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Histological and Immunochemical Characteristics of Benign Prostatic Hyperplasia in the Sudanese Patients

KEYWORDS: Benign prostatic hyperplasia, Prostate histology, Histopathology, Prostate specific antigen.

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ABSTRACT ***Background and objective****: Benign prostatic hyperplasia (BPH) is one of the most common condition affecting men over 40 years and may be complicated by urine retention. The degree of hyperplasia seems to vary due to race. Little is known about the benign prostatic hyperplasia in Sudanese population. Accordingly, this study investigates benign prostatic hyperplasia complicated by urine retention among Sudanese, using, histological and immunochemical means.* ***Methodology*** *: Hospital based, descriptive study consisted of 60 cases, divided into clinical and cadaveric groups. The clinical group of 50 cases were above the age of 40 years, who presented to Urology Department ,Omdurman Teaching Hospital. They were diagnosed as benign prostatic hyperplasia with urine retention. The cadaveric group of 10 cases, was selected from Omdurman Teaching Hospital, Department of Forensic Medicine - Mortuary. The prostates of the two groups were processed histopathological study. The findings were analyzed by using Statistical Package for Social Sciences (SPSS) to compare the results in the same group and between the two groups.* ***Results****: showed, the age was found to be a risk factor for benign prostatic hyperplasia. Histopathologically, this study revealed; the ratio of smooth muscle of hyperplastic prostate stroma was about 40% and stroma / epithelium + glandular lumen ratio was 1/1 in both groups. No difference in the percentage of connective, muscular and glandular tissues between the two groups. Immunochemically, in the clinical group, total PSA level was found to be higher in BPH Sudanese patients (mean= 8.75 ng/ml) than what is reported internationally . Free PSA mean value was 2.54 ng/ml and the ratio F/T PSA mean was 27.27%. Total PSA and free PSA increases with age in BPH. Free PSA increases with total PSA. The ratio F/T PSA increases with the free PSA. Free PSA and the ratio of F/T PSA are more accurate in diagnosis of BPH than the total PSA.*
Conclusion*: This study has proved that, the most reliable diagnosis for Sudanese patients with criteria of soft prostate, total PSA less than 8.75ng/ml, free PSA more than 2.5ng/ml and F/T PSA ratio of more than 25%; is benign prostatic hyperplasia. These findings should be considered by the physicians.*

Introduction: From the hundreds species of mammals, only humans and dogs are known to suffer from BPH [1]. Over the age of 40 years, every man has some degree of benign (noncancerous) enlargement of the prostate gland. An enlarged prostate can be caused by either hyperplasia or hypertrophy (both abbreviated BPH). Only one in ten will have obstruction (urine retention) as a result of it [2,3].

The definition for benign prostatic hyperplasia include :- international prostate symptom score (IPSS) of more than seven, prostate size more than 30gms and peak urinary flow rate (Q max) of less than 15ml/s [4].

The age-related prevalence of BPH histology found at autopsy is similar in several countries despite population diversity. Benign prostatic hyperplasia, however, occurs in approximately half of men with presumed histological changes of benign prostatic hyperplasia [5]. In the United States black and white populations have a similar incidence of BPH, although symptoms most likely develop earlier in blacks [6].

Beside older age, other risk factors for benign prostatic hyperplasia are normal androgenic function (testosterone, estrogen) and a positive family history. Possible risk factors include race, geographical location, dietary intake, cigarette smoking, alcohol consumption, male pattern baldness and chronic disease [7,8].

Testosterone which is secreted by leyding cells of the testes, in males, is converted within the prostate to dihydrotestosterone (DHT) by the enzyme 5 α-reductase. This accumulation of DHT in older men encourages the growth of prostate cells [9,10].

In male, estrogen is mainly secreted by adrenal cortex. In the ageing male estrogen plays part in distributing the delicate balance between DHT and local peptide growth factors, and hence increases the risk of BPH. Increased levels of serum estrogens, by acting on the hypothalamus, decrease the secretion of luteinizing hormone-releasing hormone (LHRH) and hence luteinizing hormone (LH) and thereby decrease serum testosterone levels and leads to atrophy of the prostate [10].

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Benign prostatic hyperplasia, as the name implies, is a benign nodular disorder that develops predominantly in the transitional and periurethral zones of the prostate. It is initially fibromuscular, becoming glandulostromal with advancing age. This overgrowth compresses the peripheral zone glands into a false capsule and causes appearance of the typical lateral lobe [10,11,12]. The hyperplastic glands are lined by tall, columnar epithelial cells and a peripheral layer of flattened basal cells. Crowding of the proliferated epithelium results in formation of papillary projection in some glands. The glandular lumina often contain inspissated proteinaceous secretory material, termed corpora amylacea[13]. Elastin and stromal component increase in BPH specially at the base and in the area of the urethra [14]. In benign prostatic hyperplasia there is an increase rate of proliferation but the ratio of proliferating basal cells to secretary cells in the gland is intact compared with normal appearing prostate epithelium [15].

The normal adult prostate contains about 50% stroma, 30% acinar lumens, and 20% epithelium [16]. The ratio of stroma to epithelium increases from 2:1 in the healthy prostate to 5:1 in BPH [17].

Prostate-Specific Antigen is first reported by Wang et.al. (1979)[18]. It is widely used as marker of prostate cancer [19]. Studies by Becker and Lilja (1997) [20] and Zhu et.al (2013) [21], showed that serum contains two distinct forms of PSA: PSA complexed which is attached to a protein molecule called α – Antichemotrypsin and free PSA. Prostate specific antigen (PSA) is synthesized by epithelial cells of the prostate under androgen receptor regulation. It appears at low serum concentrations in healthy men [22,23].

Subsequent studies have shown that free PSA alone or F/T PSA ratio are markers for differentiation between benign prostatic hyperplasia and prostate cancer when PSA is in range of 4 ng/ml to 10 ng/ml [24, 25, 26]. As the amount of free PSA makes up to more than 25% of the total PSA, prostate cancer is unlikely. If the free PSA is below 10% of the total PSA the chance of prostate cancer is much higher and the biopsy should be useful l [27]. The average amount of free PSA usually varies between approximately 0.00 – 3. 00 ng/ml depending on the disease state [25].

PSA could be elevated in many conditions related to the prostate. These include Prostate Cancer, Benign prostatic Hyperplasia (BPH), Prostatitis, Prostatic trauma and manipulation (DRE), Prostatic infarction, Recent sexual activity and Urological procedures (Cystoscopy and urinary catheterization) [28].

Materials and Methods: This study is an observational cross-sectional hospital-based study. The study was conducted in the Department of Surgery , Omdurman Teaching Hospital, Omdurman - Sudan, for clinical group, and the cadaveric group specimens were collected from Omdurman Teaching Hospital, Department of Forensic Medicine-Mortuary, between January 2009 - May 2012 .

The population targeted for the clinical group was, all male Sudanese patients above the age of 40 years, who presented to Urology department, diagnosed as benign prostatic hypertrophy with urine retention and who underwent Transvesical prostatectomy. This include fifty patients (clinical group). While the cadaveric groups include ten cadavers.

Digital rectal examination was performed by the urologist doctor to evaluate: size, shape, consistency and surface of the prostate. If consistency was hard or total PSA was more than 4 ng/ml prostatic needle biopsy was done. Cystoscopy: for evaluation of prostate, abnormal structures and urethral patency. For cadaveric group: Transabdominal incision performed above the symphysis pubis. One deep incision from the skin up to the urinary bladder was made. Prostate removed with scalpel, knife and scissor, together with its false capsule. After removal, the prostate was cleaned from false capsule. The whole prostate was removed by Transvesical prostatectomy (TVP) and immediately embedded in 10% Formalin. Its volume is at least 20 times the volume of the prostate. The collected prostates were sent to Ibn Sina Specialized Hospital, Histopathology Department Laboratory, for histopathological studies. From each prostate seven core biopsies were obtained as shown in (Table 1) (Figure 1).

The core biopsies were labeled and embedded in formalin 10% for at least 24 hours, then processed in Automatic Tissue Processor (Carrousel-type, SAKURA) for overnight. After that they were embedded in paraffin to make blocks for sliding. Each block was fixed on wood chuck. From each core biopsy three sections of 5µ were obtained by microtome, fixed on clean slide without adhesive and left to dry for at least 30minutes .The slides were arranged on racks and left in uvam for at least 30 minutes at 65o..

Fourteen sections from each prostate were stained by haematoxylin and eosin (H&E) and seven sections by Masson's Trichrome Stain (to differentiate between collagen and smooth muscle) for Histopathological study. The slides were assessed by double blind subjective assessment in all prostate sections. The results obtained by H&E and Masson's Trichrome Stains were compared. Following examination and assessment ,prostate sections were photographed using Olympus microscope model U-MD010B with microscope digital camera DP 25.

Under complete aseptic condition a sample of five ml of blood was drawn by venipuncture from all clinical group subjects to measure total and free PSA . The samples were collected in EDTA coated tubes and were centrifuged immediately for plasma collection , then frozen and measured for total and free PSA using AIA-PACK ucPA design. In this study kits used for free and total PSA were vended by BioSafe laboratories.

Table (1) and Figure (1): Show, number of core biopsies in relation with its site taken from the prostate.

Number of the core biopsy	Site of the core biopsy in the prostate
1	At the base

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2	Left transverse ,above the level of enterers of the ejaculatory duct in the prostatic urethra
3	Left posteriotransverse ,above the level of entrance of the ejaculatory duct in the prostatic urethra
4	Posterior ,above the level of entrance of the ejaculatory duct in the prostatic urethra
5	Right posteriotransverse ,above the level of entrance of the ejaculatory duct in the prostatic urethra
6	Right transverse ,above the level of entrance of the ejaculatory duct in the prostatic urethra
7	At the apex

Data analysis:
The obtained data as well as results were analyzed using the statistical software, Statistical package for Social Sciences (SPSS) version 15.

The test for significance was person correlation for means and chi square test (x2) where appropriate p value of 0.05 and less was considered statistically significant.

Ethical consideration: The study was approved by the biomedical ethical committee, college of Medicine , University of Bahri, Sudan. A consent was obtained from each of the patients who had participated in this study. The nature, aims and the procedures of this study were firstly explained to the participants. They were also assured that their confidentiality and safety will not be damaged. The patients were also assured that the participation in this study was voluntary, and that their care would not be affected any way in case they refused or quitted from study at any phase.

Results: In this descriptive retrospective study, all prostates of the clinical group, involved in this study were soft by digital rectal examination (DRE).

Table (2), shows the description of age in the clinical and cadaveric groups. The age of the clinical group ranged between 59-92 years. The mean was 74.5 years ±8.88(Mean ± STD) . Only two (4%) of the patients were in the range between 50-59 years, 15(30%) their age between 60-69 years, 17(34%) their age range between 70-79 years, 11(22%) their age between 80-89 years and five (10%) between 90-99 years. For the cadaveric group, their age ranged between 45-85 years with mean and STD of 65 years ±13.28. Two (20%) range between 40-49 years, four (40%) between 60-69 years, two (20%) between 70-79 years and two (20%) between 80-89 years. The mean difference test showed a significant difference in the age between the clinical and cadaveric groups (p = 0.007).

The total PSA level was demonstrated among the clinical group; their mean value ± STD was found to be 8.75 ng/ml ± 9.11, ranged between 1.1-33.4ng/ml (table 3).Those cases which have value less than 4 ng/ml were 21(42%), more than this value were 29(58%).while those which have value less than 10 ng/ml were 37(74%), 13(26%) more than 10 ng/ml (table 4).

The mean value ± STD of free PSA for clinical group was 2.54ng/ml ± 2.92, ranged between 0.2-13ng/ml (table 3). 20(40%) have value less than 1ng/ml , more than this value were 30(60%).while those which have value less than 2ng/ml were 29(58%), 21(42%) more than 2ng/ml (table 5).

While for ratio of free/total PSA for clinical group; the mean value was 27.27% ± 6.16, ranged between 9.4% - 38.9% (table 3).Those cases which have a ratio of less than 25%were 9(18%), more than this value were 41(82%) (Table 6).

Table (7) shows 29 cases in clinical group (58% of total cases) who have a total PSA value of more than 4.00 ng/ml with their free PSA in ng/ml and ratio of free/total PSA in percentage. Out of them, 13(44.83%) have total PSA more than 10 ng/ml and 18(62.07%) have total PSA more than 8.75 ng/ml.

No case has free PSA less than 2.5 ng/ml although their total PSA were more than 8.75 ng/ml. There were two cases which have ratio free/total PSA less than 25% with their total PSA more than10 ng/ml. There was only one case which have ratio free/total PSA less than 25% with their total PSA between 4 - 10 ng/ml.

Regarding the histopathological findings after comparing the results obtained from slides stained by rapid haematoxylin and eosin (H&E) and Masson's Trichrome; the average value of mean ±STD for connective, muscular and glandular tissues for the clinical and the cadaveric groups are represented in Tables (8); the mean percentage ±STD among the clinical group were 28.42% ± 6.50, 18.97% ± 3.86 and 52.61% ± 9.78 for connective tissue, muscular tissue and glandular tissue respectively. They are 30.8% ± 0.76 (connective tissue), 20.53% ± 1.86 (muscular tissue) and 48.67% ± 2.08 (glandular tissue) for the cadaveric group. The ratio of smooth muscle of hyperplastic stroma is about 40 % and the stroma/ epithelium+ glandular lumen ratio was 1/1 in both groups. The mean difference test between the groups showed no significant difference for connective, muscular and glandular tissues (p. value = 0.255, 0.218and 0.213 respectively).

Regarding correlation coefficient between age, PSA levels and histological results detected among each selected group, the simple regression lines are shown in figures (2) to (12).

Among the clinical group; a weakly positive correlation with PSA levels was shown in figures (2 [a]) and (2 [b]) (r = 0.369, p = 0.008 for total PSA), (r = 0.327, P = 0.020 for free PSA), and for some extend with F/T PSA (r = 0.275 p = 0.054) figure (2 [c]).

Non-significant correlation between age and histological findings was shown in figures (3 [a]), (3 [b]), and (3 [c]) (r = 0.037, p = 0.799 for connective tissue, figure (3 [a]); r = 0.002, p = 0.990 for muscular tissue, figure (3 [b]) and r = 0.024 , p= 0.870 for glandular tissue, figure (3 [c]).

There was strongly positive correlation between total PSA and free PSA (r = 0.969, p =0.000), figures (4 [a]). No significant correlation between total PSA with free/total PSA and histological findings as shown in figures (4[b]),(5 [a]),(5 [b])and (5 [c]); (r = 0.275, p = 0.053 for free/total PSA), figure (4 [b]); (r = 0.100, p = 0.491 for connective tissue), figure (5 [a]); (r = -0.027, p = 0.852 for muscular tissue), figure (5 [b]) and(r =- 0.056 , p= 0.702 for glandular tissue), figure (5 [c]).

Free PSA has weak correlation with free/total PSA (r = 0.415, p = 0.003), figure(6 [a]). No significant correlation between free PSA and histological findings as shown in figures (6 [b]),(6 [c]) and (6 [d]); (r = 0.030, p = 0.834 for connective tissue), figure (6 [b]) ;(r = 0.083, p = 0.565 for muscular tissue), figure (6 [c]) and(r =- 0.013 , p= 0.930 for glandular tissue), figure (6 [d]).

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No significant correlation between free/total PSA and histological findings as shown in figures (7 [a]),(7 [b]) and (7 [c]); (r = 0.187, p = 0.194 for connective tissue), figure (7 [a]) ;(r = 0.242, p = 0.090 for muscular tissue), figure (7 [b]) and(r = 0.220 , p= 0.125 for glandular tissue), figure (7 [c]).

Among the cadaveric group, no significant correlation between age and histological findings as shown in figures (8 [a]),(8 [b]) and (8 [c]); (r =- 0.341, p = 0.334 for connective tissue), figure (8 [a]) ;(r = - 0.334, p = 0.345 for muscular tissue), figure (8 [b]) and (r = 0.423 , p= 0.223 for glandular tissue), figure (8 [c]).

Table (2):Age description among clinical and cadaveric groups in Omdurman Teaching Hospital-2009-2012. N=60

Group	Age group	Number	Percent %	Minimum	Maximum	Mean ±STD
Clinical group	40 to 49	0	0.0%	59	92	74.5±8.88
	50 to 59	2	4.0%			
	60 to 69	15	30.0%			
	70 to 79	17	34.0%			
	80 to 89	11	22.0%			
	90 to 99	5	10.0%			
Cadaveric group	40 to 49	2	20.0%	45	85	65±13.28
	50 to 59	0	0.0%			
	60 to 69	4	40.0%			
	70 to 79	2	20.0%			
	80 to 89	2	20.0%			
	90 - 99	0	00.0%			

P = 0.007

Table (3): Total, Free and ratio F/T PSA (mean, minimum, maximum and standard deviation) among clinical group: N=50

	N	Minimum	Maximum	Mean	Std. Deviation
Total PSA	50	1.1	33.4	8.75	9.11
Free PSA	50	0.2	13.0	2.54	2.92
Ratio F/T	50	9.4%	38.9%	27.27%	6.16

Table (4): Frequency of total PSA value among clinical group:

Total PSA (ng/ml)	≤ 2.0	2.1-4.0	4.1-8.0	8.1-10.0	10.1-25.0	≤25.1	Total
N	7	14	11	5	7	6	50

Table (5): Frequency of free PSA value among clinical group:

Free PSA (ng/ml)	≤ 0.5	0.51-1.0	1.1-2.0	2.1-2.5	2.6-6.25	≤6.26	Total
N	10	10	9	4	11	6	50

Table (6): Ratio of free/total PSA in relation with the normal value(25%) for clinical group:

	N	Less	More
Ratio F/T PSA(25%)	50	9(18%)	41(82%)

Table (7): Cases in clinical group who have total PSA more than 4 ng/ml with their free PSA and ratio of free/total PSA. N=29

N0.of case	Total PSA	Free PSA	Free/Total PSA
1	4.2	1.4	33.3%
2	4.6	1.3	28.3%
3	4.6	1.3	28.3%
4	4.7	1.4	29.8%
5	4.8	1.6	33.3%
6	5.1	0.6	11.8%
7	5.2	1.5	28.8%
8	5.5	1.6	29.1%
9	6.7	2.2	32.8%
10	7.2	2.6	36.1%
11	7.9	2.1	26.6%
12	9.2	2.5	27.2%
13	9.2	2.9	31.5%
14	9.3	3	32.3%
15	9.7	2.8	28.9%
16	9.8	2.5	25.5%
17	10.9	2.9	26.6%
18	11	3.2	29.1%
19	11.6	3.1	26.7%
20	12.3	3.6	29.3%
21	12.4	2.8	22.6%
22	18.2	6.7	36.8%
23	19.7	5.8	29.4%
24	27	5.1	18.9%
25	28.3	8.1	28.6%
26	30.2	9.3	30.8%
27	31.1	8.2	26.4%
28	32.2	11	34.2%
29	33.4	13	38.9%

Table (8): Percentage of connective tissue, muscular tissue and glandular tissue among clinical and cadaveric groups: N=60

Tissue	Group	Minimum	Maximum	Mean	STD	P. value
Connective tissue	Clinical	18.29	50.00	28.42	6.50	0.255
	Cadaveric	30.00	32.29	30.80	0.76	
Muscular tissue	Clinical	11.43	26.14	18.97	3.87	0.218
	Cadaveric	18.43	24.00	20.53	1.86	
Glandular tissue	Clinical	30.71	68.57	52.61	9.78	0.213
	Cadaveric	45.71	51.43	48.67	2.08	

Figure (2): Correlation between age (years) and total PSA [a], free PSA [b], F/T PSA [c] among clinical group (N=50)

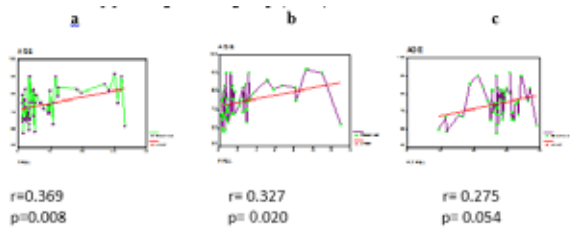

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Figure (3): Correlation between age (years) and connective tissue(A)[a], muscular tissue (B) [b], glandular tissue(C) [c] among clinical group(N=50)

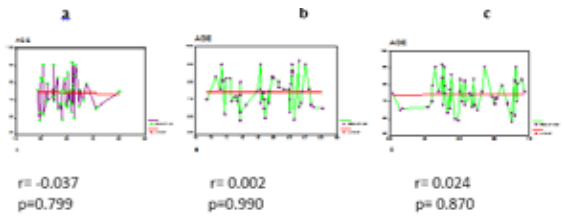

Figure (4): Correlation between total PSA and free PSA [a], F/T PSA [b] among clinical group (N=50)

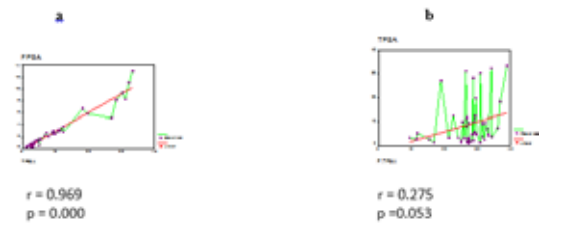

Figure (5): Correlation between total PSA and connective tissue (A) [a], muscular tissue (B) [b], glandular tissue (C) [c] among clinical group (N=50)

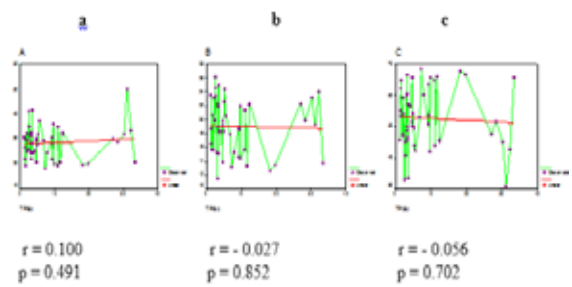

Figure (6): Correlation between free PSA and free/total PSA[a] connective tissue(A) [b], muscular tissue(B) [c], glandular tissue(C)[d] among clinical group (N=50)

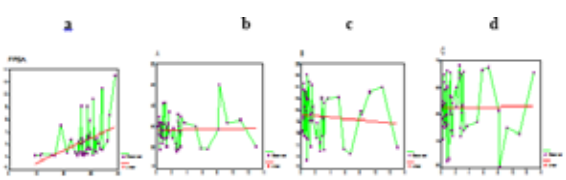

Figure (7: Correlation between free/ total PSA and connective tissue (A) [a], muscular tissue (B) [b], glandular tissue (C) [c] among clinical group. (N=50)

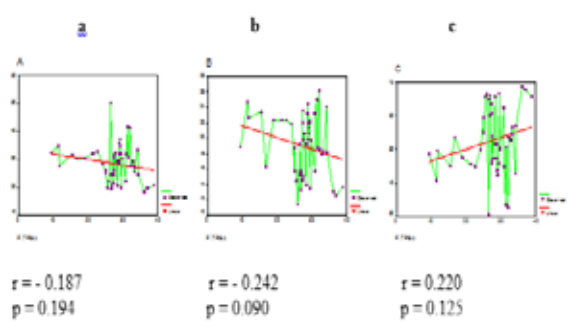

Figure (8) : Correlation between age (years) and connective tissue(A) [a], muscular tissue (B) [b], glandular tissue(C) [c] among cadaveric group. (N=10)

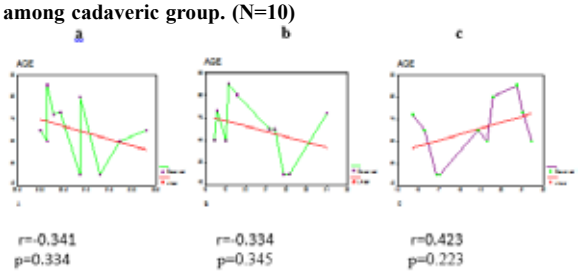

Figure (9) : The histological appearance of benign prostatic hyperplasia. The glands (papillary type) surrounded by fibromuscular stroma is shown here at high magnification. Note the well-differentiated glands with tall columnar epithelial lining cells(secretary cells) resting on basal cells (H&E staining).(× 100)

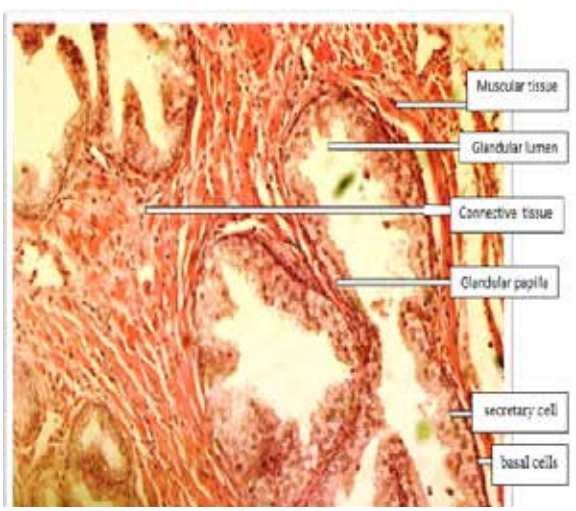

Figure (10): Benign prostatic hyperplasia can involve both glands and stroma, the former is usually more prominent. Here, a large hyperplastic nodule of glands is seen with a small pink concretion (typical of the corpora amylacea seen in benign prostatic glands) appears in the gland just to the left of center (H&E staining).(× 10)

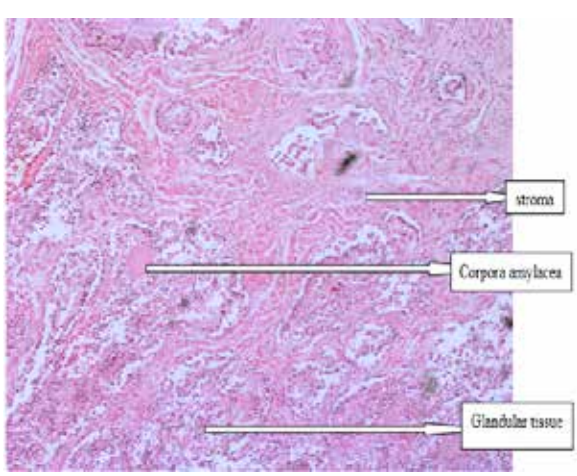

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Figure (11): Benign prostatic hyperplasia. The glands are well-differentiated (cystic type). Prostate has glandular intervening stroma. The small laminated pink concretions within the glandular lumens are known as corpora amylacea (H&E staining)(×100).

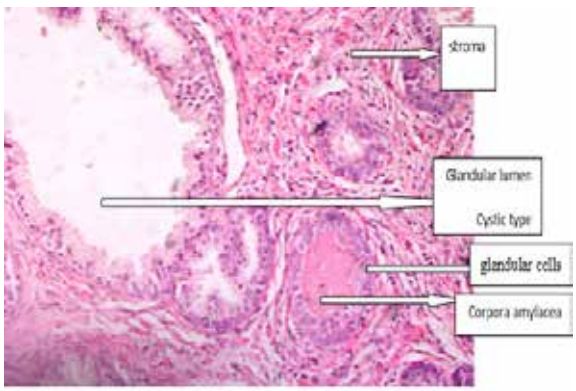
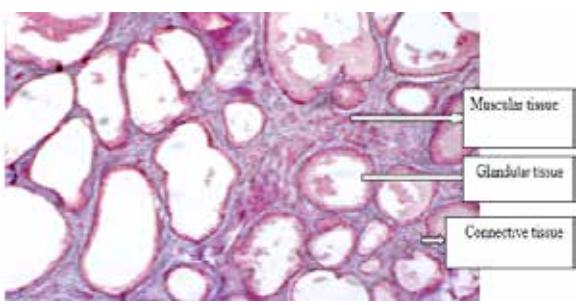


Figure (12): The glands are well-differentiated (cystic type), back to back ,has few glandular intervening stroma. The Cytoplasm and Muscles are stained red but the Collagen fibers and Mucous are blue (Masson's Trichrome stain)(×40).



Discussion: This study investigates benign prostatic hyperplasia (BPH) in Sudanese patients using different parameters: age, serum total and free PSA and their ratio and histopathological findings.

Benign prostatic hyperplasia is the most common disease affecting men of all ethnicities who are older than 40 years of age . Increasing evidence has shown that the prevalence of benign prostatic hyperplasia may differ in ethnic groups [29] It is generally accepted that significant evidence exists in the literature proving that benign prostatic hyperplasia (BPH) is a progressive disease [30].

Many studies were conducted in several parts of the world. There are few studies concerning benign prostatic hyperplasia in men older than 40 years in Sudan.

The mean age of the clinical group was 74.5 years. Most of them are between 70-79 years (as expected - the average life for Sudanese is relatively low). The estimated age of the cadaveric group was 65 years (lower than the clinical group), and there was significant difference in mean between clinical and cadaveric groups due to lower standard of life for the cadaveric group . Those findings demonstrate that, increasing of age is a risk factor for benign prostatic hyperplasia as detected earlier by studies conducted by Abd Elwahab and Osman (2011) [31] Safarinejad (2008) [32].

Zorn, et.al. (2012) [33] summarized that, in general, PSA levels greater than 4 ng/mL are usually considered suspicious. As levels increase above 10.0 ng mL, the probability of cancer increases dramatically. Nevertheless, due to the age-related growth of the prostate, the concept of adjusting the cutoff values based on age has helped reduce unnecessary prostate biopsies in older men to improve early prostate cancer detection. Below are the suggested age-adjusted values based on age and race (Table 9).

Concerning PSA, this study found that, in Sudanese suffering from benign prostatic hyperplasia. The mean value for total PSA, free PSA and ratio PSA were (8.75 ng/ml, 2.54 ng/ml and 27.27%) respectively.

This study, shows that total and free PSA are higher than as predicted internationally. Abd Elwahab and osman (2011) [31] found that, total PSA for benign prostatic hyperplasia cases was 5.5 ng/ml. The ratio of PSA is more precise (82%, more than 25%) than total and free PSA (42% less than 4 ng/ml ; 60%, more than 1 ng/ml) respectively. The present findings are in agreement with Abd Elwahab and Osman (2011) [31], Abdrabo, et. al. (2012) [34].

Table (9):- Age-Specific Reference Ranges for Serum PSA

Age Range (Years)	Asian Americans	African Americans	Caucasians
40 to 49	0 to 2.0 ng/mL	0 to 2.0 ng/mL	0 to 2.5 ng/mL
50 to 59	0 to 3.0 ng/mL	0 to 4.0 ng/mL	0 to 3.5 ng/mL
60 to 69	0 to 4.0 ng/mL	0 to 4.5 ng/mL	0 to 4.5 ng/mL
70 to 79	0 to 5.0 ng/mL	0 to 5.5 ng/mL	0 to 6.5 ng/mL

In this study, as t PSA increases the f PSA increases and after the value of 8.75 ng/ml there was no case of f PSA less than 2.5 ng/ml although there were two cases of ratio PSA less than 25%. This indicates that free PSA is more accurate than the ratio F/T PSA in prediction of benign prostatic hyperplasia if total PSA is more than 8.75 ng/ml. Abd Elwahab and Osman (2011) [31], found that, out of 13 cases of BPH with total PSA more than 10 ng/ml, only three (23.08%) have free PSA less than 2.5 ng/ml although there were five cases (38.46%) of ratio F/T PSA less than 25%.

Concerning the histological findings there was no significant difference between the means of clinical and cadaveric groups for all tissues (i.e. connective ,muscular and glandular tissues). Polat, et al (1998) [35] and Marks, et al (1994) [36], found that, the ratio of smooth muscle of hyperplasia stroma was 40% and the stroma /epithelium + glandular lumen ratio was 1/1. Those were approximately the same results found in this study (ratio of smooth muscle of hyperplasia stroma was 40% and the stroma /epithelium + glandular lumen ratio was 1/1).

The correlation coefficient and the linear simple regression between age, PSA levels and histological results detected among each selected group, were as follows:

Among the clinical group ; there was weakly positive correlation between age and total PSA , free PSA and for some extend with F/T PSA but no signification correlation with ,connective tissue ,muscular and glandular tissues. Strong positive correlation between total PSA and free PSA ,but no significant correlation between total PSA and PSA ,and histological findings.There was weak significant correlation between free PSA and PSA ,but not correlated with histological findings. No significant correlation between PSA and histological results. No statistical correlation between the tissues.

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For cadaveric group, there was no significant correlation between age and connective ,muscular and glandular tissues.

These previous findings of correlation can be summarized in :-

1- In clinical group, age was weakly correlated with total and free PSA, and for some extend with F/T PSA. Richie, et al. (1993) [37], Agarwal (2004) [38] and several others had demonstrated that PSA increases with age [37]. Same results of the present study were predicted by Canto, et.al. (2004) [39].

2- In clinical group, concerning PSA, there was strong correlation between total PSA and free PSA, free PSA was weakly correlated with free/total PSA. Prostate specific antigen testing was introduced into clinical use in the mid-1980s [40]. This specific antigen is a glycoprotein which is secreted by prostatic epithelial cells, and its serine protease activity lyses the clotted ejaculate to enhance sperm motility. It is under tight androgen regulation [41]. It has been unequivocally demonstrated that PSA is organ-specific but not disease-specific [39]. Prostate glands in humans consist of a single layer of secretory epithelial cells, which are surrounded by a continuous layer of basal cells and a basement membrane [42].

The prostate epithelium in the glandular ducts and acinar epithelium secretes PSA into the lumen, and efficiently prevents the escape of the protease into the general circulation. However, small amounts of PSA leak into the circulation and this increases in prostate disease. The ratio between the PSA concentration in seminal plasma (0.5-3)and in serum (4g/L) is approximately :1 in healthy men [43,44]. Although there are many forms that circulate in low concentrations in blood, the two principal forms that are measured by current methods are PSA complexed with α1-antichymotrypsin (complexed PSA) and uncomplexed, or free, PSA (f PSA) [45,46]. These forms quantitatively differ between patients with malignant and benign prostatic diseases [47,48] or show disease-specific properties such as benign prostatic hyperplasia-associated PSA [49]. Canto, et. al. (2004) [38] reported that : Benign prostatic specific antigen (BPSA) comprised approximately 30% of the free PSA of biopsy-negative patients.

The previous facts, demonstrate our findings in this study, concerning the relation between total PSA, free PSA and ratio of free/total PSA.

Conclusions:

This study revealed that, the age was a risk factor for benign prostatic hyperplasia(BPH).

Histopathologically, it shows that, the ratio of smooth muscle of hyperplastic prostate stroma was about 40% and stroma/epithelium+ glandular lumen ratio was 1/1 in both groups. No difference in the percentage of connective, muscular and glandular tissues between the two groups.

Immunochemically, in clinical group, total PSA level was found to be higher in BPH Sudanese patients (mean= 8.75 ng/ml) than what is reported international . Free PSA mean value was 2.54 ng/ml and the ratio F/T PSA mean was 27.27%. Total PSA and free PSA increase with age in BPH. Free PSA increases with total PSA. The ratio of F/T PSA increases with the free PSA.

Free PSA and the ratio of F/T PSA are more accurate in diagnosis of BPH than the total PSA. Free PSA is more accurate than the ratio F/T PSA in prediction of benign prostatic hyperplasia if total PSA is more than 8.75 ng/ml.

Recommendations:

1. The most reliable diagnosis for Sudanese patients with soft prostate, total PSA less than 8.75ng/ml, free PSA more than 2.5ng/ml and F/T PSA ratio more than 25%; is benign prostatic hyperplasia.

2. Old male (50 years or greater) , are advised to do routine investigations for early diagnosis of BPH for prevention and to avoid complications.

REFERENCES

[1] Berry SJ, Coffey DS, Walsh PC and Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol. 1984; 132:474-479.

[2] Blandy J.The prostate gland. In Blandy Lecture Notes on Urology. Third ed. Blackwell scientific Publications. Oxford, London, Edinburgh, Boston, Melbourne .1982: 217-236.

[3] Simpson RJ. Benign prostatic hyperplasia: British Journal of General Practice 1997; 47(417): 235-240.

[4] Gerber GS. The definition of benign prostatic hyperplasia, epidemiology and prevalence. In Mc Vary KT (ed). Management of benign prostatic hypertrophy. Human Press. Totowa, New Jersey 2004:21-33.

[5] Issac JT, Coffey DS. Aetiology and disease process of benign prostatic hyperplasia. Prostate. 1989; 2:33-50.

[6] Derbes VDP, Leche SM and Hooker CC. The incidence of benign prostatic hypertrophy among the whites and negroes of New Orleans. J Urol. 1937; 38:383-388.

[7] Cabelin MA, Te AE and Kaplan SA. Benign prostatic hyperplasia: challenges for the new millennium. Curr Opin Urol. 2000; 10(4) :301-306.

[8] Crawford ED and Dall' Era J. Benign prostatic hyperplasia and the progression of lower urinary tract symptoms- a Review. VS Genito- Urinary Disease .2006: 44-46.

[9] Roehrborn CG. 5α-Reductase inhibitors prevent the progression of benign prostatic hyperplasia. Reviews in urology .2003; 5(5):512-521.

[10] Russell RCG, Williams NS and Bulstrode CJK. The prostate and seminal vesicles. In Russell RCG, Williams NS and Bulstrode CJK. Bailey and Love's short Practice of Surgery. 24th ed. Arnold: London. 2004: 1370-1387.

[11] Anim JT, Ebrahim BH and AbdulSathar S. Benign disorders of the prostate: a histopathological Study. Ann Saudi Med. 1998(1): 22-27.

[12] Shakya G, Malla S and Shakya KN. Salient and co-morbid feature in benign prostatic hyperplasia: a histopathological Study of the prostate. Kathmandu University Medical Journal. 2003; 1(2): 104-109.

[13] Burns DK. The male genital system. In kumer V., Cotran R.S., Robbins S.L. Basic Pathology. 7th edition. Saunders 2003: 657-678.

[14] Sugimoto K, Matsumoto S, Vermura H and Ito H. Distribution of elastic fiber on prostate. HinyokikaKiyo. acr. 2008; 54(5): 321-324.

[15] Bonkhaff H, Stien U and Remberger K. The proliferative function of basal cells in the normal and hyperplastic human prostate. Prostate 1994; 24 : 114-118 .

[16] Bostwick DG. The pathology of benign prostatic hyperplasia. In Kirby RS, Fitzpatrick JM, Mc Connell JD, Roehrborn CG and Boyle P. Textbook of benign prostatic hyperplasia. Second edition . Taylor and Francis. 2004: 97-112.

[17] Bartsch G , Muller HR, Oberholzer M and Bohr HP. Light microscopic stereological analysis of the normal human prostate and of benign prostatic hyperplasia. J Urol 1979; 122: 487-491.

[18] Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate specific antigen. Invest Urol. 1979;17(2):159-63.

[19] Oesterling JE. Prostate-specific antigen: a critical assessment of the most useful tumour marker for adenocarcinoma of the prostate. J Urol 1991; 145: 907-923.

[20] Becker C, Lilja H. Individual prostate-specific antigen (PSA) forms as pros-

Volume : 6 | Issue : 10 | October 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

tate tumor markers. Clin Chim Acta. 1997 Jan 3;257(1):117-32.

[21] Zhu L, Jäämaa S, Af Hällström TM, Laiho M, Sankila A, Nordling S, Stenman UH, Koistinen H. PSA forms complexes with α1-antichymotrypsin in prostate. Prostate. 2013;73(2):219-26.

[22] Papsidero LD, Koriyama M, Wang MC, Murphy GP and Chu TM . Prostate antigen: a marker for human prostate epithelial cells. J Nat1 Cancer |Inst. 1981; 66:37-42.

[23] Payne H, Conford P. Prostate-specific antigen: An evolving role in diagnosis, monitoring, and treatment evaluation in prostate cancer. Urol Oncol. 2011;29(6):593-601.

[24] Catalona WJ ,Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, Richie JP, deKernion JB, Walsh PC, Scardino PT, Lange PH, Subong EN, Parson RE, Gasior GH, Loveland KG, Southwick PC.. Use of percentage of free prostatic -specific antigen to enhance differentiation of prostate cancer from benign prostatic disease -a prospective multicenter clinical trail .JAMA.1998;279:1542-1547.

[25] Veltri RW and Miller MC . Free/total PSA ratio improves differentiation of benign and malignant disease of the prostate: critical analysis of two different clinical populations. Urology .1999; 53(4):736-745.

[26] Morote J , Encabo G, lopez M and de Torres IM . Prediction of prostate volume based on total and free serum prostate- specific antigen; is it reliable? Euro Urol. 2000; 38:91-95.

[27] Carleton BG (1898). A Practical Treatise on the Sexual Disorders of Men. Boericke, Runyon and Ernesty.2010: 105.

[28] Mohan H. Text book of pathology. 4th edition. New Delhi. 2002: p456-460.

[29] Stephenson WP ,Chute CG ,Guess HA Schwartz S, Lieber M. Incidence and outcome of surgery for benign prostatic hyperplasia among residents of Rochester ,minnesote:1980:89. A population based study .urology. 1991;38:32-42.

[30] Emberton M, Andriole GL, de la Rosett J, et al. Benign prostatic hyperplasia: a progressive disease of aging men. Urology. 2003;61:267–273. [PubMed].

[31] Abd Elwahab B and Osman H. Ultrasound role in diagnosis of malignant and benign tumor in prostate: new methodology technic. Master thesis. Amazon.co.UK. 2011:

[32] Safarinejad MR. Prevalence of benign prostatic hyperplasia in population _based study in Iranian men 40 years old or older. Int. Urol. Nephrol .Springer. 2008;40(4):921-931.

[33] Zorn KC , Hueber P and Stöppler MC. Prostate Specific Antigen. Medicine Net, Inc. Article. 2012; 80: 582-583.

[34] Abdrabo AA ,Fadlalla AI and Fadl-Elmula IM. The significance of the free/total prostatic - specific antigen ratio in prostate cancer detection in Sudanese with intermediate total prostatic - specific antigen levels. Sudan Med J.2012;48(3): 194-199.

[35] Polat O, Gul O, Ozbey I, Gundogdu C, Bayraktar Y. Histologic evaluation in patients with benign prostatic hyperplasia treated with Finasteride and surgery alone .Tr . J. of Medical Sciences, 1998;28:157-161.

[36] Marks LS, Tretger B, Dorey FJ, Fu YS, Dekernion J . Morphometry of prostate : 1. Distribution of tissue component in hyperplastic glands. Elsevier Inc. 1994; 44(4):486-492.

[37] Richie JP, Catalona WJ, Ahmann F Hudson MA, Scardino PT, Flanigan RC, deKernion JB, Ratliff TL, Kavoussi LR, Dalkin BL. Effect of patient age on early detection of prostate cancer with serum PSA and DRE.Urology.1993;42:365-374.

[38] Canto EI, Singh I, Shariat SF, Lamb DJ, Mikolajczyk SD, Linton HJ, Rittenhouse HG, Kadmon D, Miles BJ, Slawin KM. Serum BPSA outperforms both total PSA and free PSA as a predictor of prostatic enlargement in men without prostate cancer .Elsevier Inc .Urology .2004;63:905-911.

[39] Agarwal MS, Sinha S, Juyal S, Gupta AK. Measurement of serum PSA in benign and malignant enlargements of prostate in Indian population: Relevance of PSAD in intermediate range PSA. Indian J Urol. 2004;20(2): 138-143.

[40] Brawer MK. Prostate specific antigen: cur rent status. CA- cancer journal for clinicians 1999; 49:5.

[41] Jeffery CA, Brian RM, David CM, Craighal l M. Trans rectal ultrasound and biopsy in early diagnosis of prostate cancer . Cancer Control. 2001; 8(2) :141-150.

[42] Brawer MK, Rennels MA, Nagle RB, Schifman R, Gaines JA. Serum prostate-specific antigen and prostate pathology in men having simple prostatectomy. Am J Clin Pathol . 1989 ;92:760-764.

[43] Lilja H, Oldbring J, Rannevik G, Laurell CB. Seminal vesicle-secreted proteins and their reactions during gelation and liquefaction of human semen. J Clin Invest. 1987; 80:281-285.

[44] Malm J and Lilja H. Biochemistry of prostate specific antigen, PSA. Scandinavian journal of clinical and laboratory investigation.1995;221:15-22.

[45] Lilja H. A kallikrein-like serine protease in prostatic fluid cleaves the predominant seminal vesicle protein. J Clin Invest. 1985, 76:1899–1903.

[46] Svetec D, Thompson IM. PSA screening: current controversy. Ann Oncol. 1998;9:1283-1288.

[47] Stenman UH, Leinonen J, Alfthan H, Rannikko S, Tuhkanen K, Alfthan O. A complex between prostate-specific antigen and _1-antichymotrypsin is the major form of prostate-specific antigen in serum of patients with prostatic cancer: assay of the complex improves clinical sensitivity for cancer. Cancer Res. 1991.51: 222–226.

[48] Christensson A, Björk T, Nilsson O, Dahlén U, Matikainen MT, Cockett AT, Abrahamsson PA, Lilja H. Serum prostate specific antigen complexed to 1-antichymotrypsin as an indicator of prostate cancer. J Urol. 1993;150: 100–105.

[49] Mikolajczyk SD, Millar LS, Wang TJ, Rittenhouse HG, Wolfert RL, Marks LS, Song W, Wheeler TM, Slawin KM. "BPSA," a specific molecular form of free prostate-specific antigen, is found predominantly in the transition zone of patients with nodular benign prostatic hyperplasia. Urology . 2000; 55: 41–45.