The Association between (Serum prostatic specific antigen and Dihydrotestosterone) and Efficacy of Solifenacin Therapy for Benign prostatic hypertrophy Patient in Salahalddin Society

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Abstract

Background: Benign prostatic hypertrophy (BPH) is a condition in which the prostate becomes enlarged as part of the aging process. BPH Primarily affects men over the age of 40, of all races and ethnic backgrounds. No one knows specifically why an enlarged prostate occurs. However, hormones and genetics may play a role in the condition's development some researchers believe that it may be related to a drop in testosterone levels as men age. Others believe that one enlarged prostate cause is the reawakening of cells that deliver signals to other cells in the prostate.

Objective: To evaluate the relation between serum prostatic specific antigen (PSA) and dihydrotestosterone (DHT) on the effects of 4 weeks of solifenacin therapy for BPH patients.

Patients and Methods: A total of 108 patients attending the consultation department at Tikrit teaching hospital were enrolled in this case control study during the period from November1st, 2011 to1st of August, 2012. All patients had BPH with α1-blocker treatment during the study period, a change in type and dosage of α1-blocker was not allowed, Solifenacin (5mg) once daily dose was administered to the patients for 4 weeks.

PSA level, serum DHT, IPSS, post voiding residual PVR, and prostatic size were measured before and after treatment. The patients themselves serve as their own control group. Estimation of Serum DHT and serum PSA using Elisa kit.

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Results: The relationship between PSA level and prostate size is probably the most natural reason for the correlation of urinary symptoms and serum PSA level .also found age and Higher serum DHT concentration were associated with larger prostate volume, elevate PSA level, less response to solifenacin. In the present study, strong direct and significant relationship found between storage symptom, voiding symptom and total IPSS with DHT level for men who treated with solifenacin +α-blocker than men who take α-blocker alone. While clarified non-significant differences found between PVR and the use of solifenacin +α-blocker and prostate size.

Conclusion: Serum PSA and DHT can be used to predict effect of solifenacin on BPH after α1-blockers monotherapy.

Key words: prostate specific antigen, dihydrotestosterone, solifenacin, BPH

Introduction

Benign Prostatic Hyperplasia (BPH) is a condition in which the prostate becomes enlarged as part of the aging process. Unfortunately, it occurs to varying degrees and in some men growth can be excessive and can obstruct the flow of urine and result in bothersome urinary symptoms. [1] BPH primarily affects men over the age of 40, of all races and ethnic backgrounds. In fact, approximately 80% of men over the age of 70 have some degree of BPH. Fortunately, not all men will suffer bothersome symptoms. Currently, it is estimated that 25%-50% of men with an enlarged prostate have some degree of bothersome urinary symptoms and can benefit from of some form of medical or surgical treatment [2]. No one knows specifically why an enlarged prostate occurs. However, hormones and genetics may play a role in the condition's development. Some researchers believe that it may be related to a drop in testosterone levels as men age. Others believe that one enlarged prostate cause is the "reawakening" of cells that deliver signals to other cells in the prostate [3].

Throughout their lives, men produce testosterone (an important male hormone) and small amounts of estrogen (a female hormone).As men age, the amount of active testosterone in the blood decreases, leaving a higher proportion of estrogen. Studies done with animals have suggested that an enlarged prostate may occur because the higher amount of estrogen within the gland increases the activity of substances that promote cell growth [4].

Solifenacin

Vesicare tablets contain the active ingredient solifenacin succinate, which is a type of medicine called an anticholinergic (or antimuscarinic) muscle relaxant. It works by relaxing the involuntary muscle that is found in the wall of the bladder. The muscle in the wall of the bladder is called the detrusor muscle. It can sometimes contract in uncontrollable spasms, and

this is often referred to as having an overactive bladder. The overactive detrusor muscle can increase in the number of times you need to pass urine, or cause uncontrollable urges to pass urine, or involuntary leakage of urine (urinary incontinence) [5].

Solifenacin works by relaxing the detrusor muscle in the wall of the bladder. It does this by blocking receptors called cholinergic (or muscarinic) receptors that are found on the surface of the muscle cells. This prevents a natural body chemical called acetylcholine from acting on these receptors. Normally when acetylcholine acts on these receptors, it causes the detrusor muscle to contract and the bladder to empty. By blocking acetylcholine, solifenacin helps the muscle in the bladder wall to relax. This reduces unstable, involuntary contractions of the bladder, and thereby increases the capacity of the bladder to hold urine. In turn, this reduces the need to pass urine. It may take at least four weeks of treatment for this medicine to become fully effective [6].

Patients and Methods

A total of 108 patients attending the consultation department at Tikrit teaching hospital were enrolled in this case control study .All patients had BPH with α1- blocker treatment During the study period, a change in type and dosage of α1-blocker was not allowed, Solifenacin (5mg) once daily dose was administered to the patients for 4 weeks .PSA level, serum DHT, IPSS, PVR, and prostatic size were measured before and after treatment. The patients themselves serve as their on control group. Estimation of Serum DHT and serum PSA using Elisa kit.

After taking an agreement from the patients, their names, laboratory identification numbers had been kept secret. For honesty and respect to the patients I had written the prostate marker and biochemical results. The study was carried out in the outpatient clinic of urology in Tikrit Teaching Hospital/Salahalddin government/Iraq. This study was conducted among Salahalddin men whom aged more than 50 years selected randomly (simple random study).

Criteria for Sample Selection

Inclusion criteria:

1) Male aged more than or equal to**50** years with BPH.

2) Residence: in **Salahalddin** society.

Exclusion Criteria:

1) Patient with previous prostatic surgery, transurethral resection of the prostate (TURP) or open

2) Patient with finasteride treatment

3) PVR >100 ml

Results

Mean age was (65.71±9.91) years (Confidence Interval (CI) 6.8267.60). Mean prostatic size was (51.13±18.90) cm^3 (CI 47.52-54.73). Mean serum level of PSA was (2.08±0. .846) ng/ml (CI 1.92-2.24).Mean serum level of DHT was (508.22±168.766) pg/ml (476.03-540.41).

There are strong positive correlation between serum PSA level and age (Pearson, r = 0.854) ,prostate size(Pearson, r = 0.860) ,serum DHT level (Pearson, r = 0.942) , Storage symptoms (Pearson, r =0.412), Post treatment storage symptoms (Pearson, r =0.856), Change in storage

symptoms(Pearson, r = 0.639) , voiding symptoms (Pearson, r = 0.838) , Post treatment voiding symptoms (Pearson, r = 0.775) , Total IPSS (Pearson, r =0.770) , Post treatment total IPSS (Pearson, r = 0.895) , Change in Total IPSS (Pearson, r = 0.551) , PVR (Pearson, r = 0.648) and Post treatment PVR (Pearson, r =0.605) ,P <0.001.

But there are no correlation was observed between serum PSA level and Change in voiding symptoms (Pearson, r = -0.166, p =0.016) and Change in PVR (Pearson, r =-0.035, p<0.001).as in Table (2).

Table (1) the mean ± SD of age, prostate size, PSA and DHT

Parameters	Mean ± SD	95% Confidence Interval for Mean	
		Lower	Upper
Age (years)	65.7±9.9	6.8	67.6
Prostate size (cm^3)	51±18.9	47.5	54.7
PSA (ng/ml)	2.1±0. 8	1.9	2.3
DHT (pg/ml)	508.2±168.8	476.1	540.4

Table (2) The bivariate correlation among PSA level and other parameters.

Parameters	Serum PSA level	
	Person correlation	P-value
Age	0.854**	<0.001
Prostate size	0.860**	<0.001
Serum DHT level	0.942**	<0.001
Storage symptoms	0.412**	<0.001
Post treatment storage symptoms	0.856**	<0.001
Change in storage symptoms	0.639**	<0.001
voiding symptoms	0.838**	<0.001
Post treatment voiding symptoms	0.775**	<0.001
Change in voiding symptoms	-0.166	0.016
Total IPSS	0.770**	<0.001
Post treatment total IPSS	0.895**	<0.001
Change in Total IPSS	0.551**	<0.001
PVR	0.648**	<0.001
Post treatment PVR	0.605**	<0.001
Change in PVR	-0.035	0.717

**** Significant Correlation (2-tailed).**

Serum DHT level showed **strong positive correlation** with age (Pearson, r = 0.937) ,prostate size(Pearson, r =0.886), serum PSA level(Pearson, r = 0.942) , Storage symptoms (Pearson, r =0.496), Post treatment storage symptoms (Pearson, r =0.919), Change in storage symptoms(Pearson, r = 0.625) , voiding symptoms(Pearson, r = 0.805), Post treatment voiding symptoms (Pearson, r =0.701), Total IPSS(Pearson, r = 0.778), Post treatment total IPSS(Pearson, r = 0.873) , Change in Total IPSS (Pearson, r =0.453), PVR(Pearson, r = 0.658) and Post treatment PVR(Pearson, r = 0.647) , probability for all above parameter less than 0.001.

Serum DHT level demonstrated significant correlations with Change in voiding symptoms and Change in PVR (Pearson, r = -0.299, p=0.002), (Pearson, r = 0.000, p=0.995) respectively .as in Table (3).

Table (3) The bivariate correlation among serum DHT level and other parameters.

Parameters	Serum DHT level	
	Person correlation	P-value
Age	0.937**	<0.001
Prostate size	0.886**	<0.001
Serum PSA level	0.942**	<0.001
Storage symptoms	0.496**	<0.001
Post treatment storage symptoms	0.919**	<0.001
Change in storage symptoms	0.625**	<0.001
voiding symptoms	0.805**	<0.001
Post treatment voiding symptoms	0.701**	<0.001
Change in voiding symptoms	-0.299	0.002
Total IPSS	0.778**	<0.001
Post treatment total IPSS	0.873**	<0.001
Change in Total IPSS	0.453.**	<0.001
PVR	0.658**	<0.001
Post treatment PVR	0.647**	<0.001
Change in PVR	0.000	0.995

**** Significant Correlation (2-tailed).**

prostate size of patients with BPH showed strong positive relation with age (Pearson, r = 0.830),serum DHT level(Pearson, r = 0.886), serum PSA level(Pearson, r = 0.860), Storage symptoms(Pearson, r = 0.519), Post treatment storage symptoms (Pearson, r = 0.884), Change in storage symptoms (Pearson, r = 0.553), voiding symptoms (Pearson, r = 0.771) , Post treatment voiding symptoms(Pearson, r = 0.704) , Total IPSS (Pearson, r = 0.758) , Post treatment total IPSS (Pearson, r =0.810) , Change in Total IPSS (Pearson, r = 00.308), PVR(Pearson, r = 0.649) and Post treatment PVR (Pearson, r = 0.586), p<0.001 for all above parameter . While no correlation was observed between prostate size and Change in PVR (Pearson, r =-0.135, p=0.164), as found in Table (4) .

(4).Table (4) The bivariate correlation among prostate size and other parameters.

Parameters	Prostate size	
	Person correlation	P-value
Age	0.830**	<0.001
Serum PSA level	0.860**	<0.001
Serum DHT level	0.886**	<0.001
Storage symptoms	0.519**	<0.001
Post treatment storage symptoms	0.884**	<0.001
Change in storage symptoms	0.553**	<0.001
voiding symptoms	0.771**	<0.001
Post treatment voiding symptoms	0.704**	<0.001
Change in voiding symptoms	-0.419**	<0.001
Total IPSS	0.758.**	<0.001
Post treatment total IPSS	0.810**	<0.001
Change in Total IPSS	0.304**	<0.001
PVR	0.649**	<0.001
Post treatment PVR	0.586**	<0.001
Change in PVR	-0.135	0.164

**** Significant Correlation (2-tailed).**

Linear regression model

On applying linear regression model , strong inverse relation with strong linear trend between serum PSA

level and both Change in Total IPSS and change in storage symptoms (P-value for linear trend was < 0.001 and < 0.001 respectively), as in figures (1) and (2).

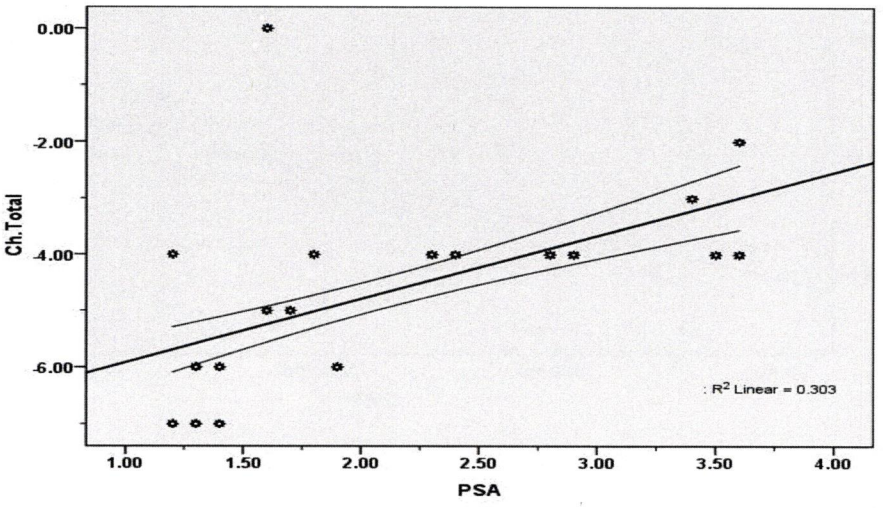

Figure (1) Regression line of the relation between serum PSA level and Change in Total IPSS

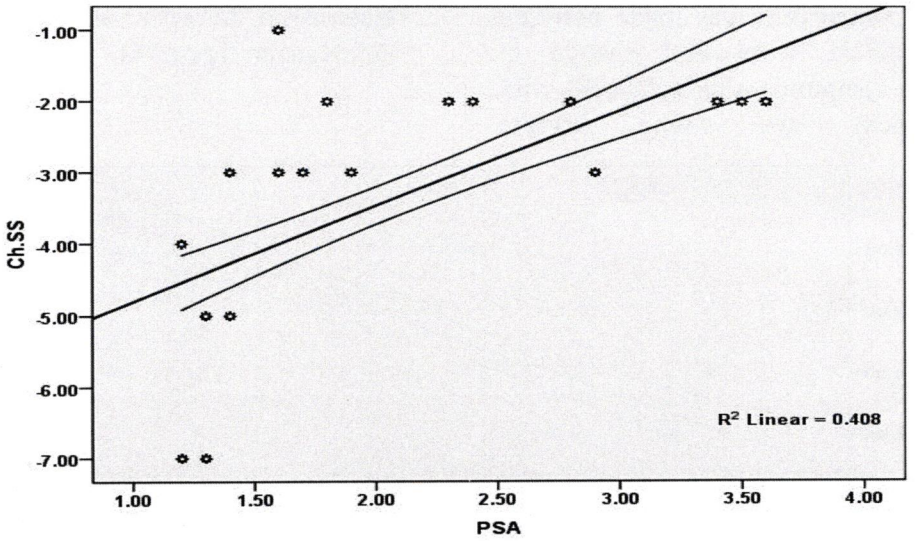

Figure (2) Regression line of the relation between serum PSA level and Change in storage symptoms

When applying linear regression model, strong inverse relation between serum DHT level and change in total IPSS among patients with BPH after treatment with 5mg of solifenacin (p value <0.001) , as in figure (3)

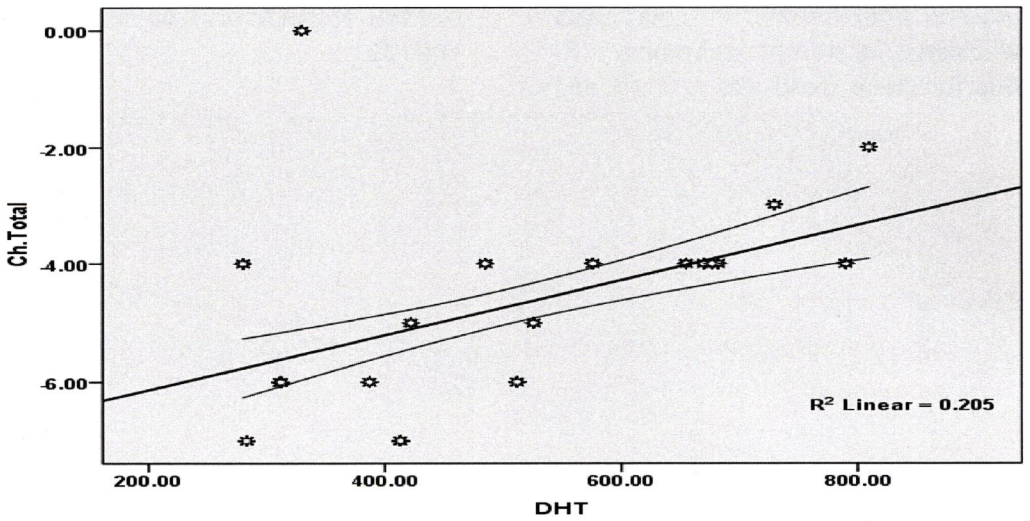

Figure (3) Regression line of the relation between serum DHT level and change in total IPSS.

When comparison was made between serum DHT level and change in storage symptoms after treatment with solifenacin, we found inverse relationship between them, p value <0.001, as in figure (4)

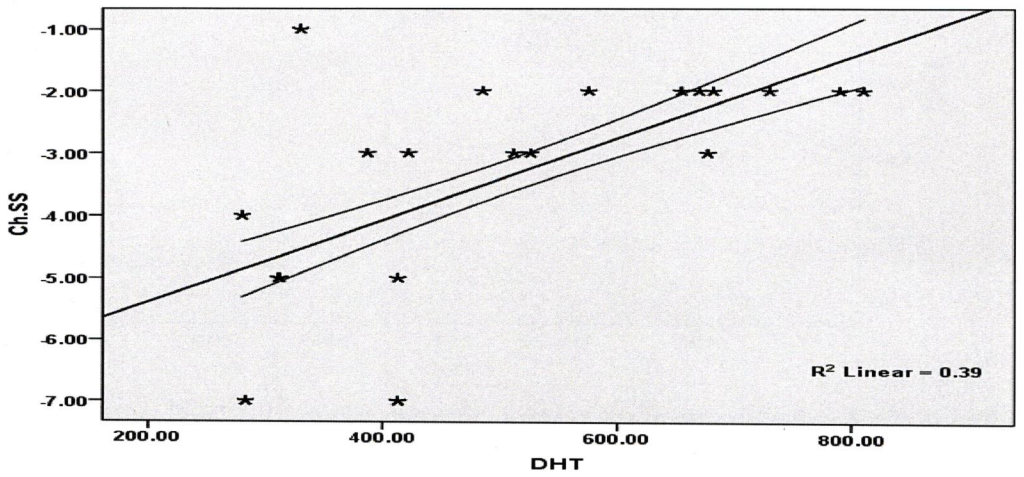

Figure (4) Regression line of the relation between serum DHT level and change in storage symptoms

Discussion

Combination of α1-blocker and anticholinergic agent as the first line treatment According to the treatment recommendations proposed by the 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases, a strength of the study is that subjects were required to have been treated with an α-blocker for ≥1 month as part of their routine clinical management and continued this treatment for the duration of the study [7] .The additional administration of solifenacin to patients treated with α1-blockers is effective in controlling remaining over active bladder (OAB) symptoms of BPH[8].

In present study, additional administration of 5mg of solifenacin for four weeks for men who failed α1-blockers monotherpy, the storage symptom score (day frequency, urgency, and nocturia) were significantly improved by additional of solifenacin (the mean decrease from 8.91±2.1 to 5.54± 2.3 points p-value <0.001), also changes observed significantly when compared between voiding symptom score (intermittency, weak stream, straining) before take of solifenacin (9.79±3.43points) decrease to (8.44 + 3.48 points) after the treatment p-value <0.001. Statistical comparisons of the mean values between before and after treatment of solifenacin were done for total IPSS (18.69± 5.02 to 13.99±5.21points) respectively p-value <0.001. These decreases in the above results due to Remaining OAB symptoms are mainly caused by detrusor over activity .There are several mechanisms to explain the highly frequent association of bladder over activity such as denervation hypersensitivity, modulated detrusor properties, increased release of urothelial neurotransmitters, and increased afferent stimulation from the urethra. Since anticholinergic agents contribute to improve OAB symptoms through the blockade of muscarinic receptors on the smooth muscle, urothelium, and afferent nerves, they may be effective to control remaining OAB symptoms after α1-blockers mono therapy. The results of this present was similar to what reported by *Naoya Masumori, et al.* in 2010.[9]

In the present study, additional administration of solifenacin for patients treated with α1-blockers revealed statically significant improvement of the PVR (37.49+ 19.04 to 40.06 + 20.17), but these results not clinically meaningful. There were no clinically meaningful changes in Q max, The results of this present study was similar to the results of *Kaplan S.A. et al* in 2009 except there was no clinically meaningful changes PVR .[10]

In this present study found age and Higher serum DHT concentration were associated with larger prostate volume, elevate PSA level, less response to solifenacin and higher prevalence of BPH , because even with a drop in the blood's testosterone level, older men continue to produce and accumulate high levels of DHT in the prostate. This accumulation of DHT may encourage the growth of cells; lead to decrease response to solifenacin treatment that agreed to the finding of *Liao CH. et al* study in 2012 on 505 men in Cardinal Tien Hospital, Taipei, Taiwan. ([11] Another prospective study reported that higher midlife serum DHT levels were associated with an increased risk of BPH. [12]

In present work, the comparison between changes in voiding symptom, change in PVR and serum DHT conc. According to dose of solifenacin and duration of therapy produced no significant differences between the use solifenacin +α-blocker and α-blocker alone. This may prove that the effect of solifenacin on serum DHT level was no correlation ship among them. This results similar to *Novara G. et al.* in 2006. [13]

In the present study a strong direct and significant relationship between storage symptom, voiding symptom and total IPSS with DHT level for men who treated with solifenacin +α-blocker than men who take α-blocker alone(The potential effects of DHT on remaining OAB of BPH may well be indirect). Additional large studies are needed to confirm these preliminary results. However, differences in the strength and the statistical significance level of this relationship were observed. These differences may originate from effect of solifenacin in addition to use of different descriptions to define the examined risk factors and endpoints as well as differences in the characteristics of the examined populations, in addition to the anticholinergic agents contribute to improve storage and voiding symptoms through the blockade of muscarinic receptors on the smooth muscle, they may be effective to control remaining OAB symptoms after α1-blockers mono therapy. The results of this present study concerning Favilla V. *et al* study in 2010.[14]

The present study clarified non-significant differences between PVR of solifenacin +α-blocker and prostate size. The results of the present study agreed with Agrawal C. S.*et al* in 2008.[15]

Conclusions

Serum PSA and DHT can be used to predict effect of solifenacin to control remaining OAB symptoms of the BPH after α1-blockers monotherapy. The relationship between PSA level and prostate size is probably the most natural reason for the correlation of urinary symptoms and serum PSA level. Also positive relationship was found between prostate size, serum DHT concentration and serum PSA level. While inverse relationship was found between the effect of solifenacin on BPH patients after α1-blockers mono therapy and both serum PSA and serum DHT concentrations.

Recommendations

1- To conduct a large study sample that represents the community to find out the efficacy of solifenacin in patients with BPH in our country.

2- To other researcher to find out the effect of solifenacin on urethral sphincter and urinary bladder morphology.

3- To study the effect of other α1-blocker and anticholinergic drugs on BPH patients.

References

4- Parsons JK, Kashefi C. Physical activity, benign prostatic hyperplasia, and lower urinary tract symptoms. Eur Urol 2008;53:1228-35.

5- Kok ET, Schouten BW, Bohnen AM, Groeneveld FP, Thomas S, BoschJL. Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men: the Krimpen Study. J Urol 2009;181:710–6.

6- Thienpont LM , Van Uytfanghe K , Blincko S et al . State-of-the-art serum testosterone measurement by isotope dilution-liquid chromatography-tandem mass spectrometry . Clin Chem 2008 ; 54 : 1290 – 7

7- Nishiyama T , Hashimoto Y , Takahashi K . The infl uence of androgen deprivation therapy on dihydrotestosterone levels in the prostatic tissue of patients with prostate cancer . Clin Cancer Res 2004 ; 10 : 7121 – 6

8- Ko Y, Malone DC, Armstrong EP"Pharmacoeconomic evaluation of antimuscarinic agents for the treatment of overactive bladder".Pharmacotherapy (Dec2006). 26 (12):1694-702

9- Chapple CR, Cardozo L, Steers WD, Govier FE. Solifenacin significantly improves all symptoms of overactive bladder syndrome. Int J Clin Pract 2006; 60: 959–6

10- Homma Y., Araki I., Igawa Y. et al., "Clinical guideline for male lower urinary tract symptoms," International Journal of Urology, vol. 16(2009):775–790

11- Yoshida M. , Inadome A., Nagata T..et al, The efficacy and safety for the combination therapy with tamsulosin hydorchloride and solifenacin succinate in benign prostatic hyperplasia patients with overactive bladder," Japanese Journal of Urological Surgery, vol. 21, (2008):603-611

12- Naoya Masumori, Taiji Tsukamoto, and Masaharu Aoki et.al The Add-On Effect of Solifenacin for Patients with Remaining Overactive Bladder after Treatment with Tamsulosin for Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Obstruction, . Hindawi Publishing Corporation Advances in Urology Volume 2010, Article ID 205251, 5 pages

13- Kaplan S.A.,.McCammon K, Fincher R., et.al, "Safety and tolerability of solifenacin add-on therapy to α-blocker treated men with residual urgency and frequency," Journal of Urology, vol. 182, no. 6,(2009) :2825–2830

14- Liao CH, Li HY, Chung SD, et.al. Significant association between serum dihydrotestosterone level and prostate volume among Taiwanese men aged 40-79 years. Aging Male. Mar;15(1):(Mar 2012):28-33

15- Trifiro MD, Parsons JK, Palazzi-Churas K, et. al: Serum sex hormones and the20-year risk of lower urinary tract symptoms in community-dwelling older men. BJU Int. ; 105(2010):1554-1559

16- Novara G, Galfano A, Ficarra V,et.al. Anticholinergic drugs in patients with bladder outlet obstruction and lower urinary tract symptoms: a systematic review. Eur Urol 50(2006):675-83

17- Favilla V, Cimino S, Castelli Tet.al. Relationship between lower urinary tract symptoms and serum levels of sex hormones in men with symptomatic benign prostatic hyperplasia. BJU Int106(11)(. 2010 Dec):1700-3.

18- Agrawal C. S., Chalise P. R., and Bhandari B. B., "Correlation of prostate volume with international prostate symptom score and quality of life in men with benign prostatic hyperplasia," Nepal Medical College Journal, vol. 10, no. 2(2008):104–107