
Assessment of Testosterone Levels, Kidney Function and Alkaline Phosphatase in Patients with Benign Prostatic Enlargement in Kirkuk City/Iraq

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Abstract: *The present study is designed to evaluate the concentration of Testosterone, Creatinine, Urea urea, and alkaline phosphatase levels in patients with benign prostatic hyperplasia. This study was conducted for the period from the beginning of October 2023 to the end of February 2024 at Kirkuk Hospital. General and specialized medical clinics in the city of Kirkuk. The study included (70) males with benign prostatic hyperplasia, ages (45-75) years, and average weight (82) kg. In addition to 20 samples of healthy people with the same rate of ages and weights of patients, study samples were distributed as follows: The first group: the control group and included (20) healthy males, and the second group: the patient group and distributed to three groups according to the age groups first category (45-55) years and included 25 patients, the second age group (56-65) years and included 20 patients, the third age group (66-75) years and included 25 patients. The results of the current study showed a significant increase ($p \leq 0.05$) in the concentration of urea, creatinine and alkaline phosphatase enzyme in patients with benign prostatic hyperplasia compared to healthy people, and the current study showed a significant decrease ($P \leq 0.05$) in testosterone concentration in patients with benign prostatic hyperplasia compared to healthy people. According to age groups, the results showed no significant differences ($p \leq 0.05$) in the concentrations of urea, creatinine and alkaline phosphatase enzyme in patients with prostatic hyperplasia, and the results showed a significant decrease ($p \leq 0.05$) in the concentration of testosterone according to the age groups of patients with benign prostatic hyperplasia.*

Keywords: *Benign prostatic hyperplasia, Testosterone, kidney function, Alkaline Phosphatase.*



1. INTRODUCTION

The prostate gland is one of the largest glands attached to the male reproductive system, as it weighs about 20 g in adult men, as a scattered shape consisting of a glandular and muscle part, which is located under the inner urine hole directly and around the area of the prostate urethra and in front of the rectum. The prostate can be seen clearly, especially when it is enlarged, as its base is directed up and applies to the lower surface of the bladder, the urethra penetrates near its front and rear borders, either its summit is upward attached to the upper tray of the vein of the [1]. The benign prostate hyperplasia is a tissue, a multi-focus, non-wicked and hyperactive, and excessive, and epithelial cells in the transitional area of the prostate, which leads to the emergence of separate prostate nodules, inflammation, fibrosis and changes in smooth muscle activity, which can cause partial or complete blockage and lead to blockage of the outlet. The resulting bladder, as well as increased muscle strength in the bladder and secondary imbalance to a decrease in urinary tract symptoms [2]. Testosterone and hydrotestosterone are among the main androgens in the body playing a vital role in the development of male secondary qualities, such as facial hair growth, sound sound and muscle growth. These hormones are mainly secreted in the testes, androgens also play an important role in the health of the prostate, where testosterone is an important source for reference that affects the growth and functions of the prostate. The male ipomomatic hormone is mainly and is mainly excreted in the testes of males and ovaries for females, [3]. Urea is a chemical compound that plays an important role in the metabolism of nitrogen in the body. As mentioned, urea belongs to non-protein nitrogen components in the blood, which is one of the main products of the demolition process that occurs on proteins in the body. Proteins convert into amino acids when proteins are digested, broken into amino acids, which are the basic protein units, removing the amino end in the process Wets, the amino end (a part that contains nitrogen) is removed from each amino acid in a process known as 'faithful decomposition,' ammonia formation removal of the amino end leads to ammonia composition (NH₃), which is a highly toxic substance for the body, converting ammonia into urea in the liver To reduce ammonia toxicity, the liver converts it to Urea through the urea cycle, urea is less harmful and more suitable for blood transfusion and urea is removed across the kidneys, where it is filtered and removed from the body with urine [4]. Alkaline phosphatase (ALP) sometimes called 'alk phos' is an enzyme naturally produced by the body's organs. Everyone produces a basic amount of this enzyme regardless of health status, gender, or age. However, some tissues within the body produce alkaline phosphatase in higher amounts than others [5].

2. RELATED WORKS

The results of the current study are consistent with those of [6] who found lower levels of testosterone in patients with benign prostatic hyperplasia compared to control. The results also coincided with the findings of the [7] study who found that elevated indicators of Urea, Creatinine, Blood Urea Nitrogen and prostate antigen (PSA) are closely associated with benign prostatic hyperplasia.



3. METHODOLOGY

Study Design

This study was conducted for the period from the beginning of October 2023 to the end of February 2024 at Kirkuk General Hospital and specialized medical clinics in the city of Kirkuk, and the study included (70) male patients with benign prostatic hyperplasia, aged (45-75) years and with an average weight of (82) kg, as well as 20 samples of healthy people with the same average age and weight of patients, the study samples were distributed as follows: The first group: the control group included (20) healthy males The second group: the patient group and was distributed into three groups according to age groups. The first age group (45-55) years and included 25 patients. The second age group (56-65) years and included 20 patients. The third age group (66-75) years and included 25 patients.

Blood Samples

As (5) ml of venous blood was withdrawn for patients and healthy people, and then the blood was placed in tubes free of anticoagulants and left for 15 minutes at room temperature, and then it was placed in a centrifuge centrifuge, at a speed of 3000 cycles / minute for 15 minutes to obtain serum and then the samples were kept in the Abendorf tubes at a degree (-20) for the purpose of use in hormonal and biochemical tests for the research study.

Biochemical Tests

Determine the concentrations of the biochemical indicators of the studied groups, including testosterone estimate in the serum, using several ready -made analyzes (KIT) with the Mini Vidas manufactured by the French company [8]. And estimate the concentration of creatinine and urea in the blood serum using the KIT (KIT) group of French Biolbo to the method [9]. And estimate the concentration of alkaline phosphatase enzyme using several ready -made analyzes from the French company Biolbo and according to the method [10].

Statistical Analysis

Statistical analysis of the results was performed using the SPSS software program based on the T-test test, where the averages of patients and healthy people were compared at a significant level ($P \leq 0.05$). The ANOVA test was used to compare between age groups and at a significant level ($P \leq 0.05$), and the values of the variables were described as a standard deviation \pm Mean [11].

4. RESULTS AND DISCUSSIONS

Testosterone Levels in Patients with Benign Prostatic Hyperplasia and Control Group.

The results of the current study in Table (1) showed a significant decrease ($P \leq 0.05$) (1) in the concentration of testosterone in patients with benign prostate enlargement as it reached (3.85 ± 0.55) ng/ml compared to the control group which amounted to (7.52 ± 1.34) ng/ml the results of the current study were compatible with the results of the study of both [12] who found low levels of testosterone in patients with adequate prostate enlargement compared With control. As for age groups, the current results appear in Table (2) the



presence of moral differences ($P \leq 0.05$) between the different age groups in patients with prostate enlargement, as the concentration of testosterone increased in the first age group (45-55) amounted to (4.10 ± 0.79) ng / ml compared to the second age group (56-65) amounted to (3.84 ± 0.41) ng/ ml compared to the third age group (66 -75) amounted to (3.56 ± 0.46) ng/ ml, and the results of the current study agreed with the study of [13] , as they found that the occurrence of testosterone deficiency increases with age, partly due to the decrease in testosterone production by 0.4% to 2.0% annually after the age of thirty. Testosterone levels decrease with age, which is a syndrome identified by the International Association for the Study of Male Aging as a deficiency of androgen or late gonads that can cause a number of physical problems, including low sexual desire, erectile dysfunction, intellectual weakness, lack of activity, fatigue, depression and irritation [14]. Studies have shown that testosterone is important for the growth of prostate and the maintenance of functional safety, and in recent years the deficiency of androgen in the elderly men, which was subsequently renamed with late reproductive glands, has become a repeated topic of discussion between masculine doctors, and doctors Skin, endocrine doctors, urinary tract doctors [15]. The total levels of testosterone decreases with age, while the size of the prostate and the spread of benign prostate increases with age, as testosterone levels are negatively linked to the size of the prostate, and that the body mass index, waist and insulin are tied negatively in older patients in addition to that, the men who are They suffer from low testosterone hormone that have a larger prostate than men who have a natural testosterone [3].

Creatinine Levels in Patients with Benign Prostatic Hyperplasia and Control Group

The results of the current study in Table (1) indicate a significant increase ($p \leq 0.05$) in creatinine concentration in patients with benign prostatic hyperplasia, reaching (0.54 ± 0.09) mg / 100 ml compared to the control group that reached (0.41 ± 0.08) mg / 100 ml, the results of the current study agreed with the findings of the results of the [16] who found elevated levels of creatinine in patients with prostate enlargement compared to the control group. As for age groups, the current results in Table (2) indicate that there are no moral differences ($P \leq 0.05$) between the different age groups in patients with prostate enlargement, as the concentration of creatinine in the first age group (45-55) reached (0.51 ± 0.11) mg / 100 ml comparison in the second age group (56-65) amounted to (0.59 ± 0.10) mg/ 100 ml and in the third age group (66-75) amounted to (0.54 ± 0.08) mg/ 100 ml, and the results of the current study agreed with the study of [17] as they mentioneda that there are no statistically significant moral differences in creatinine levels, and that age is not a factor that affects the percentage of creatine between age groups in cancer patients and prostate enlargement. The changes in the concentration of creatinine in the serum reflect more reliable changes in the glybr filtration rate compared to the changes in urea concentrations in the blood and creatinine is formed automatically with a fixed rate of creatine and its concentrations in the blood depend almost on the GFR mandate only, so the measurement of the level of creatinine in the blood depends on the blood And calculating the estimated Kabbie nomination rate is very important in determining whether a person suffers from weak kidney function. These tests provided valuable visions about the development of type 2 diabetes and the associated risk of kidney failure [18]. High creatine level is also associated with kidney injury caused by diabetes in patients with diabetic nephropathy [19].

Urea Levels in Patients with Benign Prostatic Hyperplasia and Control Group

The results of the current study in Table (1) show a significant increase ($p \leq 0.05$) in the concentration of urea in patients with benign prostatic hyperplasia, as it reached (34.06 ± 3.68) mg / 100 ml compared to the control group that amounted to (29.00 ± 4.03) mg / 100 ml, the results of the current study agreed with the findings of the results of the study of [20] , [7] who found that high indicators of Urea, Blood Urea Nitrogen and prostate antigen (PSA) are closely correlated Benign prostatic hyperplasia. According to age groups, the current results in Table (2) indicate that there are no moral differences ($P \leq 0.05$) between the different age groups in patients with prostate enlargement, as urea concentration in the first age group (45-55) reached (32.07 ± 4.10) mg. / 100 ml comparison in the second age group (56 -65) amounted to (34.88 ± 2.90) mg/ 100 ml and in the third age group (66-75) amounted to (35.23 ± 4.04) mg/ 100 ml, and the results of the current study agreed with the study of [21] , as they mentioned that there are no statistically significant moral differences in urea levels between age groups in cancer and prostate enlargement patients. High levels of urea nitrogen indicate conditions such as acute and chronic nephritis, renal tuberculosis or tumor-induced renal dysfunction in patients, as UA and BUN have been linked to kidney disease and conditions such as hyperuricemia In addition, dietary habits, especially excessive consumption of protein-containing foods, can contribute to a small increase in urinary nitrogen levels [22] . Other possible causes of weak kidney function include diabetes, high blood pressure, autoimmune disease, systemic infections, urinary tract infections, urinary tract, tumors and family history of chronic kidney disease and healing from the previous rheumatoid arthritis, low kidney mass, exposure to some drugs (blood pressure (blood pressure)) The decrease in kidney function may be attributed to one or more of these reasons [23]. High levels of urea are attributed to impaired kidney function and is one of the most common diseases among people globally [24].

Alkaline Phosphatase Levels in Patients with Benign Prostatic Hyperplasia and Control Group

The results of the current study in Table (1) showed a significant increase ($P \leq 0.05$) in the concentration of alkaline phosphatase in patients with benign prostatic hyperplasia, as it reached (251.58 ± 13.85) U/ L compared to the control group that amounted to (204.20 ± 24.77) U/L, the results of the current study agreed with the findings of the results of the study of [25], which found a significant increase in ALP levels in patients with prostatic hyperplasia. According to age groups, the current results in Table (2) indicate that there are no moral differences ($P \leq 0.05$) between the different age groups in patients with prostate enlargement, as the concentration of alkaline phosphatase in the first age group (45-55) reached (246.13 ± 18.55) U/ L. comparison in the second age group (56 -65) amounted to (253.90 ± 7.31) U/ L and in the third age group (66-75) amounted to (254.72 ± 15.70) U/L , and the results of the current study agreed with the study of [26] , as they found after comparing the levels of alkaline phosphatase in the patients of benign prostate enlargement, the lack of statistically significant moral differences between age groups. The alkaline phosphatase (Alp) is greatly expressed in the cells of the anticimum tissue and performs a decisive function in the formation of solid tissue. These enzymes have half a 7 -day age and their filter from the serum is independent of the bile duct permeability or the functional



capacity of the liver, however, remains the exact location that it occurs in it, as the liver is the main source of most patients with high levels of enzyme. The mechanism behind the height of Alp has been discussed. Research has provided convincing evidence that this increase is caused by the increase in the syntax of the bile hepatic enzyme. The increase in hepatic enzyme activity corresponds to directly With the high activity of Alp in the serum, this is primarily due to an increase in the translation of the MRNA of the alp-A process, which is easy to increase the concentration of bile acid and increase the alp secretion in the serum by leaking the channel to the hepatic sinuses [27]. The levels of this enzyme increase during the aging stage with a noticeable difference in the distribution between the sexes and the reasons behind these fluctuations are still unknown Studies indicate a positive relationship between body weight and smoking, while there is an inverse relationship with height [28].

Table 1 Concentration of testosterone, creatinine, urea and alkaline phosphatase in patients with benign prostatic hyperplasia and control group

Group Variables	Patient	Control
Testosterone (ng/ ml)	3.85 ± 0.55 b	7.52 ± 1.34 a
Creatinine (mg/ 100 ml)	0.54 ± 0.09 a	0.41 ± 0.08 b
Urea (mg/100 ml)	3.68 ± 34.06 a	4.03 ± 29.00 b
Alkaline phosphatase (U/L)	13.85 ± 251.58 a	24.77 ± 204. 20 b

* The values in the table indicate to (Mean ± S.D).

* Different letters horizontally indicate significant differences (P ≤ 0.05).

Table 2 concentration Creatinine, urea, glomerular filtration rate and total proteins by age groups in diabetics

Age group Variables	Age (45 –55)	Age (56 – 65)	Age (66 –75)
Testosterone (ng/ ml)	4.10 ± 0.79 a	3.84 ± 0.41 ab	3.56 ± 0.46 b
Creatinine (mg/ 100 ml)	0.51 ± 0.11 a	0.59 ± 0.10 a	0.54 ± 0.08 a
Urea (mg/100 ml)	32.07 ± 4.10 a	34.88 ± 2.90 a	35.23 ± 4.04 a
Alkaline phosphatase (U/L)	246.13 ± 18.55 a	25 ± 0.35 a	7.47± 0.52 a

*The values in the table indicate to (Mean ± S.D)

* Different letters horizontally indicate significant differences at (P ≤ 0.05).



5. CONCLUSIONS

We conclude from the current study that there is a significant decrease in the concentration of testosterone in patients with benign prostatic hyperplasia compared to healthy people, and the results also showed a significant increase in the concentration of urea, creatinine and alkaline phosphatase enzyme in patients with benign prostatic hyperplasia compared to healthy people. We also conclude from the study that there are no significant differences between age groups in the concentration of urea, creatinine and alkaline phosphatase, and a significant decrease in the concentration of testosterone with age.

6. REFERENCES

1. Mega Samly, S. S. (2019). Histopathological Study of Prostatic Biopsies with Reference to Immunohistochemistry on Premalignant and Malignant Lesions (Doctoral dissertation, Sree Mookambika Institute of Medical Sciences, Kulasekharam).
2. Fusco, F., Creta, M., De Nunzio, C., Iacovelli, V., Mangiapia, F., Li Marzi, V., & Finazzi Agrò, E. (2018). Progressive bladder remodeling due to bladder outlet obstruction: a systematic review of morphological and molecular evidences in humans. *BMC urology*, 18(1), 15. <https://doi.org/10.1186/s12894-018-0329-4>.
3. Xia, B. W., Zhao, S. C., Chen, Z. P., Chen, C., Liu, T. S., Yang, F., & Yan, Y. (2021). Relationship between serum total testosterone and prostate volume in aging men. *Scientific reports*, 11(1), 14122. <https://doi.org/10.1038/s41598-021-93728-1>.
4. Brown, J. C., Harhay, M. O., & Harhay, M. N. (2019). The Value of Anthropometric Measures in Nutrition and Metabolism: Comment on Anthropometrically Predicted Visceral Adipose Tissue and Blood-Based Biomarkers: A Cross-Sectional Analysis. *Nutrition and metabolic insights*, 12, 1178638819831712. <https://doi.org/10.1177/1178638819831712>.
5. Zaher, D. M., El-Gamal, M. I., Omar, H. A., Aljareh, S. N., Al-Shamma, S. A., Ali, A. J., Zaib, S., & Iqbal, J. (2020). Recent advances with alkaline phosphatase isoenzymes and their inhibitors. *Archiv der Pharmazie*, 353(5), e2000011. <https://doi.org/10.1002/ardp.202000011>.
6. Xiong, Y., Zhang, Y., Li, X., Qin, F., & Yuan, J. (2020). The prevalence and associated factors of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in aging males. *The aging male: the official journal of the International Society for the Study of the Aging Male*, 23(5), 1432–1439. <https://doi.org/10.1080/13685538.2020.1781806>.
7. Chen, X., & Han, Y. (2024). Analysis of risk factors for benign prostate enlargement with prostate calcification. *Journal of Men's Health*, 20(1), 107-113.
8. Gonçalves, L. T., Costa, D. T. D., Rouver, W. D. N., & Santos, R. L. D. (2024). Testosterone modulates vasodilation in mesenteric arteries of hypertensive rats. *Life sciences*, 338, 122405. <https://doi.org/10.1016/j.lfs.2023.122405>.
9. Hussein, S. A., Fadlalmola, H. A., Salama, S. M., Osman, E. G., & Mariod, A. A. (2022). Efficacy and Safety of Gum Arabic on Renal Failure Patients: Systematic Review and Meta-analysis. *Sudan Journal of Medical Sciences*, 17(4), 459-475.



10. Tietz, F., Haanappel, V. A. C., Mai, A., Mertens, J., & Stöver, D. (2006). Performance of LSCF cathodes in cell tests. *Journal of Power Sources*, 156(1), 20-22.
11. Al-Rawi, Khasha Mahmoud (2000) Introduction to Statistics, Second Edition, College of Agriculture and Forestry, University of Mosul.
12. Rastrelli, G., Vignozzi, L., Corona, G., & Maggi, M. (2019). Testosterone and Benign Prostatic Hyperplasia. *Sexual medicine reviews*, 7(2), 259–271. <https://doi.org/10.1016/j.sxmr.2018.10.006>.
13. Kanabar, R., Mazur, A., Plum, A., & Schmied, J. (2022). Correlates of testosterone change as men age. *The aging male: the official journal of the International Society for the Study of the Aging Male*, 25(1), 29–40. <https://doi.org/10.1080/13685538.2021.2023493>.
14. Morales, A., Lunenfeld, B., & International Society for the Study of the Aging Male (2002). Investigation, treatment and monitoring of late-onset hypogonadism in males. Official recommendations of ISSAM. *International Society for the Study of the Aging Male. The aging male: the official journal of the International Society for the Study of the Aging Male*, 5(2), 74–86.
15. Lunenfeld B. (2003). Androgen therapy in the aging male. *World journal of urology*, 21(5), 292–305. <https://doi.org/10.1007/s00345-003-0366-8>.
16. Gu, X., Wu, J., Liu, X., Hong, Y., Wu, Y., & Tian, Y. (2022). Role of Serum Creatinine Levels in Prognostic Risk Stratification of Prostate Cancer Patients. *Medical science monitor: international medical journal of experimental and clinical research*, 28, e937100. <https://doi.org/10.12659/MSM.937100>.
17. Miyazawa, Y., Sekine, Y., Arai, S., Nomura, M., Koike, H., Matsui, H., & Suzuki, K. (2022). Changes in Renal Function of Patients With Prostate Cancer: Focus on Androgen Deprivation Therapy. *Cancer diagnosis & prognosis*, 2(6), 686–690. <https://doi.org/10.21873/cdp.10160>.
18. Ostojic S. M. (2022). Low Tissue Creatine: A Therapeutic Target in Clinical Nutrition. *Nutrients*, 14(6), 1230. <https://doi.org/10.3390/nu14061230>.
19. Hamad, R. H. ., and Abdulrahman, S. J. (2024). Assessment the Role of Kidney Function and Total Proteins in Patients with Diabetic Nephropathy in Kirkuk City/ Iraq. University of Kirkuk. *Journal of Prevention, Diagnosis and Management of Human Diseases*. 2799-1202, 4(01): 13–21.
20. Al-Barzinj, R. M. G. T. (2020): Estimation levels of prostate-specific antigen, interleukin-8, oxidative stress and some inflammatory markers in sera of benign prostatic hyperplasia patients who have smoking habits as a risk factor. *Cellular and Molecular Biology*, 66(7), 124-130.
21. Zamzami, Z., Rayendra, H., & Az-Zahra, N. (2021). Associations between Kidney Dysfunction and Risk Factors in Patients with Transurethral Resection of the Prostate. *Research and reports in urology*, 13, 665–672. <https://doi.org/10.2147/RRU.S326836>.
22. Lerner, L. B., McVary, K. T., Barry, M. J., Bixler, B. R., Dahm, P., Das, A. K., Gandhi, M. C., Kaplan, S. A., Kohler, T. S., Martin, L., Parsons, J. K., Roehrborn, C. G., Stoffel, J. T., Welliver, C., & Wilt, T. J. (2021). Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART I-



- Initial Work-up and Medical Management. *The Journal of urology*, 206(4), 806–817. <https://doi.org/10.1097/JU.0000000000002183>.
23. Levey, A. S., Coresh, J., Bolton, K., Culeton, B., Harvey, K. S., Ikizler, T. A, and Briggs, J. (2002). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *American Journal of Kidney Diseases*, 39(2 SUPPL. 1).
 24. Shawkat, E. A., Bakr, B. A., and Abdulrahman, S. J. (2023). Study the levels of erythroferrone, Urea and Creatinine in Chronic kidney Disease Patient in kirkuk city. *University of Kirkuk. Academia Science Repository*, 4(6), 11-18.
 25. Elden, A. M. K. (2010). Evaluation of Acid and Alkaline Phosphates in Benign Prostatic Hyperplasia and Prostatic Cancer Patients. *Tikrit Medical Journal*, 16(2).
 26. Annibali, O., Petrucci, M. T., Santini, D., Bongarzone, V., Russano, M., Pisani, F., Venditti, O., Pantano, F., Rago, A., Siniscalchi, A., Cerchiara, E., Franceschini, L., De Rosa, L., Mariani, M., Andriani, S., Cudillo, L., Garcia, M., Cantonetti, M., Mohamed, S., Anaclerico, B Avvisati, G. (2020). Alkaline phosphatase (alp) levels in multiple myeloma and solid cancers with bone lesions: Is there any difference. *Journal of bone oncology*, 26, 100338. <https://doi.org/10.1016/j.jbo.2020.100338>.
 27. Markou G. (2021). Bioprocess Optimization for the Production of *Arthrospira (Spirulina) platensis* Biomass Enriched in the Enzyme Alkaline Phosphatase. *Bioengineering (Basel, Switzerland)*, 8(10), 142. <https://doi.org/10.3390/bioengineering8100142>.
 28. Brichacek, A. L., & Brown, C. M. (2019). Alkaline phosphatase: a potential biomarker for stroke and implications for treatment. *Metabolic brain disease*, 34(1), 3–19. <https://doi.org/10.1007/s11011-018-0322-3>.