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Exploring the relationship among superoxide dismutase, prostate specific antigen, and oxidative stress levels in benign and malignant prostate hyperplasia: Implications for oncology

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ABSTRACT

Background: The present study aimed to identify changes in superoxide dismutase and Malondialdehyde (MDA) levels and their relationship to benign and malignant prostate hyperplasia compared to healthy men.

Methods: the samples of study collected at the laboratories of the middle Euphrates hospital. The sample group was taken as follows: 32 samples of prostate cancer patients, 28 samples of benign prostate tumor with 29 samples as a control cases. The serum taken for biochemical tests of Superoxide Dismutase (SOD) and Malondyaldyhide (MDA) was measured by ELISA method.

Results: The current study shows a significant increase ($p<0.05$) in malondialdehyde level in prostate cancer in compared with the control group, but a non-significant difference was not found between benign prostate hyperplasia and the control group. There was a significant difference ($p<0.05$) between benign prostate hyperplasia and prostate cancer. In addition, the results had shown a significant decrease ($p<0.05$) in Superoxide dismutase level in patients with prostate cancer compared with both the healthy group and benign prostate hyperplasia, While non-significant difference ($p>0.05$) was shown in benign prostate hyperplasia by compare with the health group. Regarding the correlation studies, the present study shown a negative correlation between malondialdehyde and Superoxide dismutase concentrations.

Conclusion: The current study showed a marked decrease in Superoxide dismutase levels while significantly higher malondialdehyde concentration levels in the serum of patients with prostate cancer.

Keywords: Prostate cancer; Superoxide dismutase; Malondialdehyde; Prostate hyperplasia; Oncology

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INTRODUCTION

Prostate cancer (PCa) is the 2nd most common cancers among men around the world behind a lung cancer, with 1,276,106 new diagnoses and from these cases, 358,989 deaths, and considered represent 3.8% of all cancer related deaths in men within 2018 [1]. There are several types of prostate cancer, Adenocarcinoma: This is the vast majority of Prostate Cancer (PCs) and arises from the glandular cells of the prostate. Small cell carcinoma, this is a rare type of prostate cancer that arises from the neuroendocrine cells of the prostate. Sarcoma, this is a rare type of prostate cancer that arises from the connective tissue cells of the prostate. Transitional cell carcinoma, This is a rare type of prostate cancer that arises from the cells lining the urethra, and final types is squamous cell carcinoma, This is a rare type of prostate cancer that arises from the flat cells that line the prostate. It is important to note that not all prostate tumors are cancerous, and benign tumors such as adenomas can also develop in the prostate gland [2]. Prostate Cancer (PCa) incidence and mortality rates rise with advance in age around the world, with age average at diagnosis being 66 years. Prostate cancer appears as solid glandular cancer.

As a result of glandular ageing, prostate disorders for instance BPH and malignant cancer lead to disruption of homeostasis [3]. Age is a significant risk factor for the development of prostate cancer, but there is no precise etiology or explanation for the increase in risk [4]. Although the causes and risk factors for prostate cancer remain unknown, some risk factors are commonly linked to the disease's progression. Age, genetic factors, race, and family background are all non-modifiable risk factors [5,6], whereas other risk factors of PC include environmental factors, diet, and lifestyle [7,8]. Many people who are diagnosed with PC have increased level of oxidative stress because of a disturbance in the oxidant/oxidioxidant balance, which may cause an imbalance and accelerated cancer growth [9,10].

A growing body of evidence indicates that intracellular development of oxidative molecules have a key role in age-related diseases like PC [11,12]. ROS for instance, hydroxyl radicals, hydrogen peroxides and superoxide anion can cause peroxidation of lipid and DNA damage in Sulfhydryl (SH)-dependent enzymes, altering their operation [13]. Molecular oxidative damage reported to be caused by hydroxyl radicals is the cause of cellular deterioration caused by age In clinical specimens of cancer, a progressive age-related increase in 8-oxo-2-deoxyguanosine (8-oxoG) DNA damage and an accumulation of 8-oxodeoxy(8-deoxyguanos) in non-progressive tissue were discovered [14]. Premalignant and malignant changes which associated with the prostate inflammation were previously shown to be caused by increased level of Oxidative Stress (OS), as well as an increased production of ROS, and DNA damage, and

diminished antioxidant activity [15,16]. Glutathione Peroxidase (GSH-Px), catalase and Superoxide Dismutase (SOD) working against the hydro-peroxides to decrease their concentration, are a part of the cellular antioxidant defense system that prevents oxidative damage by decreasing free radicals levels [17].

SOD catalyzes the conversion (or redistribution) of superoxide to water molecules (H_2O). The superoxide results from the oxygen metabolism and, if not kept under control, can do various kinds of harm. Some enzymes, such as catalase, degrade hydrogen peroxide, which is also harmful. As a result, virtually all oxygen exposed cells use SOD as a major antioxidant [18]. Some studies have found that oxidative stress has altered pro-ox antioxidant and anticancer status in both tumor and testes samples of clinical origin, furthering our concerns about its association with growth [19].

PSA is one of biomarker for PC, when level of PSA increase in the blood can be indicative of the presence of PC, at same time, PSA levels can also increase in some other conditions, such as prostate enlargement or inflammation. Therefore, PSA is not a definitive diagnostic tool for PC, and further testing, such as a biopsy, is often required to a proper diagnosis [8].

The purpose of this research is to establish the relationship between antioxidants and oxidative stress, as well as the degree to which these factors affect the development of benign and malignant prostate cancer.

MATERIALS AND METHODS

At first, written consent were taken from all participates to achieve the current study. Serum samples were collected from men with benign prostate tumor and malignant prostate hyperplasia, as well as healthy men who visited the center of middle Euphrate cancer.

The patients' ages ranged from 50 to 83 years old on average, and the 88 samples tested included 29 samples from healthy men, benign prostate tumor was 28, and 32 samples from PCa patients. SOD, PSA, and MDA were measured by ELISA reader Huma type based on an immunological principle. Before use, all samples and the reagents brought to the lab at room temperature. To avoid foaming, all the reagents combined gently. Once the process begins, both phases completed without interruption, and biochemical experiments were carried out in the laboratories in biology department, faculty of science, university of Kufa [20]. Enzyme-linked immunosorbent assay Kits which used were SOD (Human Superoxide Dismutase) (E0700Hu), Prostate Specific Antigen (PSA) and MDA (Human Malondialdihyde) (E1371Hu) from a Chinese company called Bio-assay Technology Laboratory Company.

The statistical software, Graph Pad Prism was utilized to study the variance. Analysis of variance (One-way) was applied for the compare between groups in the calculated markers. The correlation between markers was quantified using Mega Stat (version 10.12) for Excel 2010, along with description and the correlation coefficients.

RESULTS

Due to the results of current study, the results were shown increased significantly of PSA level in both PC, (48.60 ± 6.946) and Benign prostate tumor (21.37 ± 3.196) compared with the control group, $p<0.05$ (1.406 ± 0.1412), also there was a significant increase of PSA level in benign prostate tumor (21.37 ± 3.196) by comparison with PC patients, $p<0.05$ (48.60 ± 6.946) (Figure 1).

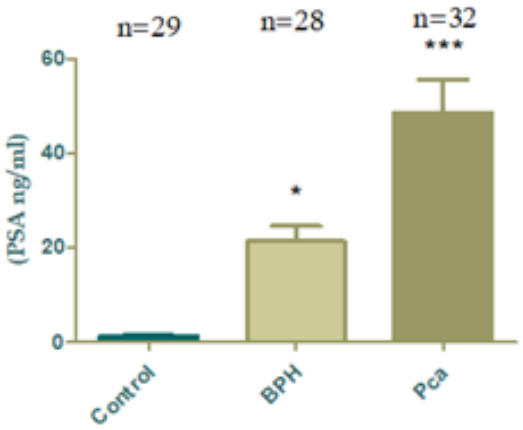

Fig. 1:. Serum PSA conc. comparison between prostate cancer, BPH with healthy men.

In addition to that there was an significantly increase in of MDA concentration in PC (20.5 ± 1.492) by comparison with the control group (14.24 ± 1.286) ($p<0.05$), although there was non-significant difference ($p>0.05$) between benign prostate hyperplasia and control group, and also non-significant difference ($p>0.05$) was found between benign prostate tumor and PC. Non-significant difference was reported between benign prostate tumor and PC, $p>0.05$, as shown in Figure 2.

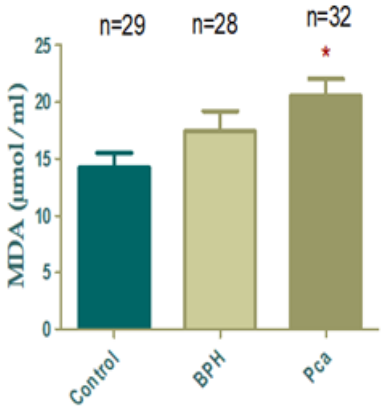

Fig. 2. Serum MDA conc. comparison between prostate cancer, BPH with healthy men.

In addition, as compared to both the control group (77.60 ± 3.041) and benign prostate hyperplasia (76.57 3.266), these findings show a substantial decrease in SOD degree in prostate cancer, $p<0.05$ (55.36 ± 2.257), While the SOD level in benign prostate hyperplasia have non-significant difference by comparison with control group, $p>0.05$ (Figure 3).

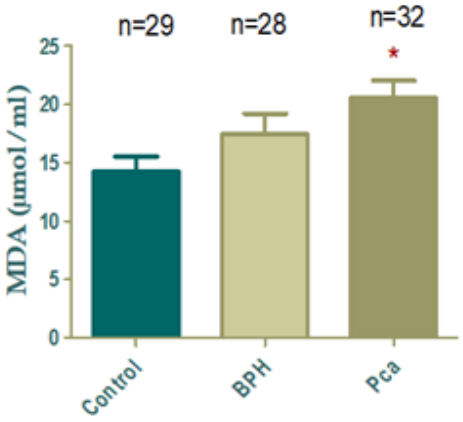

Fig. 3. Serum SOD conc. comparison between PC, BPH with control group.

The results of the current study shown a positive correlation between PSA and hK2 and between PSA and MDA, in same time a negative correlation was between PSA and SOD and between MDA and SOD levels (Figures 4-6).

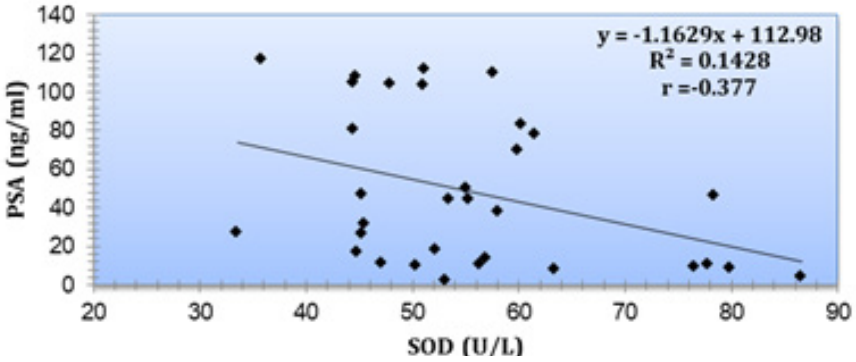

Fig. 4. Correlation of PSA (ng/ml) with SOD level (U/L).

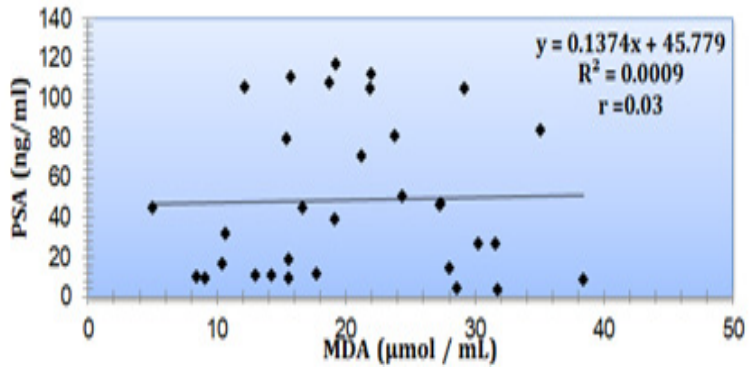

Fig. 5. Correlation of PSA (ng/ml) with MDA level (µmol/ml).

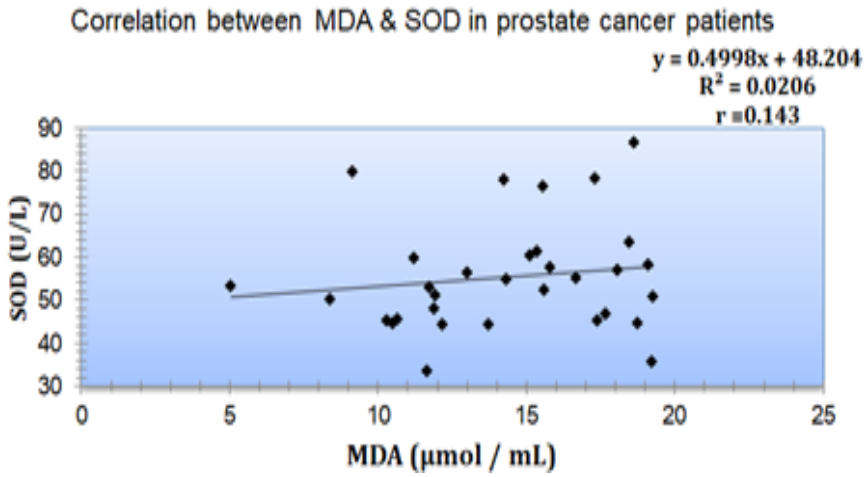

Fig. 6. MDA conc. (µmol/ml) correlation with SOD concentrations (U/L).

DISCUSSION

A tumor, also known as a neoplasm, is an excessive growth of cells, which may occur in any types of tissues or organ through the body. Tumor may be either benign, meaning they do not have ability to invade surrounding tissues, or malignant tumor, which meaning they have the ability to invade surrounding tissues and can invade any parts through the body via the lymphatic or bloodstream system.

According to the National Cancer Institute, "tumors are abnormal masses of tissue that form when cells begin to divide uncontrollably and are not regulated by the body's normal control mechanisms." The tumors can originate from any histological type of tissues in the body and can be classified based on the tissue or organ they originate from, as well as their biological behavior. The American Cancer Society further explains that tumors develop as a result of mutations or changes in the cell genome, which may result from various causes such as exposure to radiation, chemicals, or viruses, as well as genetic predisposition or simply by chance.

Cancer is complex, and environmental and dietary patterns, as well as viral and genetic influences both influence its growth. PC is one type of cancers which originate in the prostate gland, that participate in seminal fluid produces in men. PC is estimated that approximately 1 from each 8 men will be diagnosed with PC in through their life. The reasons of PC still unknown, but it may be came from a combination of environmental and genetic causes. Age is also a significant risk factor, with the majority of cases associated with advance in age (after 65 years).

Prostate cancer can be harmful at times. According to the National Cancer Institute, around three million men and women in the USA and more than two million people around the world diagnosed with prostate cancer. Due to the majority of elderly men developing this disease, the fight against it is becoming an important public health priority.

Researchers in epidemiology, biochemistry, as well as those studying in the clinical setting, have concluded that oxidative stress markers are involved in tumor growth and progression, a study achieved in 2010 showed an association between chronic inflammation and malignant tumor development, and how oxidative stress is involved in this process. It describes how ROS can cause DNA damage, and promote mutations that cause the cancer, and how inflammation can further exacerbate this process.

The findings of the analysis aimed for evaluation the relationship of oxidative stress with antioxidants in PCa and BPH. Overall, we found elevated levels of MDA in PC patients by compare with control group, and the findings are identical in BPH patients and controls, while SOD levels are decreased in PCa patients by comparison with benign prostate tumor patients and healthy controls. Ahmed Amar et al., found SOD levels lower in PCa

patients compared with BPH patients and healthy men in addition to MDA level higher in PCa patients compared with BPH patients and healthy men and this agreed with our results. Also another study measured SOD activity in prostate cancer patients and healthy controls. The results showed that SOD activity was lower in PC patients and that this was linked with oxidative stress increased and antioxidant capacity decreased. The effect of SOD in protecting cells from oxidative stress, and how decreased SOD activity can lead to increased ROS levels and oxidative damage was studied. It also notes that decreased SOD activity has been observed in prostate cancer.

This study is consistent with recent findings about the relationship between OS and various tumor types and leucocyte lipid peroxidative damage and DNA damage, which found significantly higher levels of peroxidation of lipid and damage of DNA in the breast, colorectal, as well as oral squamous cell carcinoma. The discussion of the disease is prominent in the causes of the build-up of fatty peroxidation, a key indicator of oxidative stress and degeneration, including a heightened vulnerability to cancer and aging. The MDA finds the most commonly examined lipid peroxidation biomarkers.

Regular antioxidants can mitigate and control oxidative stress to some extent, but because of their specific instruments of action, they have a limited effect on greatly elevated levels of ROS. SOD, for example, converts two atoms of superoxide into hydrogen peroxide and oxygen, but it needs to other catalase enzyme to reactant cycle complete. Several widely used antioxidants were able to replace only one receptor group before they needed to be regenerated. The benefit derived from these natural antioxidants may be overwhelmed by high levels of reactive oxygen species in the wound or illness, which further speeds up the inflammation process.

In models that monitor antioxidants before any harm occurs, the benefit of antioxidant treatment is especially obvious and few have demonstrated a significant impact after injury. It is therefore important to develop antioxidant products that are produced and restore normal levels of oxidative anxiety, along with medications that can be used after damage. The present study showed a correlated positively between MDA and SOD, meaning that the higher the MDA level, the lower the SOD level. Therefore, antioxidant treatments must be used to prevent the progression of cancer, as many previous studies found that the lack of antioxidants and the increase in ROS have a fundamental role in the development of many types of cancers.

These results did not completely agree with Kucukdurmaz et al., as they found an increase in both MDA and SOD in patients with prostate cancer. This is in contrast to current study, which found an increased in MDA and decreased in SOD level in prostate cancer patients. Deoxyribonucleic acid damage occurs over time and can lead to increasing risks of PC because of elevated amounts of free radicals combined with a reduction in antioxidants in the prostate gland. High conc. of MDA and low conc. of anti-oxidant enzymes such as SOD in PC patients indicate high levels of oxidation. While our results agree with case-control study compared levels of SOD, catalase, and MDA in PC patients and control group. The study showed that MDA concentrations in PC patients were significantly higher by comparison to control group, while SOD activity was significantly lower. Zhang et al., studied the effect of Oxidative Stress (OS) and antioxidants in the development of prostate cancer. It notes that MDA levels are elevated in prostate cancer patients, while SOD activity is decreased, indicating increased oxidative stress. The article also discusses the potential for antioxidant therapy as a therapeutic approach for prostate cancer.

The current study found the conc. of PSA was high in PC group more than control group, and this finding agree with many studies. PSA a protein made via epithelial cells in the prostate gland is regulated by an androgen receptor. When a prostatic architecture is disrupted, PSA may enter the bloodstream, leading to increased levels in serum. However, while serum PSA is specific to prostate tissue, it does not specifically indicate the presence of cancer, as benign prostate tumor and chronic inflammation of prostate can also lead to elevated levels. Since the introduction of PSA as a diagnostic tool for PC in the 1980's, the rate of late-stage PC detection has decreased, with more tumors being detected at earlier, curable stages.

PSA can form a complex with endogenous protease inhibitors, such as α1-Antichymotrypsin (ACT), resulting in the formation of a PSA-ACT complex. This complex constitutes approximately 90% of PSA in serum. In cases of PC, there was an increase in serum bound PSA conc. accompanied by free PSA decrease. Although a decision to biopsy individuals with PSA Conc. Arrange from 4.0 to 10.0 ng/mL is usually depend on total PSA conc., the free PSA percentage (% of PSA) is a more useful metric for identifying those who require biopsy. PSA tests show significant variation, and many platforms display a difference between total and free PSA that exceeds 10% relative difference.

This means that PSA results obtained from different assays cannot be used interchangeably. In addition, most tests the current calibration of PSA tests employs a reference standard that produces PSA readings roughly 25% lower than the original test, which was utilized to determine the threshold value of 4.0 ng/mL. Many men with prostate cancer have PSA levels below the upper limit of normal of 4.0 ng/mL, indicating that this cutoff value is inadequate. Therefore, individuals with PSA kinetics between 2.5 and 4.0 ng/mL should undergo prostate biopsies based on factors such as velocity, doubling time, and density, among others.

The American Cancer Society (ACS) has revised its recommendations for prostate cancer screening, highlighting the limitations of the PSA test and advising that it should only be offered to informed patients who have been fully educated about the uncertainties, risks, and possible benefits of screening. It's worth noting that the ACS hasn't endorsed regular PSA screenings since the 1990's. These guidelines were updated in response to the findings of two large, prospective clinical trials. When the PSA level is above 4.0 ng/mL, the sensitivity is around 80% and the specificity is around 50%. Standard prostate biopsies have a sensitivity of about 60% and a specificity of 100%. Due to the limited PSA test to diagnosis the prostate cancer, a research focused on developing markers specific for prostate tumors, one of these markers is such as prostate cancer antigen-3.

This opens the door to new research using enzymatic antioxidants to reduce oxidative processes and free radical accumulation, which is consider the major cause of prostate cancer. Additionally, consuming an antioxidant-rich diet may help to prevent prostate cancer.

CONCLUSION

From current study we concluded PSA level was high in patients with prostate cancer and there is a negative relationship between MDA and SOD, meaning that the level of MDA inverse proportion with SOD, and this may affects the progression of prostate cancer.

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