THE RELATIONSHIP BETWEEN SERUM SEX HORMONES WITH PROSTATIC VOLUME

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

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

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 volumerange 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
E2: 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
KLK3: 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, 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. The normal weight 18gm; 3cm in length, 4cm in width, 2cm in depth, slightly larger than a walnut, the prostatic urethra merge with two ejaculatory ducts. The prostate divided by zone to peripheral zone, central zone, transitional zone, anteriofibromuscular zone (stroma). It does not have capsule, the idea of zones first was proposed by Mc Neal” in 1968.

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

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-version 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:

<table>
<thead>
<tr>
<th>Group</th>
<th>Group1</th>
<th>Group2</th>
<th>Group3</th>
<th>Group4</th>
<th>Group5</th>
<th>Group6</th>
<th>Group7</th>
<th>Group8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>10-19y.</td>
<td>20-29y.</td>
<td>30-39y.</td>
<td>40-49y.</td>
<td>50-59y.</td>
<td>60-69y.</td>
<td>70-79y.</td>
<td>80-89y.</td>
</tr>
</tbody>
</table>

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 summary of our results and significance:

<table>
<thead>
<tr>
<th>Variables</th>
<th>Prostate size in Abdominal U/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Pearson Correlation 0.861</td>
</tr>
<tr>
<td></td>
<td>Significant &lt; 0.001</td>
</tr>
<tr>
<td>S.PSA</td>
<td>Pearson Correlation 0.508</td>
</tr>
<tr>
<td></td>
<td>Significant &lt; 0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>Pearson Correlation 0.443</td>
</tr>
<tr>
<td></td>
<td>Not Significant &lt; 0.001</td>
</tr>
<tr>
<td>S. Testosterone</td>
<td>Pearson Correlation -0.895</td>
</tr>
<tr>
<td></td>
<td>Significant &lt; 0.001</td>
</tr>
<tr>
<td>S. DHT</td>
<td>Pearson Correlation -0.794</td>
</tr>
<tr>
<td></td>
<td>Significant &lt; 0.001</td>
</tr>
<tr>
<td>S. Estradiol</td>
<td>Pearson Correlation 0.487</td>
</tr>
<tr>
<td></td>
<td>Significant &lt; 0.001</td>
</tr>
<tr>
<td>S. Progesterone</td>
<td>Pearson Correlation -0.536</td>
</tr>
<tr>
<td></td>
<td>Significant &lt; 0.001</td>
</tr>
</tbody>
</table>

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

Descriptive statistics

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>13</td>
<td>89</td>
<td>49.41</td>
</tr>
<tr>
<td></td>
<td>22.94</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>prostate size in U/S</td>
<td>14</td>
<td>65</td>
<td>32.75</td>
</tr>
</tbody>
</table>

The data for S.PSA of 80 cases were analyzed. The mean was 1.45 (range 0.22-4.2).

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.PSA</td>
<td>0.22</td>
<td>4.2</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td>0.894</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>15.7</td>
<td>30.9</td>
<td>24.17</td>
</tr>
<tr>
<td></td>
<td>2.82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.T</td>
<td>2.5</td>
<td>10</td>
<td>6.32</td>
</tr>
<tr>
<td></td>
<td>2.093</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.DHT</td>
<td>21</td>
<td>246</td>
<td>145.26</td>
</tr>
<tr>
<td></td>
<td>75.54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.E2</td>
<td>20</td>
<td>50</td>
<td>31.16</td>
</tr>
<tr>
<td></td>
<td>7.114</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The data for S.PRG of 80 cases were analyzed. The mean was 54.26 (range 20-92).

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.PRG</td>
<td>20</td>
<td>92</td>
<td>54.26</td>
</tr>
<tr>
<td></td>
<td>15.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 II-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, 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. 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, in spite 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”.

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".

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

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/m2). 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”.

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, 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.

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. 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".

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”.

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.

REFERENCES
32. David KG., Dingmans E, Freud J, Laqueur E (1935). Über krystallinisches männliches Hormone aus Hoden (Testosterone) wirksamer ales aus harn Oder aus Cholesterin bereit. (In German)
39. Prostate Enlargement - What Causes The Prostate To Enlarge. E health MD.
42. References and further description of values are given in image page in Wikimedia Commons at Commons: File: Estradiol during menstrual cycle.png.
53. Total amount multiplied by 0.022 according to 2.2% presented in: Wu CH, Motohashi T, Abdel-Rahman HA, Flickinger GL, Mikhail G (August 1976). "Free and protein-bound plasma estradiol-17 beta during


111. Gann PH, Hennekens CH, Longcope C, Verhoek-Offedahl W, Grodstein F, Stampfer MJ. A prospective study of plasma hormone levels,
nonhormonal factors, and development of benign prostatic hyperplasia. Prostate, 1995; 26: 40–49.


