World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

THE RELATIONSHIP BETWEEN SERUM SEX HORMONES WITH PROSTATIC VOLUME

[1]*Dr. Othman Jasim Mohammed Alzaidy, [2]Dr. Ali Kamal M. Sami and [3]Dr. Diar Hameed Bajalan

[1,2,3]M.B.Ch.B, F.I.C.M.S. (Urology).
[1*] Iraq - Diyala - Health Directorate - Baquba Teaching Hospitial.

***Corresponding Author: Dr. Othman Jasim M. Alzaidy**
M.B.Ch.B, F.I.C.M.S. (Urology), Iraq - Diyala - Health Directorate - Baquba Teaching Hospitial.

Article Received on 25/02/2019 **Article Revised on 16/03/2019** **Article Accepted on 06/04/2019**

ABSTRACT

Background: Previous epidemiologic investigations of the associations of sex-steroid hormones and benign prostatic hyperplasia have focused on predominately American-European populations. The objective of this study was to evaluate potential associations of body mass index and endogenous sex-steroid hormones with prostate volume in a population-based sample of Iraqi men, ages 13–89 yr. **Aim of study:** To describe relationship between prostate volume with: age, body mass index, serum prostatic specific antigen, Dihydrotestosterone, estradiol, testosterone and progesterone. **Patients and method:** Eighty patients have been selected from May 2012 to April 2013 in Sulaimanyah teaching hospital, they were divided into eight groups of 10(patients) each, according to their age. All groups were sent for the following: serum prostatic specific antigen, serum testosterone, serum dihydrotestosterone, serum progesterone, serum estradiol and body mass index were calculated for them, prostate volume were measured by abdominal ultrasound, but trans-rectal ultrasound of prostate volume were not done. (Any patient suspected for CA-prostate excluded after sending for serum prostatic specific antigen and digital rectal examination which was done in any suspected patient). **Results:** It was found that prostate volume(range from 14-65g)is directly related to increase in age(range from 13-89yrs), also increase in body mass index(which range from 15.7-30.9) is independently related to increase in prostate volume, also increase in serum estradiol (range from20-50pg/ml) is related to increase in prostate volume, increase in prostate volume is related to increase in serum prostatic specific antigen(range 0.22-4.2ng/ ml),while it is related to decrease in serum testosterone (range 2.5-10 ng/ml), serum dihydrotestosterone (range21-246pg/ml) and serum progesterone (range 20-92pg/ml). **Conclusion:** The natural history of BPH reflects both pathologic and clinical sequelae of cumulative exposures to a complex of sex-steroid hormones, growth factors, and binding proteins. The Sulaimanyah men's health study of Iraqi men highlights the importance of age and body composition and the hormonal determinants of prostate volume. In our research we found that our result is similar to other researches done in other centers, also our study is compatible with other researches in making basic information ground for evaluation of benign prostatic hyperplasia.

KEYWORDS: Sex-steroid hormones; benign prostatic hyperplasia; epidemiology; prostate volume.

Abbreviations
BMI: Body mass index
PSA: Prostatic specific antigen
DHT: Dihydrotestosterone
E_2: Estradiol
T: Testosterone
PRG: Progesterone
U/S: Ultrasound
DRE: Digital rectal examination
BPH: Benign prostatic hyperplasia
UTI: Urinary tract infection
AR: Androgen receptor
PUG: Periurethral gland
EGF: Epidermal growth factor
KGF: Keratinocyte growth factor
IGFs: Insulin like growth factors
TGF-β: Transforming growth factor-β
HSD: Hydroxysteroid dehydrogenase
SHBG: Sex hormone binding globulin
KLK_3: Kallikrein
TR: Testosterone receptor
DNA: Deoxyribonucleic acid
ER: Estrogen receptor
NPR: Normal prostate

INTRODUCTION

Prostate

The prostate is a compound tubuloalveolar exocrine gland of the male reproductive system,[1][2] the prostatic urethra developed from urogenital sinus(endodermic origin), the glandular epithelium develop from endoderm cells, mesenchyme differentiate from endoderm cell then differentiate to dense stroma and smooth muscle of prostate, condensation of mesenchyme, urethra, wolffian ducts gives rise to the adult prostate gland at 9th weeks of gestation.[3] The normal weight 18gm; 3cm in lengh, 4cm in width, 2cm in depth,[4] slightly larger than a walnut,[5] the prostatic urethra merge with two ejaculatory ducts. The prostate divided by zone to peripheral zone, central zone, transitional zone, anteriofibromuscular zone (stroma).[6] It does not have capsule,[7] the idea of zones first was proposed by" Mc Neal" in 1968.[8]

By lobes divided to median lobe and two lateral lobes.[8] Function of the prostate is to secrete a slightly alkaline fluid, milky or white in appearance,[9] helps to neutralize the acidity of vaginal tract.[10] Smooth muscle help expel semen during ejaculation.[3]

PATIENTS AND METHOD

Data entry and analysis

Each returned questionnaire was given an identity number (ID). Prior to data entry and analysis, the questions of study were coded. The data was entered into a Microsoft Excel Spreadsheet, after data cleaning; the data was transported into SPSS (Statistical Package for the Social Sciences-verstion 21.0) package software program for statistical analysis.

Descriptive statistics (means and standard deviations) were calculated for all variables, as well as correlation between variable were founded by using person correlation.

Eighty patients have been selected from May 2012 to April 2013 in Sulaimanyah teaching hospital divided into eight group of 10(patients), according to their age. All group were sent for the following: serum prostatic specific antigen, serum testosterone, serum Dihydrotestosterone, serum progesterone, serum estradiol and body mass index were calculated for them, prostatic volume were measured by abdominal ultrasound, but trans-rectal ultrasound of prostatic volume were not done. (Any patient suspected for CA-prostate excluded after sending for serum prostatic specific antigen and digital rectal examination which was done in any suspected patient).

The following table has been showing age and group of patients:

Group	Group1	Group2	Group3	Group4	Group5	Group6	Group7	Group8
Age	10-19y.	20-29y.	30-39y.	40-49y.	50-59y.	60-69y.	70-79y.	80-89y.

Prostate volumes were measured by abdominal ultrasound (Siemens, Philips), Ultrasonists did measurement prostate volumes of all patients accordingly, each patient has only one reading by the following formula:

Prostate volume formula in (cc or g) = {length x depth x width} x 0.53

All investigations of serum sex hormones were done at morning, 48hr sex activity before investigations were not stopped.

Our investigation by methods of enzymatic, hormonal, biochemical and infectious agent detection and testing:

1- Chemiluminescence / ultra sensitive method, by chemical reaction results in illumination of color light for detection. Like PSA.

2- ELFA/ Enzyme linked fluorescent assay / also ultra sensitive way for all of above detection.

3- ELIZA / Enzyme Linked Immunosorbent Assay / common use in hormonal assessment but less sensitive and specific than ELFA. Machines are:

1/ Vidas and Mini Vidas machine by biomerieux manufacturer (ELFA technique). 2/ Advia Centaur Siemens analyzer by Siemens manufacturer (immunoassay: chemiluminescent technique).

RESULT

The following table has been showing summery of our results and significance:

Variables		Prostate size in Abdominal U/S
Age	Pearson Correlation	0.861
	Significant	< 0.001
S.PSA	Pearson Correlation	0.508
	Significant	< 0.001
BMI	Pearson Correlation	0.443
	Not Significant	< 0.001
S. Testosterone	Pearson Correlation	-0.895
	Significant	< 0.001
S.DHT	Pearson Correlation	-0.794
	Significant	< 0.001
S. Estradiol	Pearson Correlation	0.487
	Significant	< 0.001
S. Progesterone	Pearson Correlation	-0.536
	Significant	< 0.001

The data for 80 cases were analyzed. The mean case age was 49.41years (range 13-89).

Descriptive statistics

	Minimum	Maximum	Mean	Std. Deviation
age	**13**	**89**	**49.41**	**22.94**

	Minimum	Maximum	Mean	Std. Deviation
Prostatic size in U/S	**14**	**65**	**32.75**	**14.54**

The data for S.PSA of 80 cases were analyzed. The mean was 1.45(range0.22-4.2).

	Minimum	Maximum	Mean	Std. Deviation
S.PSA	0.22	4.2	1.45	0.894

The data for BMI of 80cases were analyzed. The mean case BMI was 24.17 and (range 15.7-30.9).

	Minimum	Maximum	Mean	Std.Deviation
BMI	15.7	30.9	24.17	2.82

The data for S.T of 80cases were analyzed. The mean was 6.32 and (range 2.5-10).

	Minimum	Maximum	Mean	Std. Deviation
S.T	2.5	10	6.32	2.093

The data for S.DHT of 80 cases were analyzed. The mean was 145.26(range 21-246).

	Minimum	Maximum	Mean	Std. Deviation
S.DHT	21	246	145.26	75.54

The data for S.E2 of 80 cases were analyzed. The mean case S.E2 was 31.16 and (range 20-50).

	Minimum	Maximum	Mean	Std. Deviation
S.E2	20	50	31.16	7.114

The data for S.PRG of 80 cases were analyzed. The mean was 54.26(range20-92).

	Minimum	Maximum	Mean	Std. Deviation
S.PRG	20	92	54.26	15.08

DISCUSSION

In a population-based study, we assessed the nature of the interrelationships of epidemiologic risk factors and endogenous sex-steroid hormones with prostate volume in Iraqi men. Most of the available literature describing endocrine associations in BPH was based on Caucasian populations. After adjustment for age and BMI, increases in prostate volume were independently associated with increases in BMI, also has been showing in study of "Ted A Skolarus Kathleen Y Wolin, Robert L Grubb III-2007".[102]

Increases in prostate volume were marginally associated with increases in the serum levels of estradiol hormones, in particular androgens and estrogens, are thought to play major roles in the development of BPH, but the precise mechanisms by which each contributes to this process remain unclear. Testosterone and its potent intra-prostatic metabolite dihydrotestosterone (DHT) stimulate prostatic growth and are responsible for the maintenance of secondary sex characteristics. However, as noted by Lagiou and colleagues,[103] the epidemiologic evidence implicating testosterone in the pathogenesis of BPH was conflicting. Potential reasons for discrepancies may be attributed to observations limited to hospitalized patients and inappropriate comparison groups, inadequate control of confounding risk factors, or lack of standardization in diurnal blood sampling and assay methodology.[104] the marginal significance of findings in multivariable analyses suggested that the cumulative lifetime level of T and E2, in conjunction with decreased levels of SHBG, were predictive of risk of BPH. It has been demonstrated that DHT is the more potent androgen metabolite, and after binding to the androgen receptor (AR), the DHT-AR complex stimulates the transcription of a cascade of androgen responsive genes, inspite of decreasing serum DHT with advancing age is responsible for pathogenesis of BPH, as our study has been showing decrease in S.DHT with increase in prostate volume, also same result has been showing in study of "Culle Carson III and Roger Rittmaster" and " Ding VD Moller DE Feeny WP Diodolka V Nakhla AM Rhodes L Rosers W Smith RG-1998".[105]

The aging prostate is subjected to the hormonal effects of stromal and epithelial interactions and of the relatively increasing ratio of estrogens to androgens. Although our initial analyses indicated significant correlations of age-adjusted prostate volume with E2, in that, when serum E2 was increased, prostate volume also was increased. Also has been showing in study of" Roger Mason (Natural Prostate Health)-1993".[106]

Two epidemiologic studies have not demonstrated any relationship between serum IGFs levels and prostate volume,[107] or histologically confirmed BPH.[108]

The associations between prostate volume and endocrine factors observed in this study were not fully explained by confounding due to age, tobacco or alcohol consumption, or obesity, although age and BMI served as independent risk factors for prostatic enlargement. Higher levels of BMI, particularly in excess of 25 kg/m2 were predictive of increased prostate volumes in the Iraqi men. Approximately 52.5% of our study population was classified as being overweight (BMI >25 kg/m2), as compared to two other studies which (BMI was 30 kg/m^2.[109][110] Increased BMI was associated with larger prostate volumes. In Sulaimanyah men's health study Iraqi men, levels of E2 increased with increasing BMI, where as serum levels of T declined, also same result for S.T has been showing in study of "Kazuyoshi Shigehara and Mikio Namiki- 2011".[111]

Alcohol consumption and tobacco use are potential risk factors for BPH and have been postulated to alter levels of serum sex-steroid hormones. As noted by several authors,[112][113][114] most previous epidemiologic studies of risk factors for BPH have shown an inverse association of BPH with use of alcohol and cigarette smoking.

We are not observed in Sulaimanyah men's health participants that current and former alcohol drinkers had smaller prostates than never drinkers, while current smokers had smaller prostates than never smokers. However, the observed associations of cigarette smoking and alcohol drinking with prostate volume disappeared in multivariable analyses.

This study has some limitations. The cross-sectional nature of this study design did not permit evaluation of temporal trends based on repeated observations in subjects. Longitudinal studies of the associations between endogenous sex steroids, and prostate volume are needed to assess accurately the impact of these factors on the aging prostate.[115]

There was the potential for selection bias, as only half the eligible subjects completed the clinical phase of the Sulaimanyah men's health study protocol. An evaluation of potential selection bias in the Sulaimanyah men's health study observed that the participants tended to be younger and experienced more urologic symptoms when compared with non participants. [116] Selection bias would have occurred if nonparticipants differed from participants in the distribution of risk factors and hormonal profiles in relation to prostate volumes, which could not be evaluated. Finally, our most parsimonious multivariable model explained only few of the variance in prostate volume, suggesting that unmeasured growth factors or interactive lifestyle (e.g., dietary) and genetic risk factors play potentially a facilitating role in the induction and maintenance of BPH in Iraqi men.

Our study has been showing negative correlation between S.PRG and prostate volume; mean prostate volume with advancing age was increased, while S.PRG was decreased, also same result has been showing in study of "Buck, A.C. (Phytotherapy for the Prostate)-1996 ".[117]

Our study has been showing positive relationship between S.PSA and prostate volume; mean with increase in prostatic volume S.PSA was increased, also has been showing in study of "Ted A Skolarus Kathleen Y Wolin, Robert L Grubb III-2007".[102]

In summary, the present study observed that serum levels of E2, T, DHT, and PRG possibly were associated with increased prostatic volume, while BMI in our study was

not significantly associated with increased prostate volume. Prostatic enlargement in Iraqi men may involve complex interrelationships of sex-steroid hormones, increasing age, and BMI. Future longitudinal studies are needed to fully describe the temporal relationships of endogenous sex-steroid hormones, IGFs and potential interactions with epidemiologic and genetic risk factors in the natural history of increasing prostatic volume associated with BPH.

CONCLUSION

The natural history of BPH reflects both pathologic and clinical sequelae of cumulative exposures to a complex of sex-steroid hormones, growth factors, and binding proteins. The sulaimanyah men's health study of Iraqi men highlights the importance of age and body composition and the hormonal determinants of prostate volume.

In our research we found that our result is similar to other researches done in other centers, also our study is compatible with other researches in making basic information ground for evaluation of benign prostatic hyperplasia.

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