Evaluation the *prolidase* activity and oxidative stress in sera of patients with prostatic diseases

Mohammed Ghazi Shihab Hameed [1] and Rafah Razooq Hameed Al-Samarrai [2]

[1] Department of chemistry, College of education, University of Samarra, Iraq.
[2] Department of applied chemistry, College of applied science, University of Samarra, Iraqfraji1996@gmail.com, dr.rafah_alsamarrai@uosamarra.edu.iq

Abstract:

The study was conducted on 90 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, prolidase activity, glutathione-GSH, malondialdehyde_MDA and uric acid-UC were determined in sera of patients and control group.The results showed that the activity of PSA significantly elevated in G1 andG3 with no significant difference in G2, while the prolidase activity significantly decreased in G1 and G3, with significant decreased in G1,G2,and G3 for GSH and UC levels, while the level of MDA significantly elevated in three groups as compared with control group. From all the results we can conclude that the may be affected by prostate cancer and also by hyperplasia of the prostate.

Key words: Prolidase, Prostate specific antigen, glutathione, malondialdehyde,prostatic diseases.
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Introduction:

Prostatic disease is a common health problem among males, affecting the life of the patient, especially the elderly [(1)]. Prostate cancer-PC is one of the most common types of cancer among males over the age of 50, while benign Prostatic hyperplasia - BPH is the most common urinary tract disorder among elderly men, as it affects about40% of elderly males after the age of 60 years and affects their lives [(2-4)]. While prostatitis, especially chronic prostatitis, represents difficult urinary tract disorders and is responsible for the occurrence of disability in a large number of patients with the disease [(5)]. The three types of prostate disease (PC,BPH and prostatitis) correlated with oxidative stress-OS in elderly men[(6)].

The majority of these prostate disorders are age-related[(7)]. The World Health Organization - WHO classified prostate cancer as The third most common type of malignant disease with a prevalence of 7.3%, it is preceded by lung cancer with 11.4% and colorectal cancer at 10%[(8)]. PC is one of the most commonly diagnosed types in more than 60% of the world's countries (112 out of 185 countries), with northern and western Europe the largest percentage, while the regions of South Central Asia recorded the least [(9)].In the latest report of the World Health Organization, prostate cancer deaths in Iraq amounted to 171 cases, 0.12% of the totalcancer deaths, and Iraq ranks 176th in the world with the prevalence of the disease **(10)**.

Prolidase is an exo-peptidase that hydrolyzed imidodipeptides with C-terminal hydroxyproline or proline derived from the degradation of collagen[(11)], The Function of enzyme is still unclear, but it has a critical role in matrix remodeling, collagen metabolism, and cell growth [(12,13)] and also straight correlated with OS and can be used as an oxidative stress marker [(14)].

Proteins in the extracellular matrix (ECM) play a significant role in invasiveness and tumorigenicity. While the main component of the extracellular matrix is collagen which plays a central function in

the interaction with integrin. The genetic expression of confirmed collagenases by tumor cells is one of the typical features of phenotype named metastatic phenotype, presumably by degradation of ECM barriers or by modifying the extracellular matrix–cell interaction[15].In which the degradation of collagen in the final step is catalyzed by intracellular prolidase [16].

Prostatic benign hyperplasia is described by the generation of stromal cells and increased the deposition of ECM involving proteoglycans, glycoproteins and collagens[17]. So the aim of this study was compare nd evaluate the activity of prolidase and oxidative stress parameters in sera of prostatic diseases.

Subjects and methods:

-Subjects samples: The study was conducted on 90 serum samples (males) dividedinto 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 someexternal 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. Theparameters include:

- Prolidase activity was determined by spectrophotometric method according the method of [18].
- PSA, GSH, and MDA were determined according to the kits provided from American company "Human", using Sandwich ELISA double antibody method.
- Uric acid-UC was determined by spectrophotometric method according the method of kits provided by Biolabo company,

-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≤0.05.

Results and discussion:

The current study included determination the levels of prostate-specific antigen, prolidase activity, glutathione, malondialaldehyde, and UC in the sera of patients under investigation, and the results obtained showed in Table 1.

Table (1) the mean ± SD of the biochemical parameters under investigation

Groups	SD±Mean				
	PSA(ng/ml)	Prolidase(U/l)	GSH(mmol/l)	MDA(nmol/ml)	UC(mg/dl)
Control	0.567±1.191 c	0.512±1.804 b	6.887±34.127 a	0.980±4.705 b	1.342±4.299 b
G1	26.012±56.401 a	0.423±2.432 a	1.564±7.568 c	2.485±11.079 a	1.119±6.551 a
G2	0.529±1.159 c	0.354±2.370 a	3.144±12.439 b	2.174±11.322 a	1.140±5.041 b
G3	1.932±5.748 b	0.588±1.948 b	2.567±13.032 b	2.732±12.142 a	0.748±4.348 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 prostate-specific antigen level was (56.401 ± 26.012) ng/ml in in the group of patients with prostate cancer and (1.159 ± 0.529) ng/ml in the group of patients with benign prostatic hyperplasia and (5.748 ± 1.932) ng/ml in patients with prostatitis, compared to (1.191±0.567) ng/ml in healthy subjects (control group, The results

showed a significant increase (P≤0.05) in the level of prostate-specific antigen 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).

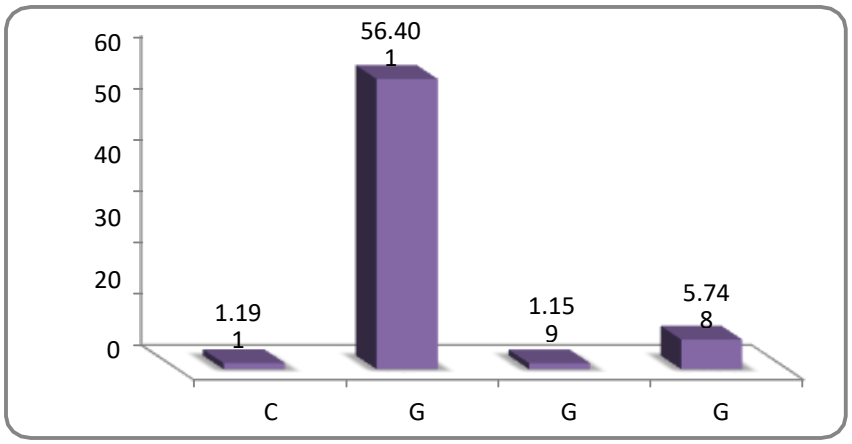

Figure (1): The mean of the level of prostate-specific antigen in the blood serum ofthe study groups.

The results of the G1 group agree with the results of Cosma et l., [(19)], 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 prostate cancer) in patients with benign prostatic hyperplasia and prostatitis [(20)]. 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 [(21)] 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 prostate cancer. Pansadoro and his group [(22)] 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 ± standard deviation of the activity level of prolidase enzyme was (2.432± 0.423) U/L in patients of the G1 group and (2.370±0.354) U/L in patients in the G2 group and (1.948± 0.588) U/L in patients in the G3 group, compared to (1.804± 0.512) U/L 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).

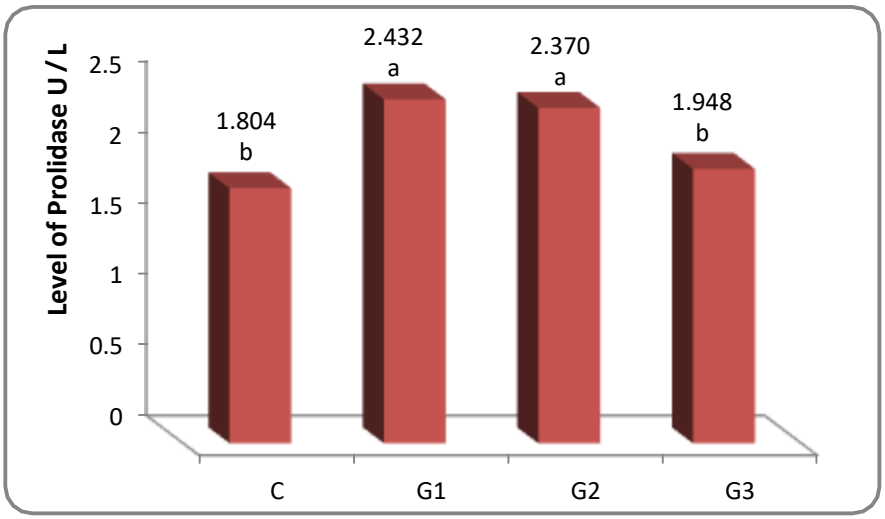

Figure (2): The level of prolidase enzyme in the blood serum of the study groups The results of the current study for groups G1 and G2 agree with the results of Kucukdurmaz *et al* [23] who indicated an increase of the enzyme activity in prostate cancer patients and BPH patients compared to the healthy group, with no significant differences between prostate cancer patients and BPH patients. The enzyme prolidase has been linked to many types of cancer. The activity of the enzyme prolidase is elevated in patients with oral squamous cell carcinoma [24], and it is elevated in breast cancer tissue [25]. Collagen is an essential component of the extra cellular matrix. ECM for many tissues, including the prostate, and the results of the histochemical analysis, morphometric analysis, and prostate tissue indicated the presence of three basic types of collagen in the prostate, namely IV, III, and I. Since the prostate tissue in BPH patients is characterized by a change in collagen content, it is characterized by an increase in type I and IV and a decrease in type III collagen with an increase the visceral intracellular material infiltrates, the tumor cells it also depends on the destruction of collagen and the intercellular visceral material by proteolytic enzymes liberated from the cancer cells themselves or even benign enlarged cells, and since the visceral enzymes are a group of enzymes necessary for the cleavage of the metallo proteinases are a group of enzymes necessary to cleave the protein of the intercellular visceral material that act as a barrier to the invasion of cancer cells [26], The enzyme prolidase is one of the metallo proteinases that release proline or hydroxyproline from the carboxy-terminal end of oligo peptides and participate in collagen transformation and cell growth [27] and thus works to regulate the last step of collagen breakdown. The catalyst for the rate limiting factor of collagen metabolism, and since the spread and invasion of cancer cells depends on the intercellular visceral material, its lysis and thus its disappearance, so the prolipase increases in its activity to contribute to the invasion of cancer cells [26].

Some studies have indicated that it is considered a therapeutic target in the treatment of cancer, as by inhibiting the enzyme, the progression of the cancerous invasion of cells can be inhibited [28]. Studies did not refer to the evaluation of the effectiveness of the enzyme prolidase in patients with prostatitis, as the results of the current study showed that the activity of the enzyme did not change in the disease.

As for the glutathione level, Table (1) shows that the mean ± standard deviation of the glutathione level was (7.568± 1.564) mmol/L in patients of G1group and (12.439±3.144) mmol/L in patients of G2 group and (13.032± 2.567) mmol/L in patients patients of the G3 group, while the healthy were (34.127± 6.887) mmol/L (control group). The results showed a significant decrease in the patients of G3, G2, and G1 groups as compared to the healthy group, and the results showed a significant increase in the G2 and G3 groups compared to the group G1 with no significant differences between the groups G2 and G3. as shown in Figure (3).

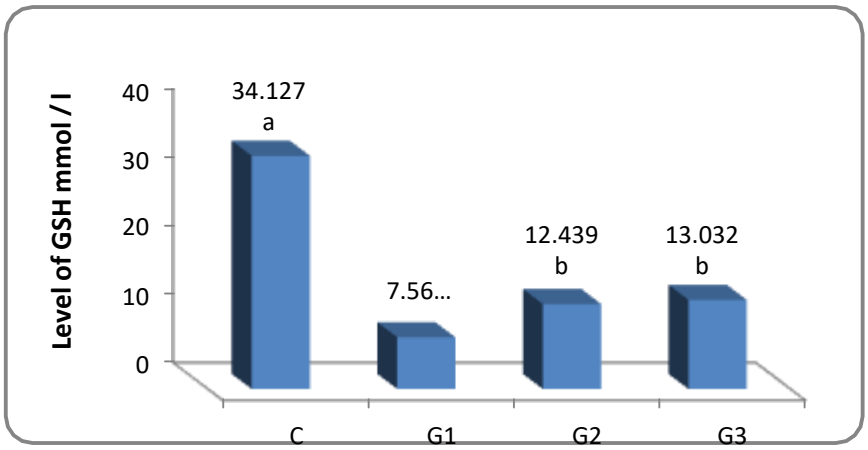

Figure (3): The level of glutathione in the blood serum of the study groups.

The results of the current study in the G1 group are in agreement with the results of several studies, including [29,30], as glutathione in the effective reduced form plays an important role in preserving the cell from the risk of free radicals, especially the effective types of oxygen, as it works to get rid of them, in addition to its important role in Replenish other antioxidants and thus protect the cell from the risk of oxidativestress [30]. In the cytoplasm of a living cell, low concentrations (several micromoles) of the reduced form of glutathione act very efficiently to remove hydrogen peroxide. However, this process causes an increase in the level of oxidized glutathione GSSG, but it can be converted to the reduced form by the redox cycle by NADPH to maintain the level of reduced glutathione at sufficient levels inside the cell [31]. It is known that the generation of MDA resulting from lipid peroxidation, it can cause oxidative stress, and it is one of the most dangerous mutagenic molecules and therefore may be a risk factor for causing cancer. However, glutathione is the molecule responsible for detoxing MDA and other lipid peroxidation compounds from inside the cell, thus removing the toxic effect of these substances. However, a decrease in the level of glutathione due to consumption to remove free radicals and reduce the risk ofoxidative stress, may cause the accumulation of glutathione in an oxidative form atthe expense of the reduced form enables free radicals to cause cell damage and the development of cancer [32]. This explains the noticeable decrease in the level of GSH in patients with prostate cancer compared to patients with benign prostatic hyperplasia and prostatitis in the current study. The results of the current study of the G2 group agree with the results of Szewczyk-Golec *et al* [33], as the study indicated a decrease in the level of antioxidants in the elderly who suffer from prostate cancer or benign prostatic hyperplasia. It also agrees with the results of Srivastava and Mittal [34] who indicated that the decrease in the level of glutathione (the reduced form) may be a result of its effect in suppressing the active types of oxygen in the blood.

Table (1) shows that the mean ± standard deviation of the malondialaldehyde level was (11.079± 2.485) nmol /ml in patients of the G1 group and (11.322± 2.174) nmol/ml in patients in the G2 group and (12.142± 2.732) nmol/ml in patients of the G3 group, and (4.705± 0.980) nmol/ml in the healthy ones as a control group. The results showed a significant increase ($p \leq 0.05$) in prostate patients G3, G2, G1, compared with the healthy group with no significant differences in the groups of patients G3, G2, G1, despite the slight increase in the G3 group, as shown in Figure (4).

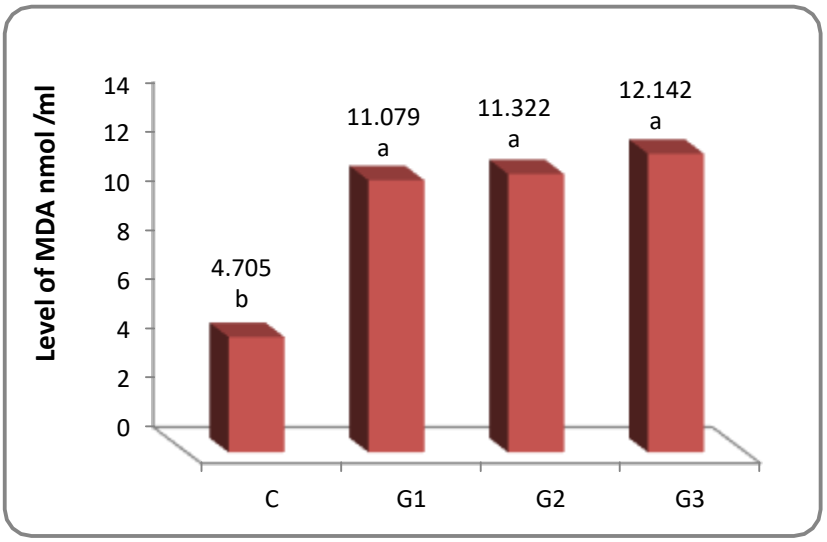

Figure (4): The level of malondialaldehyde in the blood serum of the study groups. Several studies indicated an elevated level of MDA in patients with prostate cancer, as Saleh and Mustafa indicated an elevated level of MDA in patients with prostate cancer [(35)], and it agrees with the results of Saheb [(36)] who indicated the possibility of using MDA as a diagnostic indicator of the disease. Similar to PSA. The high level of MDA may be due to the increase in the level of ROS, which causes lipid peroxidation, which is included in the composition of the living cell.

Peroxidation of unsaturated fatty poly acids by ROS results in the release of malondialdehyde [(37)]. Saheb [(36)] also pointed out the high level of MDA in patients with benign prostatic hyperplasia, with no significant differences in the level of MDA between patients with prostate cancer and benign prostatic hyperplasia, and this is consistent with the results of our current study.

As the level of malondialdehyde did not show a significant difference between prostate cancer patients and BPH patients, but it showed a significant increase compared to the control group, in the last study of Merendino *et al*., [(37)] indicated that the level of MDA rises in BPH patients with a positive correlation between the patients' MDA and PSA levels. The study attributed the reason for the high level of MDA in patients to the effect of oxidative stress on cells, through the occurrence of what is known as resistance to programmed cell death and the stimulation of free radicals in cells on non-programmed division. Studies have not indicated a study of the level of MDA in patients with prostatitis. However, the increase may be attributed to the fact that MDA is considered an important indicator in cases of inflammation, as it rises in many inflammatory diseases such as pancreatitis [(38)] and in cases of urinary tract infection [(39)] as well as arthritis [(40)]. MDA and 4-hydroxy-2-nonenal-4HNE are formed by the effect of free radicals on unsaturated fats and the occurrence of lipid peroxidation.

As for the UC level, Table (1) shows that the mean ± standard deviation of the UC level was (6.551± 1.119) mg/dL in patients of the G1 group and (5.041± 1.140) in patients in the G2 group and (4.348± 0.748) mg/dL in patients of the G3 group, and (4.299± 1.342) mg/dL in the healthy group as a control group.

The results showed a significant increase at the level of probability ($p \leq 0.05$) in patients of the G1 group compared to the healthy group with no significant differences between the two groups G2 and G3 compared to the healthy group despite the slight increase in the group G3 and a significant increase in the group G1 compared to the two groups G3, G2 with no showing Significant differences for the G2 group compared to the G3 group, as shown in Figure (5).

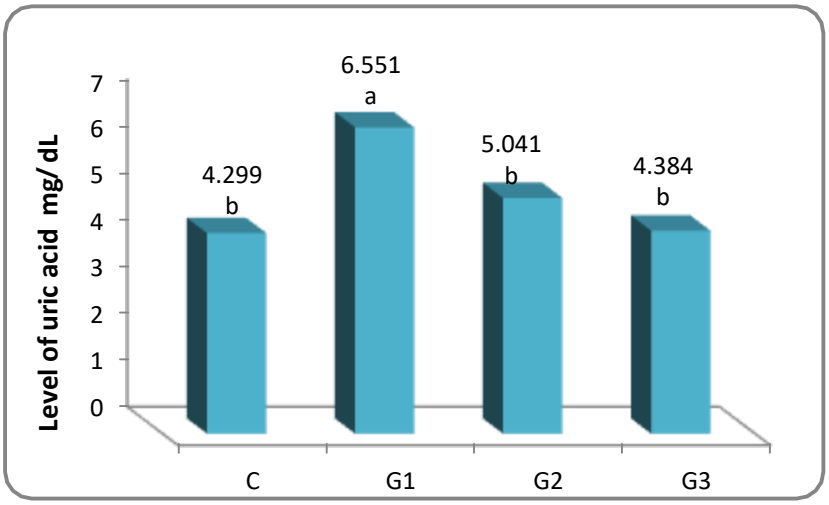

Figure (5): The level of UC in the blood serum of the study groups.

The results of the current study agree with the results of Sangkop *et al* [41], who indicated the high effectiveness of UC in patients with prostate cancer, and the study indicated that its low level could be therapeutically beneficial. It was also found that a high level of UC may be a cause of prostatic calculus [42]. The results of the current study do not agree with the results of the G2 group, as Li and his group [43] indicated that patients with BPH often accompanied by symptoms of gout, that is, they have a high level of UC. While the results of the current study agree with the results of Li and his group [44] who indicated that the high level of UC may cause the development of the disease to cancer in old males.

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