.9±24.4) and (4.3±3.2) ng/ml respectively. Clinical and endocrinological characteristics of the study population are given in Table I.

Prostate volumes of different age groups are shown in Figure 1. It shows that prostate volume was increased significantly with increase age.

Eleven patients (16.6%) had NIDDM diagnosed 1-5 years before and kept on oral hypoglycemic drugs with different levels of blood sugar. 16 patients (24.2%) had hypertension and 15 patients (22.7%) have positive family history of BPH. None of these factors appeared to have significant contribution to prostate volume. Figure II.

Patients were classified into two groups: 29 patients with prostate volume ≤40 ml and 37 patients with prostate volume >40 ml (As there is evidence that men with prostate volumes exceeding 40 cm3 have a greater response to 5α-reductase inhibitors,17 therefore, some experts limit the diagnosis of BPH to men with prostate volumes exceeding 40 ml.18) There was a significant difference in the mean age between the two groups (59.5 ml vs. 67.2 ml, p value <0.01), therefore; age-adjusted values were used to compare IPSS and sex hormone levels between the two groups. Neither IPSS nor bother score were significantly differ between the two groups. Mean estradiol level was significantly higher in patients with larger prostate volumes, after age adjustment. None of the other sex hormones showed significance difference between the two groups (Table II).

Regarding Pearson's rank correlation test, Prostate volume correlated significantly with age (r=0.344, p value=0.005) and PSA (r=0.278, p=0.035), but not with any of the sex hormones. IPSS was not correlated with age or prostate volume. IPSS had significant negative correlation with total testosterone (r=-0.334, p=0.031), but not with other sex hormones or PSA. Bother score didn't show any correlation with study parameters (Table III).

Taking age in consideration as covariable; the age-adjusted correlations revealed the same results, as prostate volume was correlated significantly with PSA, and IPSS was correlated negatively with total testosterone. The other parameters didn't show significant correlations (Table IV).

Discussion

Lower Urinary Tract Symptoms (LUTS) are considered quite troublesome for aging men. LUTS affect public health mainly because of its impact on quality of life[19,20] the costs required for diagnosis and management of benign prostatic hyperplasia[21], and the pharmaceuticals and interventions that is needed for this management[22].

Mean prostate volume was (45.5±24.8) ml with significant increase of prostate volume with age. These results are nearly identical to those in the study in Iran and it is also consistent with some other studies[23-25].

Prostate volume didn't correlate significantly with IPSS or bother scores and these results are consistent with other studies[5,26,27] apart from that of Liu and Wang[28]. This may be because of the multifactorial etiology of LUTS and that, even in patients with BPH, the symptoms of LUTS may be caused by dynamic changes and the contribution of bladder dysfunction which had gained an increasing importance.

Diabetic patients didn't appear to have larger prostate volume than non-diabetics. This result is similar to with that of Burke

et al[29] who, using the Olmsted County Study (OCS) data, reported that diabetes was not associated with an increase in prostate volume and its contribution to LUTS was through dynamic changes. While other studies found that non-insulin dependent diabetes mellitus (NIDDM) is associated with faster growing prostate[30,31].

The study demonstrated no significant difference in prostate volume in those with or without family history of BPH. This is consistent with that Tan et al[32] but differ from other studies in which men with inherited forms of BPH tended to have larger prostates than men with sporadic BPH[12,33,34].

Family history of BPH is defined as (3 or more family members with BPH, including the proband)[12]. Most of our patients didn't record more than one other family member with history of BPH, so either most of cases of BPH are sporadic or these patients wasn't diagnosed probably because they didn't seek treatment.

There was no significant effect of hypertension on prostate volume. This may be because of small sample size or because that the common link between hypertension and LUTS is the increased activity of sympathetic nervous system[35]; so the contribution of hypertension to LUTS may be via increase in prostatic tone rather than prostatic enlargement.

There was no correlation between free or total testosterone with prostate volume and this similar to the results of Favilla et al. and some other studies[27,36-38]. Sauver et al.[39] found that patients with larger prostate volume has lower free testosterone levels and attributed that to the increase of 5-α reductase activity.

The lack of correlation between testosterone and prostate volume support the concept of permissive role of testosterone in BPH development, as supplementation of men with androgens does not appear to increase the incident risk of BPH or LUTS. Furthermore, BPH prevalence increases with age, while levels of serum androgens decline[10].

Although androgens are essential for the coordinated growth of the prostate, local estrogenic activity is equally essential for the modulation of normal prostate development[40], In addition, levels of serum testosterone drop by about 35% between the ages of 21 and 85 against a constant level of estradiol. Estradiol/ testosterone ratio reach 1/80 in elderly but it may reach 1/8 in prostate which may be sufficient to promote the growth of BPH[41,42].

Estradiol showed significant association and correlation with prostate volume and this is consistent with some studies[9,36,39]. Roberts et al[37] restricted such correlation to patients with normal testosterone while others didn't find significant correlation between estradiol and prostate volume[27,43,44]. The difference between these studies may be because of different testosterone levels as androgen is essential for action of estrogen and a proper E2/T ratio is required to induce BPH development[42].

There are several mechanisms by which estradiol may affect prostate glands:

First is the differential action of estradiol on estrogen receptors (ERs). There are two main types of estrogen receptors :Erα which is mainly distributed in the stroma of prostate specially in the periurithral zone and its stimulation causes aberrant proliferation, inflammation, and the development of premalignant lesions[45], on the other hand ERβ that is present in prostatic epithelium has antiprolifrative and proapoptotic effects[46]. There is increased estradiol binding sites and in situ estrogen production in the stroma of BPH indicating upregulation of ERα and increase action of estradiol through this receptor[47,48] and this is the basis for the promising role of using some selective estrogen receptor modulator (SERM) in treatment of BPH[49].

The second possible mechanism of estrogen action is that upregulation of

ERα is also associated with upregulation of fibroblast growth factor two (FGF2) as well as other growth factors which may lead to BPH development[50].

The third mechanism is that estradiol was found to increase cAMP production. This may be mediated by G-protein coupled receptor-30 (GPR30) in the prostatic cells leading to subsequent phosphorylation of regulatory proteins[10,51]. This may cause proliferation or act as basis for the fourth mechanism as estrogen was found to sensitize prostatic stromal cells to the action of androgen[52].

Finally, Estradiol was shown to induce inflammation in the lateral lobe of rat prostate suggesting a similar role in human BPH[53].

Total testosterone was negatively correlated with IPSS. The effect of testosterone on LUTS might be explained by its effects on α1-adrenergic receptors, phosphodiesterase type 5 activity, Rho-kinase activation/endothelin activity and neural nitric oxide synthase (NOS), all of which are known to be androgen dependent[54].

Table I: Patient's clinical and endocrinological characteristics

Variable	Mean ± SD	Range
Age (years)	63.8 ± 9.5	36 - 85
Prostate volume (ml)	45.5 ± 24.8	10 - 152
IPSS	6.5 ± 17.3	8 - 33
Bother	1.4 ± 3.8	0 - 16
LH (mIU/ml)	5.9 ± 6.7	0.1 - 24.0
FSH (mIU/ml)	13.0 ± 11.5	1.1 – 92.0
Total Testosterone (ng/ml)	4.6 ± 2.4	1.6 – 11.6
Free Testosterone (pg/ml)	6.5 ± 4.8	0.5 - 16.3
Estradiol (pg/ml)	24.4 ± 47.9	3.4 – 93.6
PSA (ng/ml)	3.2 ± 4.3	0.05 – 16.2

Table II: Clinical and endocrine characteristics according to prostate volume

Prostate volume	Unadjusted values(mean±SD)			Age adjusted values(mean±SD)		
	≤ 40 ml	> 40 ml	p val	≤ 40 ml	> 40 ml	p val
Age (year)	59.5±10.0**	67.2±7.5**	0.001	-	-	-
IPSS	16.3 ± 15.4	18.0 ± 7.2	0.283	15.6±5.5	18.0±7.2	0.119
Bother	3.6 ± 1.7	3.9 ± 1.2	0.475	4.0 ± 1.8	3.9 ± 1.2	0.787
FSH (mIU/ml)	12.1 ± 17.4	10.9 ± 8.3	0.711	13.7±17.2	10.9± 8.3	0.391
LH (mIU/ml)	5.8 ± 5.7	7.4 ± 6.0	0.275	7.3 ± 6.9	7.4 ± 6.0	0.905
TotalTesto.(ng/ml)	5.3 ± 2.3	4.0 ± 2.4	0.072	4.6 ± 2.0	4.0 ± 2.4	0.360
Free Testo.(pg/ml)	7.5 ± 4.3	5.7 ± 5.0	0.140	7.0 ± 4.6	5.7 ± 5.0	0.293
Estradiol (pg/ml)	42.6 ± 22.0	52.0 ± 25.6	0.126	22.8*± 8	52.0±25.6*	0.029
PSA (ng/ml)	3.5 ± 2.7	4.9 ± 3.5	0.113	2.2 ±4.0	4.9 ± 3.5	0.261

* p value < 0.05
** p value < 0.01

Table III: Correlations of the study parameters with IPSS and prostate volume

	Prostate	IPSS	Bother
Age	0.344**	0.015	0.080
Prostate volume	1	-0.055	-0.154
LH	0.130	0.042	0.068
FSH	-0.014	0.050	0.002
Estradiol	0.128	-0.152	0.072
Free Testosterone	0.026	-0.124	-0.226
Total Testosterone	-0.237	-0.334*	-0.248
PSA	0.278*	-0.020	-0.115

* Correlation is significant with p value <0.05
** Correlation is significant with p value <0.01

Table IV: Age-adjusted correlations of the study parameters with IPSS and prostate volume

Control variable = age	Prostate	IPSS	Bother
Prostate volume	1	-0.064	-0.196
LH	0.013	0.044	0.040
FSH	-0.123	0.055	-0.035
Estradiol	0.167	-0.159	0.085
Free Testosterone	0.111	-0.130	-0.214
Total Testosterone	-0.127	-0.336*	-0.246
PSA	0.290*	-0.020	-0.122

* Correlation is significant with p value < 0.05

Figure 1: Prostate volume in different age groups

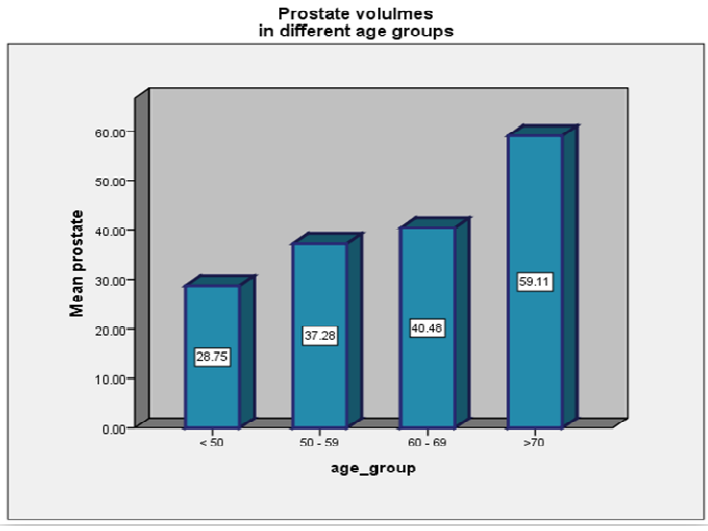
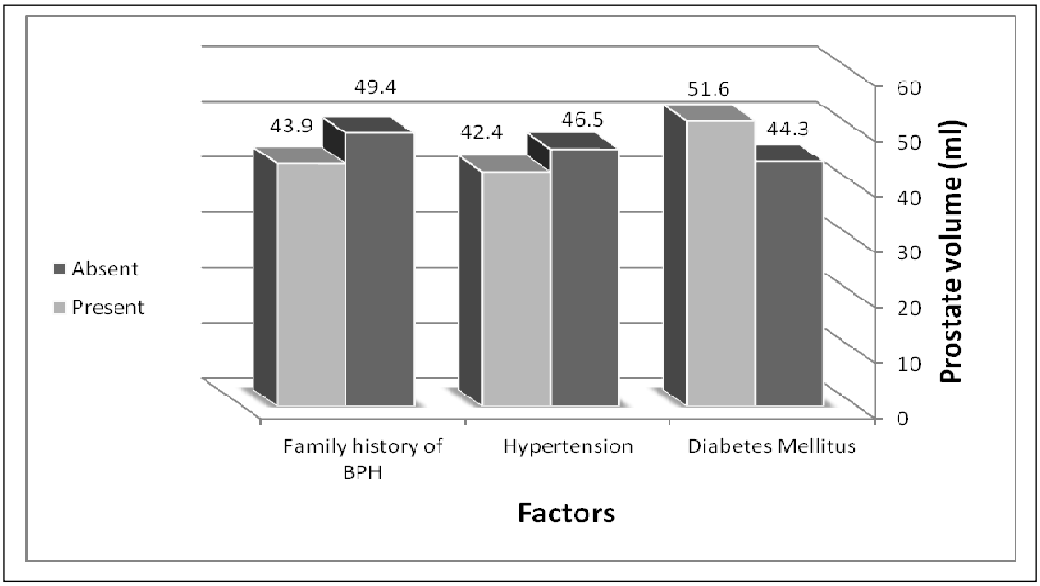


Figure 2: Relationship between several clinical factors and prostate volume



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