Original Article

Effect of Estradiol on the Severity of Lower Urinary Tract Symptoms in Men

Ihsan Shakir Mahmood, Jamal A. Al-Dohan, Murtadha M. Salih Al-Musafer[1]

Departments of Biochemistry and [1]Surgery, College of Medicine, University of Basrah, Basrah, Iraq

Abstract

Objective: The aim of this study is to investigate the relationship between estradiol (E_2) level and the severity of lower urinary tract symptoms (LUTS) in men. **Materials and Methods:** This study involved 82 patients suffering from LUTS for >1 month, with age ranged from 36 to 85 years old who attended Basra General Hospital outpatient clinic of urological surgery seeking for management. The medical and surgical histories were taken through special questionnaire and the severity of LUTS was assessed using the international prostate symptom score (IPSS). General and urological examinations were conducted to them. Four milliliters of venous blood was drawn from each patient to measure luteinizing hormone (LH), follicle-stimulating hormone (FSH), E_2, and prostate-specific antigen and the results were used to assess the presence of any association with IPSS or prostate volume. Furthermore, fasting blood sugar, blood urea, serum creatinine, and thyroid-stimulating hormone were measured to identify unknown diabetic patients and exclude those with renal failure or thyrotoxicosis. **Results:** The IPSS, irritative, obstructive, and bother scores were (13.9 ± 9.4), (5.6 ± 4.6), (6.6 ± 4.4), and (2.99 ± 1.91), respectively. Mean serum FSH, LH, and E_2 were (11.0 ± 12.6) mIU/ml, (6.26 ± 5.40) mIU/ml, and (39.9 ± 23.3) pg/ml, respectively. There were no correlations in the current study between gonadotropins and IPSS or any of its subgroups, but men with moderate-to-severe LUTS tended to have a significantly lower mean of FSH ($P < 0.05$). E_2 didnot correlate with age or prostate volume. E_2 showed significant associations and correlations with the IPSS, irritative, and bother scores, and these correlations persisted after adjustment for age and prostate volume. **Conclusion:** E_2 has a significant relationship with LUTS severity and may act as an independent risk factor for LUTS.

Keywords: Estradiol, lower urinary tract symptoms, sex hormones

Introduction

In the past, several terms such as prostatism, clinical benign prostatic hyperplasia (BPH), and symptomatic 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 >40 years. Prevalence rises markedly with age;[3,4] the prevalence of LUTS increases to >70% in the seventh decade of life, in comparison to about 8% in the fourth decade and BPH is the most common cause of LUTS in all age groups.[5] LUTS result in an increased risk of falls, diminish health-related quality of life (Qol), and associate with sadness, depression, impairment in instrumental activities of daily living, and the loss of work time.[6,7]

Access this article online

Quick Response Code:

Website: www.medjbabylon.org

DOI: 10.4103/MJBL.MJBL_5_20

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 a permissive role in the development of BPH. For example, anti-androgen therapy with flutamide or 5α-reductase inhibitors and surgical castration cause rapid reduction in prostate volume, 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

Address for corresponding: Dr. Ihsan Shakir Mahmood, Department of Biochemistry, College of Medicine, University of Basrah, Basrah, Iraq.
E-mail: ihsan.shakir@yahoo.com

Submitted: 29-01-2020 **Accepted:** 18-03-2020 **Published Online:** 17-06-2020

How to cite this article: Mahmood IS, Al-Dohan JA, Al-Musafer MM. Effect of estradiol on the severity of lower urinary tract symptoms in men. Med J Babylon 2020;17:133-8.

increasing age, absolutely or relative to testosterone levels;[11] however, serum levels of estradiol (E_2) do not necessarily reflect tissue levels of E_2.[12] In this regard, prostate *in situ* E_2 production may influence local estrogen regulated processes. Such local production of E_2 has been implicated in prostatic hyperplasia, and the loss of aromatase expression causes a decreased estrogen-induced prostate proliferation.[10,13]

Different actions of E_2 may be mediated by the stromal estrogen receptor α (ER-α) which has proliferative role and epithelial ER-β which induces apoptosis to regulate abnormal growth.[13,14] Evidence indicates that estrogen action mediated through the separate receptors may contribute to the etiology and progression of multiple prostate diseased states.[11]

Materials and Methods

Ninety-one total patients were initially included in this etiological study which was carried out from the first of November 2011 to the end of January 2013. Nine patients were excluded; seven of them were diagnosed with prostatic cancer, one because of hyperthyroidism and one because of diabetes mellitus. Eighty-two men represented the final population of the study, their ages ranged from 36 to 85 years, they have different residence all around Basra and they were examined by the urologists.

Any patient known to have prostatic cancer or taking antiandrogen was excluded from the study. In addition, 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 the international prostate symptom score (IPSS) questionnaire that contains questions addressing seven symptoms which are straining, intermittency and weak stream (obstructive symptoms), frequency, urgency, and nocturia (irritative) in addition to incomplete emptying. Each symptom with an item score ranging from 0 to 5, resulting in a total score of 35. Patients with score of 0–7 regarded as mild and those with ≥8 as moderate to severe. In addition, a question Qol was used to obtain a bother score ranging from 1 to 6.

General and urological examinations were done to the patients, and then an ultrasound was done to them to check the renal system and measure prostate volume.

Four milliliters of venous blood was drawn from each patient to measure luteinizing hormone (LH), follicle-stimulating hormone (FSH) (ELISA Kit, Monobind Inc., USA), E_2, and prostate-specific antigen (PSA) (ELISA Kit, BioCheck Inc., USA). Furthermore, fasting blood sugar, serum creatinine (BIOLABO SA, France), blood urea (bioMerieux sa, France), and thyroid-stimulating hormone (ELISA Kit, Monobind Inc., USA) were measured to identify unknown diabetic patients and exclude those with renal failure or thyrotoxicosis.

The results were expressed in the form of a mean ± standard deviation (SD). The difference between the means of any parameter in study in different groups was assessed using the independent samples *t*-test. The association among categorical variables was assessed using the Chi-square test. The correlation between two different parameters was assessed using Pearson's correlation coefficients and the significantly associated factors with IPSS on Pearson's rank correlation test were estimated using multivariate linear regression models. $P < 0.05$ was considered the lowest limit of statistical significance.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee.

Results

The final study population consisted of 82 men with a mean (range) age of 61.7 (36–85) years. Mean (range) IPSS total, voiding, and storage symptoms scores were 13.9 (0–33), 5.6 (0–15), and 6.6 (0–15), respectively. Mean ± SD of IPSS total scores of the mild, moderate, and severe LUTS groups were 2.8 ± 2.4, 13.8 ± 3.7, and 25.4 ± 4.5, respectively. Mean ± SD of a prostate volume was 39.3 ± 23.7 ml. Mean ± SD of serum FSH, LH, E_2, and PSA were 11.0 ± 12.6 mIU/ml, 6.3 ± 5.4 mIU/ml, 39.9 ± 23.3 pg/ml, and 3.75 ± 3.00 ng/ml, respectively. Clinical and endocrinological characteristics of the study population are given in Table 1.

Patients were classified into two groups as follows: those with IPSS <8 regarded as mild and those with IPSS ≥8

Table 1: Patients' clinical and endocrinological characteristics

Variable	Mean±SD	Range
Age (years)	61.7±10.4	36-85
Prostate volume (ml)	39.3±23.7	10-152
IPSS total	9.4±13.9	0-33
Obstructive	4.6±5.6	0-15
Irritative	4.4±6.6	0-15
Incomplete emptying	1.68±1.85	0-5
Frequency	2.28±1.69	0-5
Intermittency	2.02±1.87	0-5
Urgency	1.80±1.70	0-5
Weak stream	2.17±1.96	0-5
Straining	1.65±1.39	0-5
Nocturia	1.75±2.50	0-5
Bother	1.91±2.99	0-6
FSH (mIU/ml)	12.6±11.6	1.1-92.0
LH (mIU/ml)	5.4±6.3	0.1-24.0
Estradiol (pg/ml)	23.3±39.9	2.0-93.6
PSA (ng/ml)	3.00±3.75	0-16.2

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, PSA: Prostate-specific antigen, SD: Standard deviation, IPSS: International Prostate Symptom Score

as moderate to severe. There were statistically significant differences in the mean age and prostate volume between the two groups ($P < 0.01$). Serum FSH level was significantly higher in the moderate-to-severe patients' group only after age adjustment (18.9 mIU/ml vs. 11.4 mIU/ml, $P < 0.05$), while LH did not show any difference between the two groups. Serum E_2 and PSA showed significant differences between patients with IPSS <8 and ≥8; both before age adjustment (E2: 23.3 pg/ml vs. 46.0 pg/ml, $P < 0.05$; PSA: 2.5 ng/ml vs. 4.0 ng/ml, $P < 0.05$) and after age adjustment (E2: 15.6 pg/ml vs. 46.0 pg/ml, $P < 0.05$; PSA: 1.5 ng/ml vs. 4.2 ng/ml, $P < 0.01$), as shown in Table 2.

There were significant associations between gonadotropins and the severity of LUTS (FSH, $P = 0.014$; LH, $P = 0.016$), after age adjustment; as about 80% of patients with normal LH or FSH lies within the moderate-to-severe group.

On the other hand, all patients with high (E_2 level >60 pg/ml) have moderate-to-severe LUTS; indicating a strong association between E_2 and LUTS severity ($P = 0.003$).

Regarding Pearson's rank correlation test, total IPSS was significantly correlated with age ($r = 0.429$, $P < 0.001$), prostate volume ($r = 0.253$, $P = 0.025$), and E_2 levels ($r = 0.228$, $P = 0.045$). Obstructive score was significantly correlated with age only ($r = 0.348$, $P = 0.001$). The irritative score was significantly correlated with age ($r = 0.455$, $P < 0.001$), prostate volume ($r = 0.317$, $P = 0.005$), and E_2 levels ($r = 0.281$, $P = 0.013$). Bother score was correlated significantly with age ($r = 0.409$, $P = 0.001$) and E_2 levels ($r = 0.376$, $P = 0.002$). Prostate volume did not show any correlation with hormonal levels, but was positively correlated with age ($r = 0.416$, $P < 0.001$) and PSA ($r = 0.315$, $P = 0.009$). Gonadotropins did not show any correlation with IPSS or prostate volume, as shown in Table 3.

The results from the multivariate linear regression models indicated that age and E_2 were significantly associated with the total IPSS, as shown in Table 4.

Discussion

LUTS are considered quite troublesome for aging men. LUTS affect public health mainly because of their impact on Qol,[15,16] the costs required for the diagnosis and management of BPH,[17] and the pharmaceuticals and interventions that is needed for this management.[18]

The mean ± SD of IPSS was 13.9 ± 9.4 and the irritative score was slightly higher than the obstructive score and these results are consistent with that of the Boston area community health survey[3] and the results from the European Investigation into Cancer and Nutrition study,[19] but they differ from the results of the International Continence Society "BPH" (ICS-BPH) study and some other studies which found irritative symptoms

Table 2: Clinical and endocrinological characteristics of patients according to the International Prostate Symptom Score severity

IPSS	Mean±SD					
	Unadjusted values			Age adjusted values		
	<8	≥8	*P*	<8	≥8	*P*
Age (year)	55.2±9.2	64.2±9.8	<0.001	-	-	-
Prostate volume (ml)	27.4±13.3	44.3±25.4	0.004	25.2±13.0	44.3±25.4	0.001
FSH (mIU/ml)	10.0±9.7	11.4±13.6	0.673	18.9±13.5	11.4±13.6	0.026
LH (mIU/ml)	6.2±3.9	6.3±5.9	0.973	8.4±4.4	6.3±5.9	0.127
Estradiol (pg/ml)	23.3±13.3	46.0±23.2	<0.001	15.0±15.6	46.0±23.2	<0.001
PSA (ng/ml)	2.5±2.2	4.0±2.7	0.026	1.5±1.5	3.2±4.2	<0.001

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, PSA: Prostate-specific antigen, SD: Standard deviation, IPSS: International Prostate Symptom Score

Table 3: Pearson's correlations of clinical and endocrinological variables with the International Prostate Symptom Score and prostate volume

	IPSS				Prostate volume
	Total	Irritative	Obstructive	Bother	
Age	0.429**	0.455**	0.348**	0.409**	0.416**
Prostate volume	0.253*	0.317**	0.167	0.184	1
LH	0.024	−0.007	0.097	0.049	0.141
FSH	0.047	0.069	0.073	0.025	0.017
Estradiol	0.228*	0.281*	0.137	0.376**	0.210
PSA	0.174	0.090	0.231	0.085	0.315**

*Correlation is significant with $P<0.05$, **Correlation is significant with $P<0.01$. FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, PSA: Prostate-specific antigen, IPSS: International Prostate Symptom Score

Table 4: Multiple linear regression-derived β coefficients and *P* values for factors significantly associated with IPSS

Factor	β coefficient	*P*
Age	0.322	0.008**
Prostate volume	0.006	0.960
Estradiol	0.264	0.020*

*Correlation is significant with $P<0.05$, **Correlation is significant with $P<0.01$

to be less frequent but more bothersome.[5,20,21] The reason may be because some studies had considered incomplete emptying as an obstructive symptom or because of the difference in the studies' populations.

This study found weak, yet significant, correlation of IPSS and prostate volume which is similar to that found by Liu *et al.*,[22] yet this significance disappeared in multivariate linear regression. This may be because of the multifactorial etiology of LUTS and that, even in patients with BPH, LUTS may be caused by dynamic changes; also, this may be due to the contribution of bladder dysfunction which has gained an increasing importance. Some studies found no correlation between IPSS and prostate volume.[5,21,23]

There was not any correlation between gonadotropins and IPSS or any of its subgroups. These results are consistent with other studies,[23-25] but differ from the results of Zeng *et al.*[26] who found positive correlations between gonadotropins and IPSS in aging Chinese men.

There was a significant association between gonadotropins and the severity of LUTS, after age adjustment; this may be due to the increased serum level of estrogen that was found in patients with moderate-to-severe LUTS; estrogen is known to exert negative feedback on pituitary,[27,28] hypothalamus,[29] or both[30,31] to decrease gonadotropins, mainly FSH, especially in elderly patients, in whom levels of inhibin is decreased.[32,33]

Although androgens are essential for the coordinated growth of the prostate; local estrogenic activity is equally essential for the modulation of normal prostate development,[34] in addition, levels of serum testosterone drop by about 35% between the ages of 21 and 85 years against a constant level of E_2. E_2/testosterone ratio reaches 1/80 in the elderly, but it may reach 1/8 in prostate, which may be sufficient to promote the growth of BPH.[35,36]

E_2 did not correlate with prostate volume and this is consistent with some studies.[23,24,26] Roberts *et al.*[37] restricted such correlation to patients with normal testosterone while others find significant correlation between E_2 and prostate volume.[9,25,38,39] The difference between these studies may be because of different testosterone levels as androgen is essential for the action of estrogen and a proper E_2/T ratio is required to induce BPH development.[36]

E_2 showed significant associations and correlations with IPSS, irritative, and bother scores and these correlations persisted after adjustment for age and prostate volume indicating that E_2 may act as an independent risk factor for LUTS. Few studies found significant correlations between E_2 and IPSS.[39,40] Platz *et al.*[41] found an association between E_2 and LUTS severity, but it did not reach clinical significance, whereas other studies found no correlation between E_2 and IPSS or one of its subgroups.[23,24,26,42,43]

There are several mechanisms by which E_2 may affect prostate glands:

First is the differential action of E_2 on ERs. There are two main types of ERs: ER-α which is mainly distributed in the stroma of prostate, especially in the periurithral zone and its stimulation causes aberrant proliferation, inflammation, and the development of premalignant lesions,[44] on the other hand, ER-β that is present in prostatic epithelium has antiproliferative and proapoptotic effects.[45] There is an increased E_2 binding sites and *in situ* estrogen production in the stroma of BPH indicating upregulation of ERα and increasing action of E_2 through these receptors[46,47] and this is the basis for the promising role of using some selective ER modulators in the treatment of BPH.[48]

The second possible mechanism of estrogen action is that upregulation of ERα is also associated with upregulation of fibroblast growth factor two as well as other growth factors which may lead to BPH development.[49]

Third, E_2 was found to increase cAMP production. This may be mediated by G-protein coupled receptor-30 in the prostatic cells, leading to subsequent phosphorylation of regulatory proteins.[10,50] 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.[51]

Finally, E_2 was shown to induce inflammation in the lateral lobe of rat prostate suggesting a similar role in human BPH.[52]

Conclusion

It is concluded from the results of the present study that serum level of estradiol (E2) has a significant relationship with lower urinary tract symptoms (LUTS) severity and may act as an independent risk factor for LUTS.

Acknowledgments

Special thanks to the staff in the biochemistry department/ College of Medicine and to the staff in Basra General Hospital for their kind support and cooperation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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