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## **Evaluation the level of human kallikrein-2-hk2, prostate specific antigen and some biochemical parameters in sera of patients with prostate disease**

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**Abstract**---The study was conducted on 90 serum samples of people with prostate diseases (G1-include 24 samples for patients with prostate cancer-PC , G2- include 24 samples for patients with benign prostatic hyperplasia-BPH and 22 samples for patients with prostatitis G3), compared with 20 samples for healthy individuals as control group. Prostate-specific antigen-PSA, human kallikrein-2-hK2, fibrinogen gamma-FGG, total anti-oxidant capacity-TAC, Vitamin D<sub>3</sub>-VD<sub>3</sub>. The results showed that the activity of PSA significantly elevated in G1 and G3 with no significant difference in G2, with significant increase in G1 for PSA and the hK2, FGG and TAC. so The results showed a significant increase in the group G2 in human kallikrein-2 with no significant difference in G3 compared with control group, and a significant increase in FGG levels in the group G2 and G3 compared with control group with no significant difference between G3, G1 with a significant increase in the group G2 and G3 in TAC levels compared with the control group, with significant decreased in VD<sub>3</sub> levels in group G3 and no significant difference in groups G1, G2 compared with control group.

**Keywords**---Prostate specific antigen, human kallikrein-2, fibrinogen gamma, total anti-oxidant capacity, vitamin D<sub>3</sub>.

## Introduction

Prostate diseases-PC are one of the most common health problems among males, as they directly affect the lifestyle of patients, especially the elderly<sup>(1)</sup>. PC is the most common type of prostate disease after the age of fifty years<sup>(2)</sup>, It is generally slow-growing cancer, as the majority of men with this disease live for many years without symptoms, but it is a life-threatening disease if the disease is not treated in the early stages<sup>(3)</sup>. The cancer cells in the prostate can metastasize anywhere in the body, most often in the lymph nodes and the bones<sup>(4)</sup>.

The second type of prostate disease is benign prostatic hyperplasia-BPH which causes urinary tract disorders in elderly males, as it affects approximately 40% of elderly males after the age of 60 years and also affects their lifestyle<sup>(5-7)</sup>. The disease is one of the symptomatic diseases of the lower urinary tract, which may be accompanied by symptoms of non-prostatic diseases such as bladder dysfunction<sup>(8,9)</sup>, Aging and some chronic diseases as well as obesity and an unhealthy lifestyle are risk factors for the disease<sup>(10)</sup>, Gradual enlargement of the epithelial cells of the prostate gland occurs as the beginning of the emergence of the tumor, as well as the smooth cells, and consequently, an enlargement of the tissue of the gland occurs Thus, it causes urine retention and urinary tract infections, in addition to the formation of stones in the bladder and kidney disorders<sup>(11-13)</sup>. The third type of prostate disease is prostatitis, especially chronic prostatitis, which represents difficult urinary tract disorders and causes disability in a large number of patients with the disease<sup>(14)</sup>, Prostatitis is the third most common urinary tract disease in men after PC and BPH<sup>(15,16)</sup>, Almost half of all men suffer from prostatitis during their lifetime<sup>(17)</sup>, PC and BPH mainly occur in older males, while prostatitis occurs at all ages, especially in young and middle-aged adults<sup>(18)</sup>.

Prostate-specific antigen-PSA, a glycoprotein with a molecular weight of 33,000 Daltons, which contains 273 amino acid residues. It is produced exclusively by the prostate gland and is found in semen, and is a diagnostic marker of PC <sup>(19-21)</sup>. And that it is responsible for coagulation and liquefaction of semen, and is important in sperm fertility<sup>(22)</sup>. It makes the medium in which the sperm is located more liquid, and helps it penetrate the wall of the egg<sup>(20)</sup>. An increase in the level of PSA in the blood may be associated with an increase in the size of the prostate gland and the occurrence of tissue damage caused by prostate diseases such as PC, BPH and prostatitis<sup>(22)</sup>. The measurement of the level of PSA is mainly used in cases of diagnosing PC However, its level may rise in some non-cancerous diseases such as prostatitis and BPH, but the increase in its level is less compared to PC It is considered an indicator of the development of 25% of cases of PC if the level of PSA is between 4-10 ng/cm<sup>3</sup><sup>(23)</sup>, It is used to monitor the progress of the disease, so its role may not be limited to diagnosis only, but also to follow up the speed of disease progress and its response to treatment<sup>(24)</sup>.

Human kallikrein hk2 specifically belongs to the protein family Kallikrein-2 to which PSA belongs. Studies have indicated its importance in the early detection of PC as an adjunct to PSA<sup>(25)</sup>. Human kallikrein is prostate-specific kallikrein <sup>(26)</sup>, which becomes unmeasurable after prostatectomy<sup>(27)</sup>. An average serum kallikrein level of 10% is within a range of (1-20%) of PSA levels, as the level of HK2

increases during the development of PC, It can be used in conjunction with PSA for the purpose of distinguishing between PC and BPH<sup>(28)</sup>. So the present study evaluates the efficiency of PSA and hK2 to diagnosis of prostatic diseases.

### Subjects and Methods

Subjects samples: The study was conducted on 90 serum samples (males) divided into four groups:

Group1-G1 : 24sample from patients with PC.

Group2-G2: 24sample from patients with BPH.

Group-G3 : 22 sample from patients with prostatitis.

Control group: 20 samples for healthy people

The age range of the patients and control groups ranged between (90-40) years, Patients' samples were collected from Salahudeen hospital in Tikrit and from some external clinical Lab from the period 10/15/2021 to 10/2/2022.

Methods: Serum sample were obtained from the collected blood and then the parameters under investigation were determined according the standard method. The parameters include:

- PSA, hK2, fibrinogen gamma-FGG, total antioxidant capacity-TAC and Vitamin D<sub>3</sub>.VD3 were determined according to the kits provided from American D<sub>3</sub>.VD3 company "Human", using Sandwich ELISA double antibody method.

Statistical analysis: The SPSS Sciences Social statistical program for Package Statistical - was used by using "Duncan's polynomial" test to compare between the group of patients and the healthy group as a control group, at the level of probability  $P \leq 0.05$ .

### Results and Discussion

The current study included determination the levels of PSA, human kallikrein-2, FGG, TAC and VD<sub>3</sub>, in the sera of patients under investigation, and the results obtained showed in Table 1.

Table (1) the mean  $\pm$  SD of the biochemical parameters under investigation

Groups	SD $\pm$ Mean				
	PSA(ng/ml)	KLK2(ng/ml)	FGG(ng/ml)	TAC(nmol/L)	VD3(ng/ml)
Control	0.567 $\pm$ 1.191 c	0.284 $\pm$ 1.361 c	403.845 $\pm$ 796.616 c	0.649 $\pm$ 4.754 d	30.88 $\pm$ 119.12 a
G1	26.012 $\pm$ 56.401 a	1.337 $\pm$ 6.438 a	283.629 $\pm$ 2138.21 a	0.726 $\pm$ 8.337 a	19.22 $\pm$ 110.48 a
G2	0.529 $\pm$ 1.159 c	0.535 $\pm$ 2.039 b	259.377 $\pm$ 1277.084 b	1.178 $\pm$ 6.888 b	27.87 $\pm$ 100.46 a
G3	1.932 $\pm$ 5.748 b	0.191 $\pm$ 1.287 c	487.541 $\pm$ 2323.452 a	0.523 $\pm$ 6.332 c	20.64 $\pm$ 80.46 b

Different letters indicate the presence of moral differences, while the similar means that there are no moral differences.

Table (1) shows that the mean and standard deviation of the PSA level was  $(56.401 \pm 26.012)$  ng/ml in in the group of patients with PC and  $(1.159 \pm 0.529)$  ng/ml in the group of patients with BPH and  $(5.748 \pm 1.932)$  ng/ml in patients with prostatitis, compared to  $(1.191 \pm 0.567)$  ng/ml in healthy subjects ( control group, The results showed a significant increase ( $P \leq 0.05$ ) in the level of PSA in the blood serum of the two groups G3, G1 compared to the healthy group, while there was no significant difference for the G2 group compared to the healthy group, while the results showed a significant increase for the G1 group compared to the G3 and G2 groups, as in Figure (1).

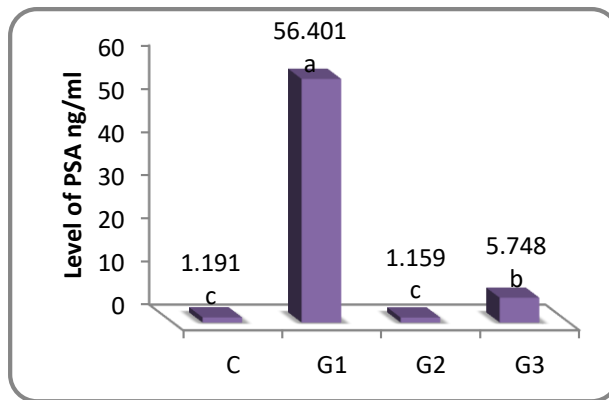


Figure (1): The mean of the level of PSA in the blood serum of the study groups.

The results of the G1 group agree with the results of Cosma et al (29) who indicated in their study an elevated PSA level in the G1 group, but they indicated that some patients had a PSA value of less than 20 ng/ml. The PSA level may also be elevated (a much lower level than in patients with PC) in patients with BPH and prostatitis (30). However, the results of the current study do not indicate an increase in the level of PSA in the G2 group compared to the control group with a significant increase in patients with prostatitis. Laino (31), also indicated that prostatitis may cause a little rise in the level of PSA, and this is consistent with the results of our current study. It showed a significant increase in the level of PSA, as the study indicated that among the 1851 patients who had an annual increase in the level of PSA by 2 ng / ml they had a risk indicator for the development of their infection from prostatitis to PC. Pansadoro and his group (32), indicated that approximately 71% of patients with acute prostatitis had an elevated PSA level, and this explains the fluctuation in PSA values in the study in patients with prostatitis. Table (1) shows that the mean  $\pm$  standard deviation of the level of human kallikrein-2 was  $(6.438 \pm 1.337)$  ng/ml in patients of the G1 group and  $(2.039 \pm 0.535)$  ng/ml in patients in the G2 group and  $(1.287 \pm 0.191)$  ng/ml in patients in the G3 group, compared to  $(1.361 \pm 0.284)$  ng/ml in the healthy as a control group, as shown in Table (1).

The results showed a significant increase in the two groups G2, G1 compared to the healthy group and the inflammatory group, with no significant differences for each of the G1 group compared to the G2 group and the G3 group compared to

the healthy group. Figure (2). The results showed a significant increase in the two groups G1, G2 compared to the healthy group and the inflammatory group with no significant differences for each of the G3 group compared to the healthy group. Figure (2).

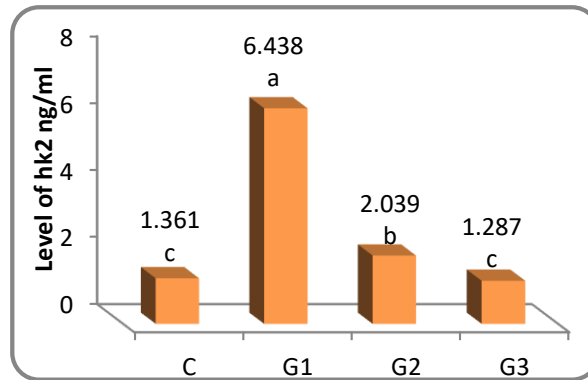


Figure (2): The level of human kallikrein-2 in the blood serum of the study groups.

The results of the current study for group G1 agree with the results of Nam et al <sup>(33)</sup>, who indicated an increase level of the human kallikrein-2 in PC patients, as the study indicated a strong link relationship between the level of human kallikrein-2 in serum blood and the risk of PC, especially those who have a high level of prostate specific antigen, Albertsen et al <sup>(34)</sup>, also indicated that that the level of both hk2 and PSA depends largely on the stage of the disease and the extent of its spread. Thus, they may be considered warning signs of the development of PC in patients and the extent of its spread. The results of the current study regarding the results of kallikrein-2 in the serum of patients with BPH agree with result of Saedi et al <sup>(35)</sup> Those who indicated that hk2 may be a diagnostic sign for patients with BPH, but its level is less affected as the increase in its concentration is less compared to patients with PC. Whereas, hk2 is considered an indicator for early diagnosis of PC, and thus many patients avoid undergoing a tissue biopsy to confirm the disease <sup>(36)</sup>. Nakamura <sup>(37)</sup> et al who indicated to the level of hk2 in BPH patients are significantly lower compared to PC patients and higher than healthy controls, and this is consistent with the results of the current study. The study aimed to evaluate the possibility of adopting hk2 as a diagnostic marker to differentiate between PC and BPH. has recommended Magklara <sup>(38)</sup> et al To the need to use hk2 and PSA together for the purpose of diagnosing PC in patients who have not high levels of PSA, More specifically, the study recommended the use of the ratio PSA / hk2 so if the ratio is between (4.5-2.5)  $\mu\text{g} / \text{liter}$  There is a higher chance of getting PC, so a biopsy test should be done to confirm it. Nakamura <sup>(37)</sup> et al who indicated to the About 54% of BPH patients avoided biopsy based on PSA/hk2 results. Studies did not refer to the evaluation of the level of hk2 in patients with prostatitis, but that Zhang <sup>(39)</sup> et al In an experimental study, they indicated that the level of kallikrein is lower in mice with prostatitis compared to mice with BPH.

As for the FGG level, Table (1) shows that the mean  $\pm$  standard deviation of the FGG level was (2138.21  $\pm$  283.629) ng/ml in patients of the G1 group and (1277.084  $\pm$  259.377)ng/ml in patients in the G2 group and (2323.452  $\pm$  487.541) ng/ml in patients of the G3 group, and (796.616  $\pm$  403.845) ng/ml in the healthy group as a control group. The results showed a significant increase ( $p \leq 0.05$ ) in prostate patients G1, G2, G3, compared with the healthy group with no significant differences in the group G1 compared with group G3 . as shown in Figure (3).

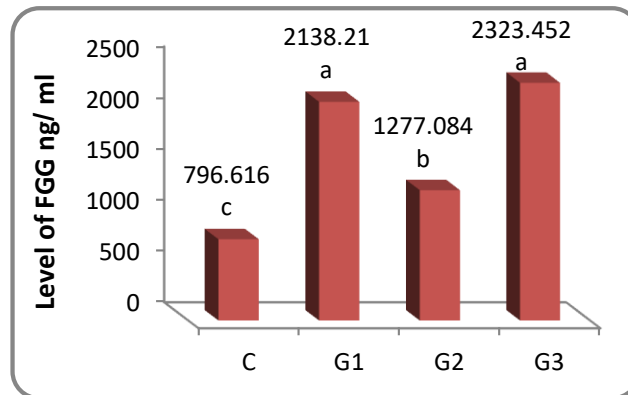


Figure (3): The level of FGG in the human blood plasma of the study groups.

As previously mentioned, fibrinogen-gamma is cleaved by thromsin to fibrin when tissue damage occurs, and fibrin is the most abundant compound in blood clots<sup>(40)</sup> So conducted Gerner et al <sup>(41)</sup> Examination of fibrin deposition in cancer patients using the two-dimensional electrophoresis technique of the cancerous tumor in addition to the blood plasma, The results of their study indicated the deposition of fibrin in different types of cancerous tumors with high concentrations of FGG in the blood plasma of cancer patients, and this explains the high level of FGG in PC patients in the results of the current study, As the high level of gamma fibrinogen may enhance the development and progression of cancer cells<sup>(42)</sup> ,This may explain the development of some cases of prostatitis into PC in some patients. Indicated Ma et al <sup>(43)</sup> Prostate cancer showed significant elevation of fibrinogen levels, especially in patients who had high PSA levels, Therefore, the study recommended that patients with high levels of FGG be monitored. The study also indicated that the proportion of FGG in patients with PC is higher than in patients with BPH although the two recorded a significant increase compared to the control, and this is consistent with the results of the current study.

As for the TAC level, Table (1) shows that the mean  $\pm$  standard deviation of the Total TAC level was (8.337  $\pm$  0.726) nmol/L in patients of the G1 group and (6.888  $\pm$  1.178)nmol/L in patients in the G2 group and (6.332  $\pm$  0.523) nmol/L in patients of the G3 group, and (4.754  $\pm$  0.649) nmol/L in the healthy group as a control group. The results showed a significant increase ( $p \leq 0.05$ ) in prostate patients G1, G2, G3, compared with the healthy group and results showed a significant increase in group G1 compared with the groups G2,G3 also significant increase in group G2 compared with the G3 as shown in Figure (4).

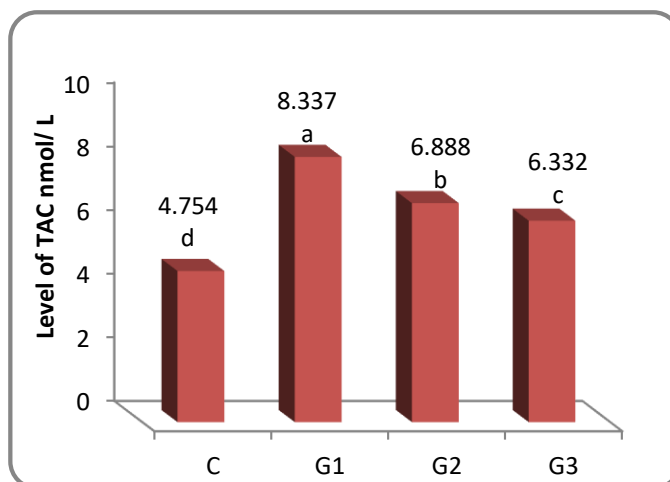


Figure (4): The level of TAC in the blood serum of the study groups.

The level of TAC is defined as a measure of the amount of free radicals that are gained by the test solution used for measurement<sup>(44)</sup> It is an indicator of oxidative stress . It is clear from the results of the current study that the patients are oxidatively stressed, as they have a high level of malondialdehyde and a decrease in the level of glutathione in the blood serum. The studies also indicated that the level of total antioxidants varies with the degree of disease, whether for patients with PC or patients with BPH, so the study suggested evaluating the level of TAC to monitor the progress of the disease<sup>(45)</sup>.

As for the VD3 level, Table (1) shows that the mean  $\pm$  standard deviation of the VD3 level was  $(110.48 \pm 19.22)$  ng /ml in patients of the G1 group and  $(100.46 \pm 27.87)$ ng/ml in patients in the G2 group and  $(80.46 \pm 20.64)$  ng/ml in patients of the G3 group, and  $(119.12 \pm 30.88)$  ng/ml in the healthy group as a control group. The results showed no significant differences in the groups of patients G1, G2 compared with the healthy group It also showed a significant decrease in the G3 compared with the the healthy group and showed a significant increase ( $p \leq 0.05$ ) in prostate patients G1, G2, G3, compared with the healthy group and results showed a significant increase in group G1 compared with the groups G2, G3 also significant increase in group G2 compared with the G3. It showed a significant increase in groups G1, G2 compared with the group G3 and with nonsignificant increase in groups G1,G2 as shown in Figure (5).

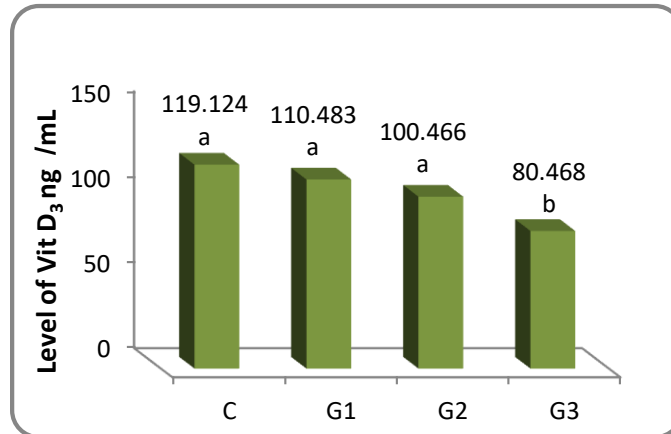


Figure (5): The level of VD<sub>3</sub> in the blood serum of the study groups.

Several studies have examined the possible role of VD<sub>3</sub> in treating cancer or causing disease when it is deficient, Studies have indicated that treatment with VD<sub>3</sub> supplements inhibits the development of cancer in experimental studies<sup>(46,47)</sup> Especially after the discovery of VD<sub>3</sub> receptors in cancer cells <sup>(46)</sup>. Several epidemiological studies have indicated a low level of VD<sub>3</sub> in patients with PC<sup>(48,49)</sup> Therefore, it has been adopted within the therapeutic protocols in the treatment of PC and even benign prostate hyperplasia, and this explains the normal level of the vitamin in the groups G2,G3.

### Conclusion

From the above results, we can conclude that PSA and hK2 are specific diagnostic markers for prostatic disease, and the three types of prostate disease are under an oxidative stress state, especially for prostate cancer patients.

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