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Relation Between Serum Zinc Level, Prostatic Size and PSA Level in Benign Prostatic Hyperplasia of Libyan Patients

Zeid Saleh Sasi [1*]

[1] Histopathology Department, College of Medicine, Derna University, Derna, Libya

*Corresponding author: E-mail addresses: drzeidsasi@gmail.com

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is the most common benign tumour of the prostate. BPH usually appears after the age of 40 and progresses slowly. The enlarged prostate may compress the urethra, which passes through the middle of the prostate, preventing urine from flowing from the bladder to the outside. Complete obstruction can develop if BPH is a huge enlargement. Aim of the Study: Study the relation between serum zinc and PSA in Derna City BPH patients. Materials and Methods: The case-control study lasts seven months, from April to the end of October, at Al-wahda Teaching Hospital in Derna City, Libya. It entailed gathering 60 blood samples, which were separated into two groups. The first group (A) consisted of 40 patients with benign prostatic hyperplasia ranging in age from 45 to 75 years which were classified into three sub-groups (45-54), (55-64), (66-75); while the second group (B) consisted of 20 be healthy males aged 45 to 75 years as same classified of sub-groups of patients. All participants in this study provided diagnosis permission. the patient's prostate volumes (PV) were equal to or more than 58 millilitres. 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). Results: The study showed that the mean prostate size was elevated significantly in the BPH group (64.36 ± 2.9 cc) as compared with the control group (22.44 ± 2.1 cc) (P=0.001). There is a significant increase in the PSA levels of benign prostatic hyperplasia patients, (3.57±0.57ng/ml), as compared with control subjects, (1.14±0.278 ng/ml) (P=0.001). There is a significant reduction in the serum zinc concentration of benign prostatic hyperplasia patients, (64.57±6.73ng/ml), as compared with control subjects, (110.6±12.37) (p=0.01). 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 markedly lower serum zinc than age-matched healthy controls. Prostate size is greater in benign prostatic hyperplasia patients than age-matched healthy controls.

1. INTRODUCTION

Benign Prostate Hyperplasia (BPH)

Although the size of the prostate varies with age, in young and healthy men, the normal gland size is about 3 × 3 × 5 cm (25 ml volume) and it weighs between 15 and 20 g.

Usually, this remains stable until men reach their 40's, the age in which a series of histological changes occurs: the gland grows and blocks the urethra or bladder, causing difficulty in urinating and interference in sexual functions that may eventually lead to benign prostatic hyperplasia (BPH). (Rodríguez-López et al., 2007, Amis, 1994), BPH is defined by histological alterations primarily within this prostatic transition zone, characterized by the proliferation of the epithelium and smooth muscle (Auffenberg et al., 2009). According to (McNeal, 1990), BPH develops in two phases. Within the first 20 years of BPH development, it is defined by an increase in the number of BPH nodules, while during the second phase; BPH is primarily characterized by an increase in the size of glandular nodules (McNeal, 1990, McConnell, 1991). Problems for patients can arise in two ways, by direct bladder outlet obstruction (BOO) due to size of the enlarged prostate (static component) or by an increase in smooth muscle tone within the prostate (dynamic component), potentially manifesting in lower urinary tract symptoms (LUTS) (Patel et al., 2014, Mobley, 2015), BPH is a common age-related phenomenon in men. While half of the men in their 60 s (50–60%) develop hyperplasia, by the time men reach the age of 70 and 80 years of age, 80–90% are affected (Roehrborn et al.,2002), Although not every man with BPH will necessarily be affected by significant LUTs, most common complaints include weak urine flow, straining, hesitancy, pro-longed voiding, complete or partial retention of urine, overflow incontinence of the bladder or irritative symptoms such as nocturia, painful urination and urge incontinence (Roehrborn, 2005).

Zinc role in BPH

The prostate gland consists of three glandular zones, namely a central (CZ), peripheral (PZ) and transition zone (TZ), with widely differing susceptibilities to PCa and BPH. PZ is the largest part of the prostate, constituting 70% of the gland; it is responsible for the production and secretion of Zn and citrate and is the most frequent site of PCa. In contrast, TZ (which accounts for 2–5% of the gland) is the almost exclusive site of BPH (Laczko et al.,2005). The normal human prostate accumulates the highest levels of Zn of any soft tissue in the body, because Zn is an essential trace element required for proper prostatic gland function. Its presence inhibits mitochondrial aconitase activity, i.e., limiting the oxidation of citrate and mitochondrial terminal oxidation and respiration, and has anti-proliferative effects, such as induction of mitochondrial apoptogenesis and suppression of NFκB activity (Costello et al., 2006, Sztalmachova et al.,2012), Interestingly, while many studies indicate that Zn levels are significantly disturbed in such states as BPH or PCa, the role of Zn in the etiology of these proliferative changes is not fully known. Numerous studies have described a significant, even several-fold increase of Zn levels in BPH tissues· (Costello et al., 2011, Costello et al., 2016, Sapota et al.,2009). Unfortunately, serum Zn concentration does not seem to be a reliable biomarker of Zn status in the body, and does not reflect its level in the prostate. Some data indicate a decreased Zn concentration in PCa patients (Wakwe et al., 2019, Christudoss et al.,2011, Kaba et al.,2014, Onyema-iloh et al.,2015, chen et al.,2015),While other data suggest increased Zn concentration (Yao et al.,1977),or no association at all (park et al.,2013), Therefore, post-mortem analysis of prostate tissue seems to provide a more accurate assessment of the role of Zn in the development of both PCa and BPH.

PSA and volume of prostate

Baseline prostate volume has been linked to progression of BPH (eg, acute urinary retention and surgery for BPH) (Lieber et al., 2001, Marberger et al., 2000), Furthermore, prostate volume (PV) has been shown to be a prognostic factor for treatment outcome with the two commonly used classes of agent for BPH: 5α-reductase inhibitors (5-ARIs) and α1-blockers (Boyle et al., 1996), Current guidelines from the American Urological Association (Madersbacher et al .,2007) ,on the short-term management of BPH recommend as an option α1-blockers for men with symptoms secondary to BPH and 5-ARIs or combination therapy for men with symptoms and demonstrable prostate enlargement. Therefore, PV estimations are important both for an understanding of the natural history of the disease and to establish the most appropriate initial treatment for an individual patient. However, currently, guidelines for the initial evaluation of BPH for general practitioners, shared care clinics, and urology offices are generally not driven by PV, but they do use symptom severity and bother as criteria for further decisions in diagnostic work-up and therapy. The reason for this is the perceived lack of reliability of digital rectal examination (DRE) in general in estimating PV and the lack of expertise of some of these practitioners in the estimation of PV by DRE or transrectal ultrasound (TRUS). Furthermore, there is limited availability of TRUS for PV estimation. Therefore, a fast and accurate method for estimating PV is needed to facilitate treatment decisions and care of the patient with BPH in the community setting and in urology offices.

The planimetric method of PV assessment by TRUS is considered the gold standard due to its high accuracy and high reproducibility (Tong et al., 1998, chenven et al., 2001, Torp-Pedersen et al., 1988, Hendrikx et al., 1989, Terris et al., 1991, bangma et al., 1996), However, this method is too laborious to be used routinely in normal practice, even for those with access to TRUS.

For most practitioners it is not practical to perform TRUS as an initial test in patients presenting with LUTS. Therefore, in everyday clinical practice, a quick, reliable, and reproducible alternative method for measuring PV is needed. For this reason, more rapid and convenient proxies such as DRE and serum prostate-specific antigen (PSA) have been recommended (Roehrborn et al., 1997, Roehrborn et al., 1999). However, these studies examined PSA as a proxy for PV in a selected and largely clinical trial population. The actual performance of PSA as a proxy for PV in the general population is unknown. Our study assesses the utility of PSA as a proxy for PV in the general population because this population is most representative of the group of men initially diagnosed with BPH.

2. MATERIAL AND METHOD

The case-control study stays seven months, from April to the end of October, at Al-wahda Teaching Hospital in derna city, Libya. It entailed gathering 60 blood samples, which were separated into two groups. The first group (A) consisted of 40 patients with benign prostatic hyperplasia ranging in age from 45 to 75 years which classified into three sub-groups (45-54),(55-64),(66-75) ; while the second group (B) consisted of 20 apparently be healthy males aged 45 to 75 years as same classified of sub-groups of patients. All participants in this study provided diagnose permission. the patient's prostate volumes (PV) were equal to or more than 58 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).

Statistical analysis

Data were tabulated, coded, and analyzed using the SPSS version 26.0 (SPSS 26.0, Inc., and Chicago, IL). Descriptive statistics included percentage mean, and SD were calculated. Differences between groups were analyzed using paired t-test and ANOVA. A difference was considered statistically significant when the $P < 0.05$. Pearson correlation coefficient assessed for the relationship between the studies variables.

3. ETHIC APPROVAL

Scientific research ethics permission from Bioethics Subcommittee for College of Medical Technology, Derna (CMTNSB) was taken under NBC number. **017. H. 24. 2.**

4. RESULT

A total of 60 men (40 patients and 20 controls) were admitted to the urology ward at Alwahda Hospital. Their mean age 62.95±8.25 years range from 45 to 75 years. Most of patients were in age 66-75 years. The mean age of patients was 64.7±7.66 years and the mean age of control was 59.45±8.44 years, all are seen in (Table 1).

Table 1: Age of participants

Age groups	No (%)	Case No (%)	Control No (%)
45-55	14(23.3)	6(15)	(40)
56-65	18(30.0)	11(27.5)	7(35)
66-75	28(46.7)	23(57.5)	5(25)
Mean±SD	62.95±8.25	64.7±7.66	59.45±8.44

Out of the 60 participants, the mean serum PSA was 2.766±1.26ng/ml, the mean serum zinc level was 79.897±23.6 and the mean of prostate size was 52.06±21.98cc seen in (Table 2).

Table 2: Descriptive statistics of PSA, serum zinc level and prostate size

	Minimum	Maximum	Mean	Std. Deviation
PSA (ng/ml)	0.60	4.95	2.766	1.26
serum zinc level (ng/ml)	52.7	128.0	79.897	23.6
prostate size (cc)	18.50	76.0	52.06	21.98

Table (3) illustrates relation between 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, (3.57±0.57 ng/ml), as compare with control subjects, (1.14±0.278 ng/ml; P=0.001). Also the table discus relation between the serum zinc level in benign prostatic hyperplasia patients and normal healthy controls. There is significant reduction in the serum zinc level of benign prostatic hyperplasia patients, (64.57±6.73 ng/ml), as compare with control subjects, (110.6±12.37 ng/ml; P=0.001).

Table 3: compare between PSA, serum zinc level and prostate size in both cases group and controls group

	Group		t-test	P-value
	Case Mean±SD	Control Mean±SD		
AGE	64.7±7.66	59.45±8.44	2.42	0.019
PSA(ng/ml)	3.57±0.57	1.14±0.278	17.88	0.001
Serum zinc level(ng/ml)	64.57±6.73	110.6±12.37	-18.69	0.001
Prostate size(cc)	67.1±5.47	21.98±3.14	34.06	0.001

There was a strong positive correlation between size prostate and serum PSA levels (P = 0.001) which illustrate in (Fig. 1).

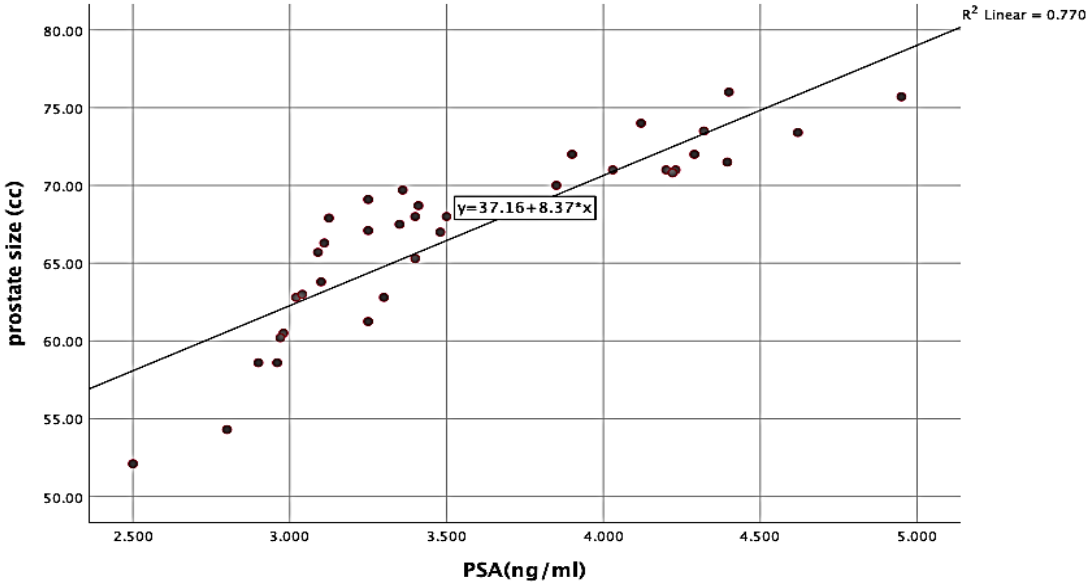

Figure 1: illustrate correlation between size prostate and PSA in benign prostatic hyperplasia.

There was a strong negative correlation between serum zinc and serum PSA levels (ρ = 0.001) seen clearly in (Fig. 2).

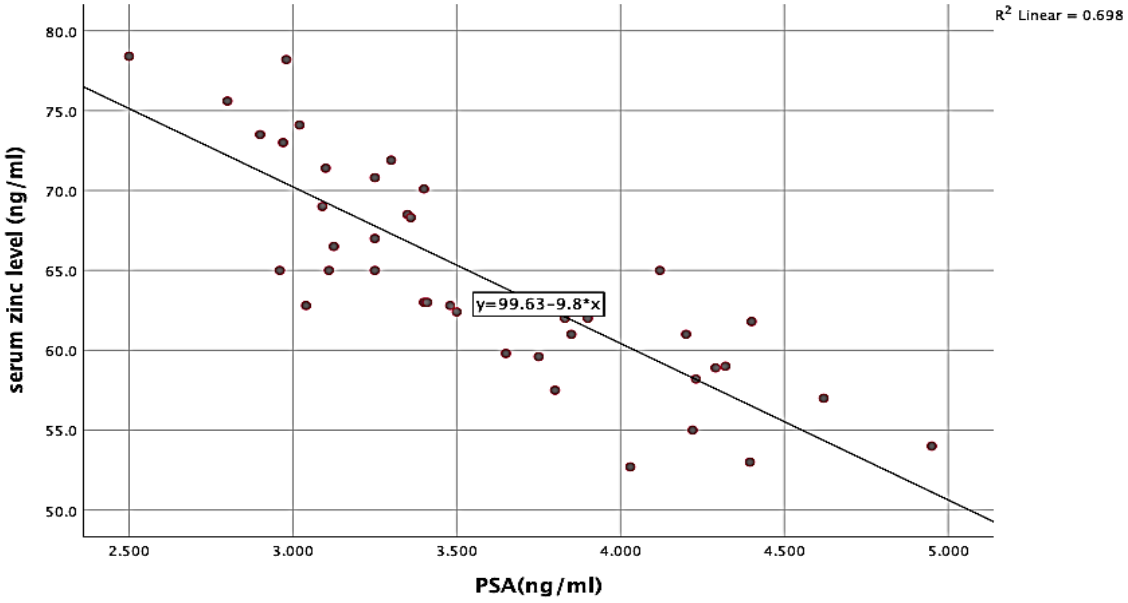

Figure 2: illustrate correlation between serum zinc and PSA in benign prostatic hyperplasia.

There was moderate negative correlation between serum zinc and age (ρ = 0.001) seen in (Fig. 3).

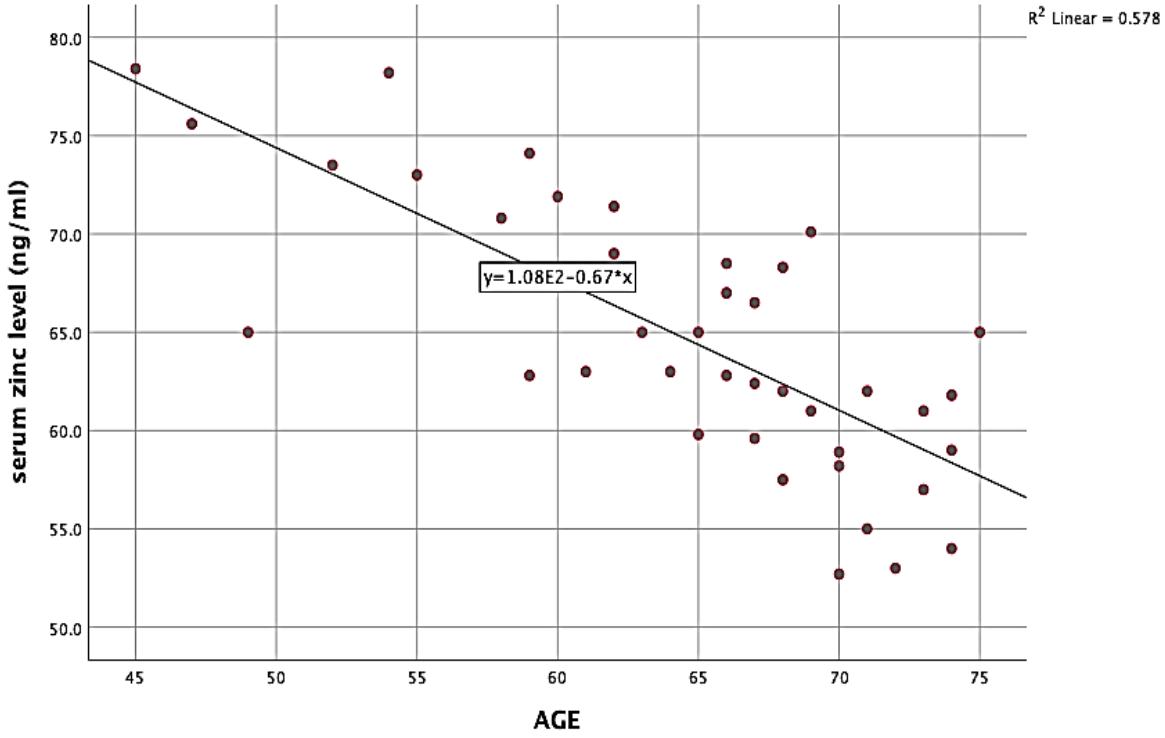

Figure 3: Correlation between age and serum zinc in benign prostatic hyperplasia

There was moderate positive correlation between age and PSA (ρ = 0.001) illustrate in (Fig. 4).

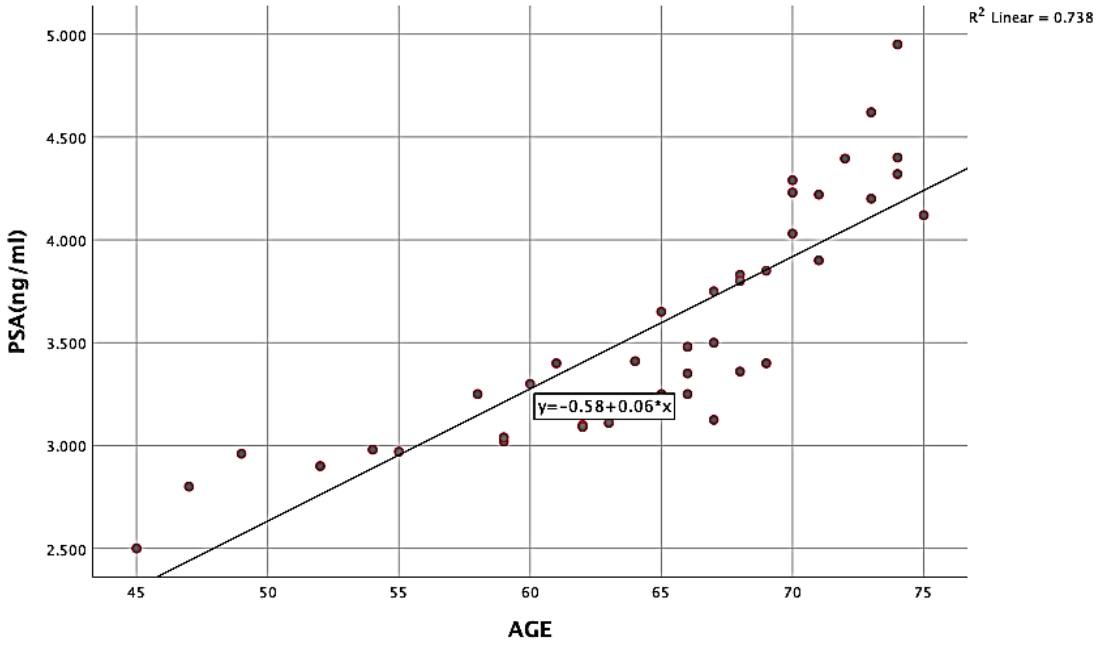

Figure 4: Correlation between age and PSA in benign prostatic hyperplasia

There was strong positive correlation between age and prostate size (P = 0.001) illustrate in (Fig. 5)

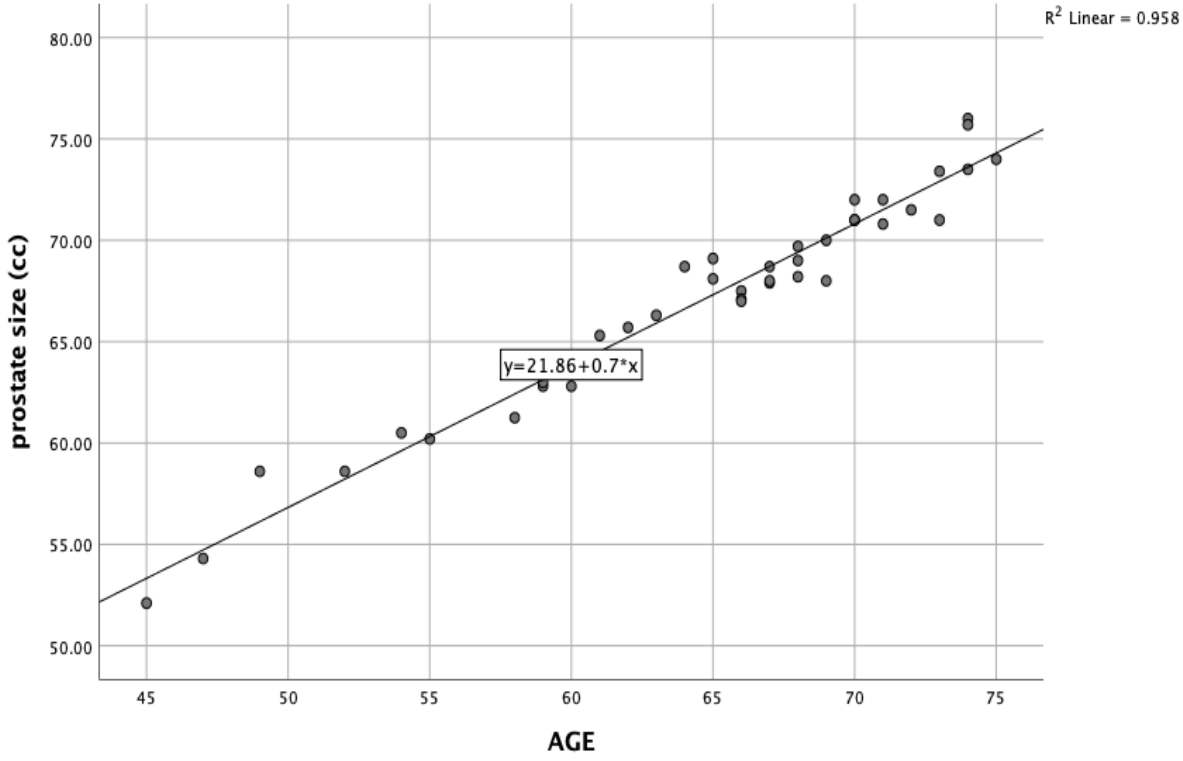

Figure 5: Correlation between age and prostate size in benign prostatic hyperplasia.

There was moderate negative correlation between serum zinc and prostate size (ρ = 0.001) (Fig. 6).

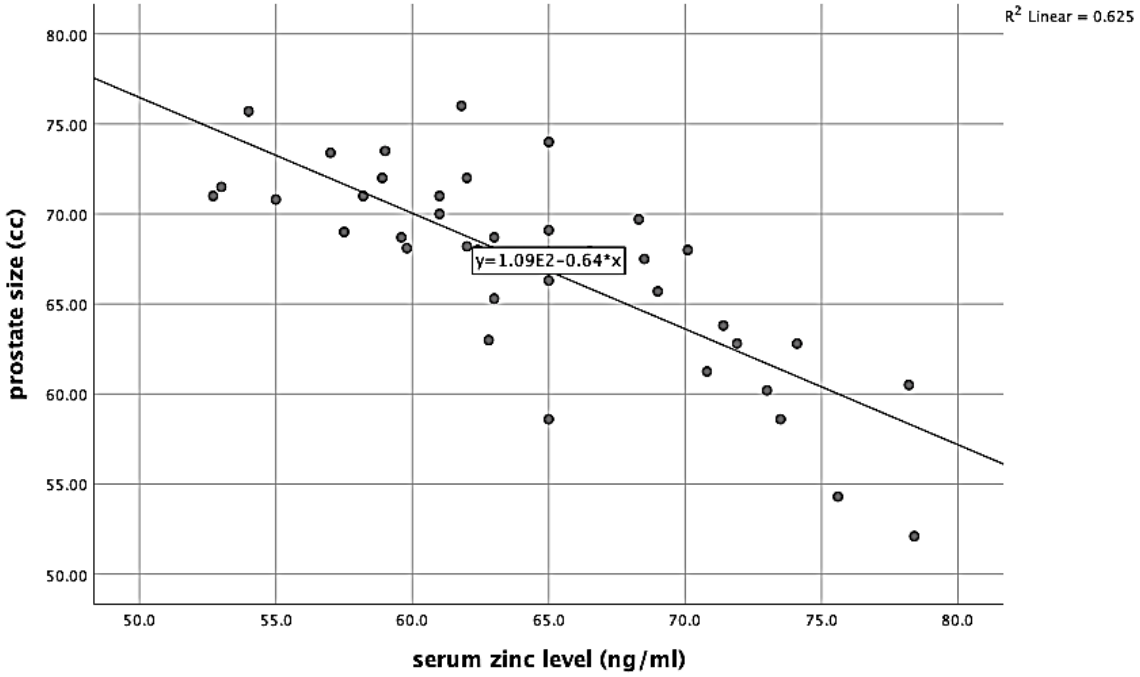

Figure 6: Correlation between serum zinc and prostate size in benign prostatic hyperplasia.

There was significant increase size prostate in older age group among benign prostatic hyperplasia patients and normal healthy control subjects of same age group (p=0.001) seen in (Table 4).

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

Age (Years)	Case Mean±SD	P-value	Control Mean±SD	P-value
45-55	57.38±3.4	0.001	19.59±0.8	0.001
56-65	65.16±2.7		22.14±2.1	
66-75	70.56±2.7		25.6±3.4	

There was a significant decrease in mean serum zinc levels in older age group among benign prostatic hyperplasia patients (P=0.001) as compared with controls shown in (Table 5).

Table 5: Relation of serum zinc with the age of benign prostatic hyperplasia.

Age (Years)	Case Mean±SD	P-value	Control Mean±SD	P-value
45-55	73.95±4.9	0.001	110.87±12.8	0.174
56-65	66.89±4.7		116.0±5.7	
66-75	61.01±4.9		102.4±16.1	

There was significant increase in serum PSA in older age group among benign prostatic hyperplasia patients as compare with normal healthy control subjects of same age group (p=0.001) seen in (Table 6).

Table 6: Relation of PSA with the age of benign prostatic hyperplasia.

Age (Years)	Case Mean±SD	P-value	Control Mean±SD	P-value
45-55	2.85±0.9	0.001	1.08±0.4	0.675
56-65	3.24±0.2		1.2±0.3	
66-75	3.9±4.8		1.1±0.2	

5. DISCUSSION

The present result regarding PSA in BPH patients agree with (Ene, *et al*. 2014, Yousif, *et al.* 2023, Cinislioglu, *et al*. 2022), which found a significant elevation in the concentration of serum PSA in patients, as compare with normal healthy control men. The present study found a there is significant enlargement in the size of prostate in cases BPH patients group agree with (Cinislioglu, *et al.* 2022). According to the findings of the study, there was a substantial rise in the PSA concentration of benign prostatic hyperplasia patients which positive correlate with size of prostate of BPH patients which agree with (Lee *et al.* 2008 Morote *et al.* 2000, Tsukamoto *et al.* 2007), Serum PSA levels correlate with prostate size and the androgen responsive PSA gene, synthesized via the androgenic receptors 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,in presrnt study PSA serum levels positive correlate with prostatic size which agreement with (Putra et al.2014, Anyimba et al.2023 Alawad et al.2014).

Also in our study found strongly positive correlation between PSA serum levels and age, these result were agreement with (Shao et al 2023, Alawad et al 2014, Sasanka et al 2015), on other hand our study results about correlation between PSA levels and age in contrast with (Erdogan et al 2020, Liu et al 2020). 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 (Singh et al., 2019). We suggest that the PSA level should not be considered-aging-related but rather age-associated disease-related (BPH).

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 (Mahde et al., 2020). 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 (Tawfeq et al., 2023, Nawal et al., 2018, Sarhat, 2015), So that the present study which found a significant reduction in serum zinc in BPH patients agrees with (Christudoss, et al 2011, Feng, et al 2002, Sauer, et al 2020).

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). Five previous literatures studied serum zinc concentration in BPH patients; three of those studies (Yao et al.1977, Liu et al., 1993, Ogunlewe, et al., 1989), as significant higher than that of normal controls, which controversial to present study; while two studies (Ji et al., 2007, Christudoss et al., 2011), reported that the zinc concentration of BPH patients was significantly lower than that of normal controls, which agreement with our study.

The present study found moderate correlation between serum zinc levels and PSA levels which not agreement with (Ene et al., 2014, Radhi et al., 2023).

6. 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 is greater in benign prostatic hyperplasia patients than age-matched healthy controls.

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