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Original Research Article

Relationship between PSA and Serum Zinc in BPH-Afflicted Iraqi Men

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Abstract: ***Background*:** Benign prostatic hyperplasia (BPH) is a common benign tumor of the prostate that becomes more common as men age. The enlarged prostate may compress the urinary tube (urethra), which runs through the middle of the prostate, preventing urine from flowing from the bladder to the outside. Complete obstruction can develop if BPH is severe enough. BPH usually appears after the age of 40 and progresses slowly. ***Aim of the Study*:** Studying the connections between serum zinc and PSA in Iraqi BPH patients is the aim of this investigation. ***Patients and Methods*:** The case-control study lasted three months, from mid-November to the end of February, at Al-Kindi Teaching Hospital and Ghazy Al-Hariri Hospital in Baghdad Governorate, Iraq. It entailed gathering 90 blood samples, which were separated into two groups. The first group (A) consisted of 60 patients with benign prostatic hyperplasia ranging in age from 45 to 80 years, while the second group (B) consisted of 30 apparently be healthy males aged 45 to 80 years. All participants in this study provided diagnose permission. Patients diagnosed with benign prostate hyperplasia had an international prostate symptom score of 18 or higher; the patient's prostate volumes (PV) were equal to or more than 25 milliliters. Radiologists with competence in the department used transabdominal ultrasound equipment manufactured in Germany by Siemens to figure out how big the prostate gland is. Both groups had their serum zinc and PSA levels measured by ELISA (Enzyme-Linked Immunosorbent Assay) assays The calculation of BMI was be calculated with the help of given standard formula. BMI = [(Weight in Kilograms / (Height in Meters x Height in Meters)]. ***Results*:** The study that the mean prostate size was elevated significantly in the BPH group (54.0 ± 8.4 cc) as compared with the control group (19.66 ± 2.88 cc (P:0.01). There is a significant increase in the PSA concentration of benign prostatic hyperplasia patients, (3.14 ± 0.95 ng/ml), as compare with control subjects, (0.84 ± 0.10 ng/ml) (P:0.01). There is significant reduction in the serum zinc concentration of benign prostatic hyperplasia patients, (70.4 ± 9.63 ng/ml), as compare with control subjects, (99.3 ± 10.5; p≤0.01). The higher percentage of benign prostatic hyperplasia in patients above 66 years, and the lowest is in age group 45-55 years. ***Conclusion*:** Benign prostatic hyperplasia patients of all ages had considerably higher serum PSA than age-matched healthy controls. Benign prostatic hyperplasia patients of all ages had considerably lower serum zinc than age-matched healthy controls. Prostate size and PSA are greater in benign prostatic hyperplasia patients of all BMIs. Benign prostatic hyperplasia patients had significantly lower serum zinc than healthy controls of the same BMI.

Keywords: Benign prostatic hyperplasia, Prostatic Specific Antigen, Serum Zinc, Body Mass Index.

INTRODUCTION

Benign Prostate Hyperplasia (BPH)

Benign Prostate Hyperplasia (BPH) is a non-cancerous development or enlargement of the prostate tissue that is a common cause of lower urinary tract symptoms (LUTS) in men. LUTS refers to the discomfort that can be caused by problems with the lower urinary tract [1]. Histological BPH is more prevalent in older men, where it affects approximately 40% of men in their 50s and 60s and 90% of men over the age of 80. This condition is more prevalent in older men [2, 3].

BPH patients first develop hyperplasia in the periurethral gland (PUG) in their 40s, then in the transition zone (TZ), the major site of BPH. BPH develops in the transition zone. The adenoma may compress the prostatic urethra, causing bladder outflow obstruction (BOO) [4]. Each of the three lobes of TZ—two lateral and one median—can generate LUTS symptoms [5].

Hyperplasia can compress the urethra, restrict urine flow, and cause urine dribbling. However, if the bladder isn't emptied, ion sets in. Stagnant urine can generate bladder stones, thus the bladder muscle strengthens to overcome it. Urine back up in the kidney can cause renal injury and uremia, the toxic symptoms of kidney failure. In severe circumstances, BPH can cause sepsis, bladder damage, kidney failure, and death [6].

Prostatic Specific Antigen (PSA)

PSA is a glycoprotein having a molecular weight of 33kDa and an estimated carbohydrate content of 7% and is virtually exclusively present in prostatic epithelial cells [8, 9]. PSA is present in seminal plasma in an enzymatically active free form, whereas PSA is present in the circulation in an inactivated form due to interaction with protease inhibitors [8]. Seminal plasma concentrations are typically between 0.5 and 5.0 mg/mL, but normal serum values in men without prostatic disease between the ages of 50 and 80 are typically between 1.0 and 4.0 ng/mL [9].

Biochemically Characteristics of PSA

PSA is a single-chain glycoprotein that includes 93% amino acids and 7% carbs. It is a monomer with 240 residues of amino acids and 4 side chains made of carbohydrates. According to evidence, O-linked carbohydrate side chains are coupled to the amino acids (serine), (threonine), and asparagine, where an N-linked carbohydrate side chain departs (serine). Isoleucine makes up the N-terminal amino acid, while proline makes up the C-terminal residue [9]. One potential biologic role of PSA In semen dissolving the gel that forms during ejaculation by digesting semenogelin-I and -II and fibronectin, causing sperm to be released, This is necessary for sperm function [8].

Zinc

It is regarded as one of the essential trace elements that ensure the body's appropriate homeostasis where This element must be consumed through food because the body cannot store it. It is crucial for maintaining hormonal balance, spermatogenesis, capacitation, acrosome response, and the lining of the male reproductive organs [10]. An adult's daily requirement for zinc is roughly 15-20 mg [11]. The prostate has the highest concentration of zinc among all the organs. Prostate epithelium cells' immediate surroundings are where zinc concentrates the most. The prostate has a zinc level in its tissues of 150 μg/g, which is three times higher than other soft tissues. Its content in the prostate is 100 times higher than that in plasma [12, 13].

Biochemically Characteristics of Zinc

Zinc is essential for healthy growth, development, reproduction, and immunity because it serves a variety of functions in every cell of the body [14]. The relevance of zinc as a crucial trace element is second only to that of iron. The major biochemical function of zinc is demonstrated by its impact on the activity of more than 300 enzymes belonging to classes such as oxidoreductases, transferases, hydrolases, leases, isomerases, and lipases. Due to its importance in the structure, regulation, and catalysis of various enzymes, zinc is indirectly involved in DNA and RNA synthesis and metabolism, protein synthesis and metabolism, and glucose and cholesterol metabolism [15]. Zinc is essential for testosterone to be converted to its active form, dihydrotestosterone. The 5-reductase enzyme involved in this conversion is a zinc-dependent enzyme. Zinc also regulates the male reproductive system via gonadotropic hormones [16].

PATIENT, MATERIAL AND METHOD

Study Design

The case-control study lasted three months, from mid-November to the end of February, at Al-Kindi Teaching Hospital and Ghazy Al-Hariri Hospital in Baghdad Governorate, Iraq. It entailed gathering 90 blood samples, which were separated into two groups. The first group (A) consisted of 60 patients with benign prostatic hyperplasia ranging in age from 45 to 80 years, while the second group (B) consisted of 30 30 apparently be healthy males aged 45 to 80 years. All participants in this study provided approved permission with a questioner.

Ethical Approval

The Scientific Committee of the Faculty of Medicine at Tikrit University awarded the research protocol formal clearance, which had previously accepted the methodology. The Baghdad AL-Russafa Health Department and the Medical City Health Department provided clearance for collecting patient samples.

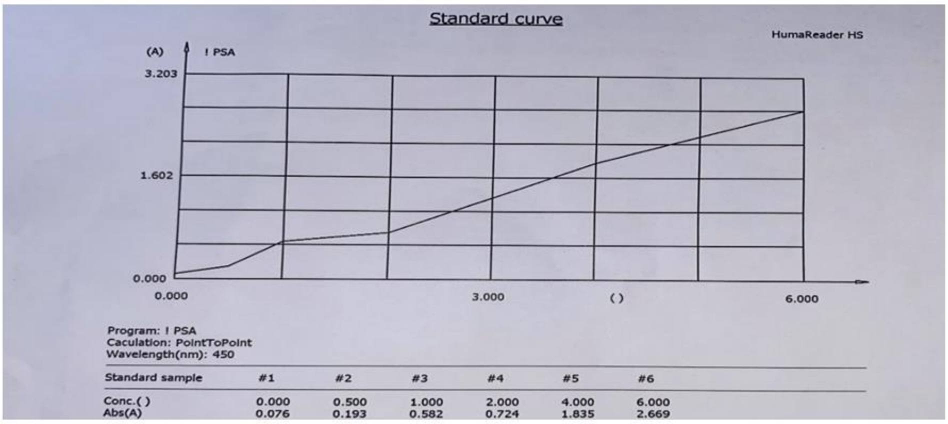
Exclusion Criteria
Prostate volume less than 28 cc, prostate cancer, prostatitis, chronic renal failure, and prostate, hypothalamus, testis, and pituitary surgery

Methods
Determine of PSA
The human prostate-specific antigen (PSA) ELISA kit is to assay PSA levels in Human Serum.

Principle
This Enzyme-Linked Immunosorbent Assay (ELISA) kit uses Sandwich-ELISA as the method. The Micro ELISA strip plate provided in this kit has been pre-coated with an antibody specific to PSA. Standards or samples are added to the appropriate Micro Elisa strip plate wells and combined with the specific antibody. Then a Horseradish Peroxidase (HRP)- conjugated antibody specific for PSA is added to each Micro ELISA strip plate well and incubated. Free components are washed away. The TMB substrate solution is added to each well. Only those wells that contain PSA and HRP-conjugated PSA antibodies will appear blue in color and then turn yellow after the addition of the stop solution. The optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm. The OD value is proportional to the concentration of PSA. You can calculate the concentration of PSA in the samples by comparing the OD of the samples to the standard curve.

Sample Preparation
After collection of the whole blood, allow the blood to clot by leaving it undisturbed at room temperature. This usually takes 10-20 minutes. Remove the clot by centrifuging at 2,000-3,000 rpm for 20 minutes. If precipitates appear during reservation, the sample should be centrifugated again.

Reaction: The color of the well should change from blue to yellow.



Determine Zinc by ELISA
Principle
Zinc Assay Kit is a convenient colorimetric assay in which Zinc binds to a ligand with the development of absorbance at 560nm. It can be used with biological samples such as serum.

Reagent Preparation:
The reagents are ready to use as supplied. Add 4 parts of Zinc reagent 1 to 1 part Zinc reagent 2. Make only as much Zinc reaction mix as is needed for samples and standards to be run. Each sample or standard requires 200 µl of reagent mix. Once mixed, the Zinc reaction mix is good for 2 days at room temperature or 1 week at 4°C.

Sample Preparation:
Samples containing significant amounts of protein serum should be deproteinized by adding 50 µl of the 7% TCA solution to 50 µl of the sample. Spin at top speed for 5 minutes. Add 20-50 l of the sample(s) to a 96 well plate; bring the volume to 50 µl/well with dH2O.

Reaction: Add 200 µl of Zinc reaction mix to each standard and sample; incubate 10 minutes at room temperature.
Read: Measure OD at 560 nm in a microplate reader.

Calculation:

Correct background by subtracting the value derived from the 0 Zinc Standard from all readings (The background reading can be significant and must be subtracted). Plot the Zinc Standard curve. Read Zinc sample concentrations from the standard curve:

Normal Ranges of Studied Parameters

Table 3: Normal ranges of the parameters

Parameters	Normal Value
PSA	< 1.29 ng/mL
Serum Zinc	80-130 ng/mL

Body Mass Index

The body mass index (BMI) was determined by entering each participant's height in meters and weight in kilograms into an online calculator. The BMI was then computed using the formula: BMI = [(Weight in Kilogram's / (Height in Meters x Height in Meters)], which is based on the official formula: BMI = [(Weight in Kilogram's / (Height in Meters x Height in Meters)].The World Health Organization (WHO) classification for body weight status is underweight (18.5 kg/m2), normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), and obese (>30 kg/m2) [17].

Statistical Analysis

All patients signed an informed consent to take part in the study, and the study was approved by ethical committee of Tikrit University, College of Medicine. All data were presented as mean and standard deviation (SD), Statistical analysis was implemented with correlation Analysis and t test, A P value of less than 0.05 was regarded significant. Analysis was performed by IBM SPSS Statistics for Windows version 23.0.

RESULTS

Prostate Size

Figure 1 show the size of prostate in patients and normal healthy control subjects. In prostate patients, there is significant enlargement in the size of prostate, (54.0 ± 8.4 cc), as compared with control subjects, (19.66 ± 2.88 cc) .

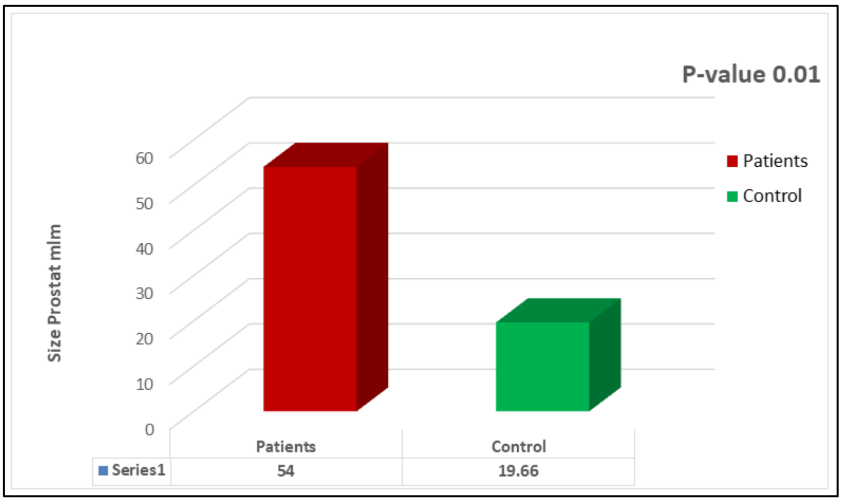


Figure 1: Show the prostate size in benign prostatic hyperplasia patients and controls.

Prostate Serum Antigen (PSA)

Figure 2 shows the serum PSA concentration in benign prostatic hyperplasia patients and normal healthy controls. There is a significant increase in the PSA concentration of benign prostatic hyperplasia patients, (3.14 ± 0.95 ng/ml), as compare with control subjects, (0.84 ± 0.10 ng/ml; $p \leq 0.01$).

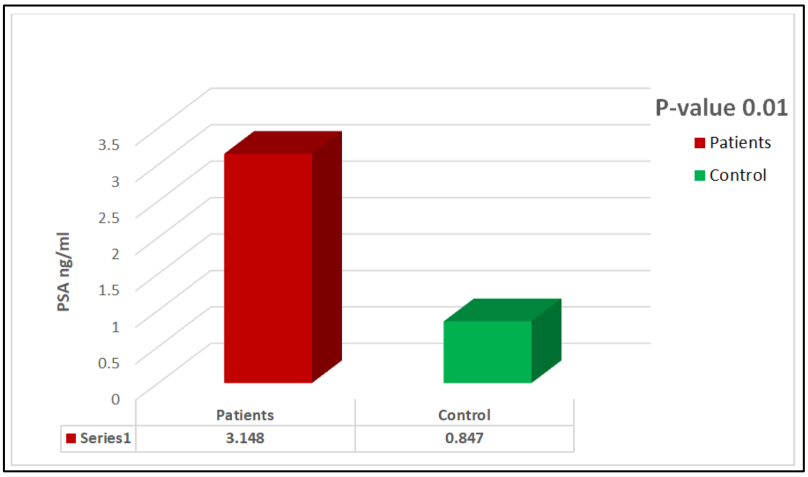


Figure 2: Show the PSA concentration in benign prostatic hyperplasia patients and controls.

Serum Zinc and BPH

Figure 3 show the serum zinc concentration in benign prostatic hyperplasia patients and normal healthy controls. There is significant reduction in the serum zinc concentration of benign prostatic hyperplasia patients, (70.4 ± 9.63 ng/ml), as compare with control subjects, (99.3 ± 10.5 ng/ml; p≤0.01).

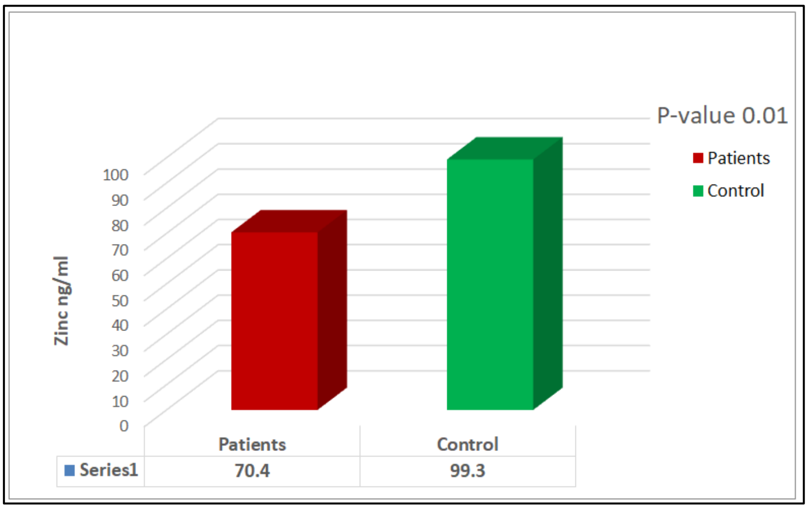


Figure 3: Shows the zinc concentration in benign prostatic hyperplasia patients and controls

Result of Size Prostate According to Age Groups

Table 4 shows the volume of the prostate in both patients with benign prostatic hyperplasia and control group.

Table 4: Relation of Size Prostate with the age of benign prostatic hyperplasia

Studied groups	Age groups	Size Prostate (CC)
benign prostatic hyperplasia (n: 60)	45-55	52.0 a ± 8.4
	56-65	59.67 a ± 7.72
	> 66	62.59 a ± 8.4
Control Group (n: 30)	45-55	18.37 b ± 2.63
	56-65	21.26 b ± 2.12
	> 66	22.62 b ± 0.67
P. value	0.01	

Result of PSA in BPH Patients in Relation To Age Group

Table 5 show the concentration of PSA in benign prostatic hyperplasia patients and control subjects. There is significant elevation in serum PSA in all age groups of benign prostatic hyperplasia patients as compare with normal healthy control subject's counterpart of same age group, (p≤0.01). However, there are no significant differences regarding serum PSA between age groups of benign prostatic hyperplasia patients.

Table 5: Relation of PSA with the age of benign prostatic hyperplasia

Studied groups	Age groups	PSA (ng/ml)
benign prostatic hyperplasia (n: 60)	45-55	3.37 a ± 0.46
	56-65	3.07 a ± 0.99
	> 66	3.15 a ± 0.98
Control Group (n: 30)	45-55	0.86 b ± 0.09
	56-65	0.77 b ± 0.16
	> 66	0.86 b ± 0.69
P. value	0.01	

Result of Serum Zinc in BPH Patients in Relation to Age Group

Table 6 show the concentration of serum zinc in benign prostatic hyperplasia patients and control subjects. There is significant reduction in serum zinc in all age groups of benign prostatic hyperplasia patients as compare with normal healthy control subject's counterpart of same age group, ($p \leq 0.01$). However, there are no significant differences regarding serum zinc between age groups of benign prostatic hyperplasia patients.

Table 6: Relation of Zinc with the age of benign prostatic hyperplasia

Studied groups	Agegroups	Zinc (ng/ml)
benign prostatic hyperplasia (n: 60)	45-55	67.52 a ± 8.05
	56-65	70.29 a± 7.81
	> 66	70.75 a ± 9.66
Control Group (n:30)	45-55	96.46 b ± 8.47
	56-65	107.87 b ± 9.96
	> 66	99.93 b ± 5.31
P. value	0.01	

Result of PSA in BPH Patients in Relation to BMI

Table **7** show the concentration of serum PSA in benign prostatic hyperplasia patients and control subjects according to BMI. There is significant increase in serum PSA in all BMI groups of benign prostatic hyperplasia patients as compare with normal healthy control subject's counterpart of same BMI group, ($p \leq 0.01$). However, there is no significant difference regarding serum PSA between BMI groups of benign prostatic hyperplasia patients.

Table 7: Relation of PSA with the BMI of benign prostatic hyperplasia

Studied groups	BMI Group	PSA (ng/ml)
benign prostatic hyperplasia (n: 60)	18.9-23.9	2.87 a ± 0.03
	24-28.9	3.31 a ± 1.29
	> 29	3.05 a ± 0.67
Control Group (n: 30)	18.9-23.9	0.78 b ± 0.14
	24-28.9	0.85 b ± 0.152
	> 29	0.85 b ± 0.09
P. value	0.01	

Result of Zinc in BPH Patients in Relation To BMI

Table 8 show the concentration of serum zinc in benign prostatic hyperplasia patients and control subjects. There is significant reduction in serum zinc in all age groups of benign prostatic hyperplasia patients as compare with normal healthy control subject's counterpart of same BMI group, ($p \leq 0.01$). However, there is no significant difference regarding serum zinc between BMI groups of benign prostatic hyperplasia patients.

Table 8: Relation of Zinc with the BMI of benign prostatic hyperplasia

Studied groups	BMI group	Zinc (ng/ml)
benign prostatic hyperplasia (n: 60)	18.9-23.9	68.65 b ± 9.58
	24-28.9	69.71 b± 8.92
	> 29	71.13 b ± 8.27
Control Group (n:30)	18.9-23.9	95.02 a ± 6.09
	24-28.9	102.71 a ± 2.07
	> 29	99.33 a ± 7.08
P. value	0.01	

Correlation between Parameters in Benign Prostatic Hyperplasia Patients

Table 9: Correlation between parameters in benign prostatic hyperplasia patients

Parameter's study	PSA (ng/ml)		ZINC (ng/ml)	
	R	P.V	R	P.V
Size Prostate	- 0.186	0.325	0.009	0.962
PSA	_______	______	0.176	0.351
Testosterone	_______	_____	- 0.023	0.904

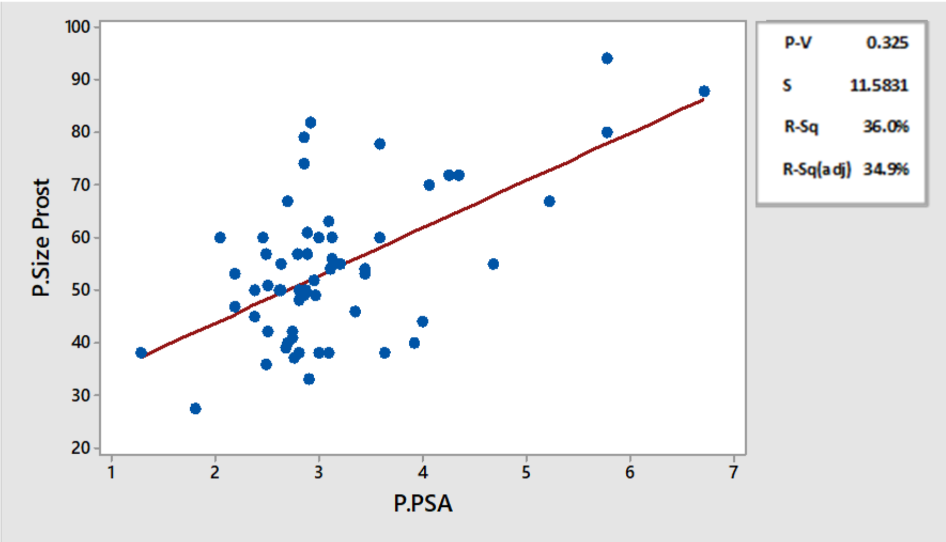


Figure 4: Correlation between size prostate and PSA in benign prostatic hyperplasia

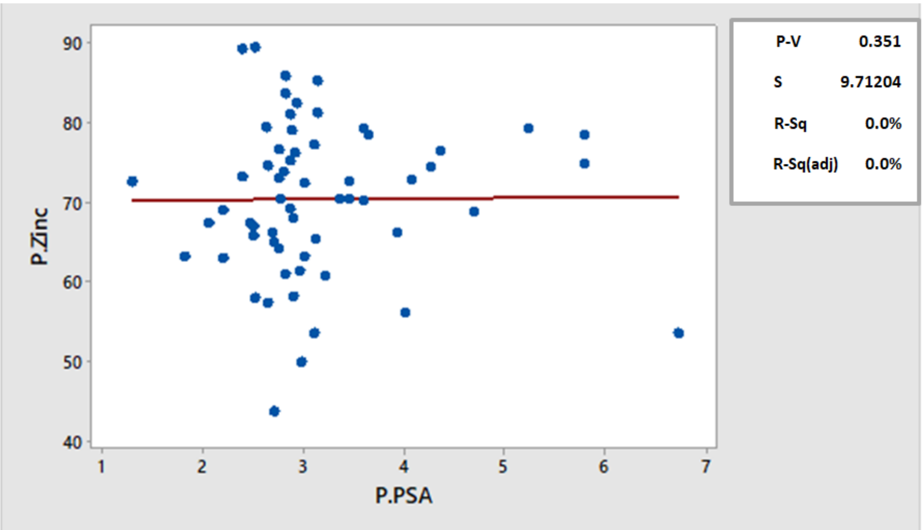


Figure 5: Correlation between Zinc and PSA in benign prostatic hyperplasia

DISCUSSION

The present study found a there is significant enlargement in the size of prostate in patients agree with previous finding that benign Prostate. According to the findings of the study, there was a substantial rise in the PSA concentration of benign prostatic hyperplasia patients agree with previous studies found that, a significant elevation in the concentration of serum PSA in patients, as compare with normal healthy control men [18-20]. Serum PSA levels correlate with prostate size and the androgen responsive PSA gene, synthesized via the AR signaling pathway, is specifically expressed in prostatic tissue and upregulated as BPH progresses. In patients with BPH, DHT binds to AR, in turn causing it to interact with androgen-response elements in the PSA promoter region, thereby increasing the PSA transcriptional activity [21].

PSA test is commonly used as an efficient tumor marker for other prostate illnesses, such as prostatitis, prostate cancer, and benign prostate hyperplasia [22]. A primary care doctor can diagnose BPH if there are additional good diagnostic results along with an increased PSA level [23].

In the present study, there is significant reduction in the concentration of serum zinc in BPH patients, as compare with normal healthy control men. Because of its function in apoptosis and the termination of the Krebs cycle, zinc is absolutely necessary for maintaining the health of the prostate. This one-of-a-kind metabolic pathway in prostate cells causes citrate to be released into the prostatic fluid, which is a key component of sperm, but it inhibits the production of energy. Because of this, when prostate cells become cancerous or hyperplasic and lose their capacity to store zinc, the Krebs cycle releases energy, which makes the development of prostate cancer cells and BPH more energy-efficient. This shows that pathological circumstances of the prostate gland in patients with BPH or cancer may be related with an adjustment in biochemical parameters such as a reduction in the level of zinc in tissue and zinc in plasma, as well as an increase in the amount of zinc that is excreted in urine [24]. A lot of studies mentioned the importance of zinc in prostate physiopathology, showing its favorable action in modulating some enzymatic systems (5-alpha-reductase, aconitase, phosphomonoesterase), in testicular androgen metabolism, and spermatogenesis [25-27]. The present study agrees with previous researches which found a significant reduction in serum zinc in BPH patients [20, 27, 28]. Christudoss *et al*., concluded that "BPH or prostate carcinoma may be associated with a reduction in the levels of tissue zinc, plasma zinc, and an increase in urine zinc/creatinine [20]. The findings of the current study are consistent with those of earlier studies, which found benign prostatic hyperplasia (BPH) is one of the most common medical conditions in older men [29-31]. The present result regarding PSA in BPH patients agree with previous findings, which found a significant elevation in the concentration of serum PSA in patients, as compare with normal healthy control men [19, 32, 33].

On the other hand, these findings were in contrast with which study's findings on in found a relationship between PSA and age [34, 35]. PSA values also tend to rise with increasing age due to the fact that the prostate gets larger as one gets older. This provides an explanation for why PSA levels are found to be elevated in patients who have benign prostatic hyperplasia [36]. We suggest that the PSA level should not be considered-aging-related but rather age-associated disease-related (BPH). The current study found a considerable drop in the serum zinc in all age groups of BPH patients (45-55, 56-65 and above 66 years). The present result agrees with several previous studies, Sauer AK *et al.,* [37] and Rawaa A *et al.,* [38]. Due to its role of zinc in apoptosis and truncation of the Krebs cycle (citrate buildup), high amounts of zinc are necessary for sustaining prostate health and function. While the high amounts of citrate released in the prostatic fluid, a main component of semen, are guaranteed by this particular metabolic process in prostate cells, it adversely impacts the process of energy production. It follows that when prostate cells experience BPH and lose their capacity to store zinc, the Krebs cycle continues to release energy, making the proliferation of malignant cells in the prostate more energy-efficient for the cells. Indeed, zinc levels are reduced by more than 50% in prostatic tissue generated from BPH .guys with BPH already had much higher zinc excretion in their urine than guys with a healthy prostate [37]. The present study does not agree with previous finding regarding the relation between BMI and serum PSA [39, 40]. Probably smaller studies are more likely to show no association between BMI and PSA, whereas larger studies more often show an association between these two aspects. According to the findings of the study, there was a considerable drop the serum zinc in all groups of BMI in BPH patients as compare with control healthy subjects of same BMI. The present result agrees with several previous studies, Rawaa *et al.,* [38] and Sauer AK *et al.,* [37] (114, 115). In the present study, there is a negative relationship between prostate size and PSA concentration, (- 0.186). A negative correlation was obtained, but with no statistical signification - between serum zinc and PSA (r= - 0.186) in patients with BPH. The present study agree with previous one [41]. The negative relation between serum zinc and PSA, between zinc and testosterone in patients with BPH, agrees with previous study [19].

CONCLUSIONS

Taking into account the results of this study, we can say the following:

In the BPH group, the average size of the prostate and PSA was the biggest, while in the normal group, the average size of the prostate and PSA was the smallest. When BPH patients are compared to normal, healthy control guys, there is a big drop in the amount of zinc in their blood. There is a link between the size of the prostate and getting older can be explained by the fact that benign prostatic hyperplasia (BPH), which is common in older men, is one of the most common medical problems. There are no big changes in serum PSA levels between people with benign prostatic hyperplasia of different ages should not be tied to getting older, but rather to a disease that comes with getting older (BPH).

CONFORMITY TO THE REQUIREMENTS OF ETHICAL STANDARDS

Before the start of the study, each participant was given an explanation of the method and the dangers that would subsequently be encountered as a result of their involvement. After receiving this information, they each gave their informed consent to take part in the study. The ethical committee of the Director of Baghdad AL-Russafa Health

Department and the Medical City Health Department both gave their blessing to the study, and all of the procedures were carried out in a manner that was consistent with the principles outlined in the Declaration of Helsinki.

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