

Changes in antioxidant status and lipid peroxidation in Nigerian patients with prostate carcinoma

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KEY WORDS

antioxidant, lipid peroxidation, Nigerian, prostate cancer, prostate-specific antigen

ABSTRACT

INTRODUCTION Oxidative stress has been implicated in the etiology of several pathologies.

OBJECTIVES The study was designed to investigate the levels of antioxidants and lipid peroxidation (LPO) in relation to prostate-specific antigen (PSA) levels in blood of Nigerian prostate cancer (PCa) patients.

PATIENTS AND METHODS One hundred twenty PCa patients were assigned to 3 groups; group 1 (low grade) with a PSA level of 5–10 ng/ml ($n = 33$), group 2 (medium grade) with PSA of 11–20 ng/ml ($n = 45$) and group 3 (high grade) with PSA >20 ng/ml ($n = 42$). The control group comprised 50 healthy subjects with PSA <3.0 ng/ml.

RESULTS Subjects with a PSA level of 11–20 ng/ml and PSA >20 ng/ml had significantly lower uric acid and reduced glutathione levels ($p < 0.05$). A significant reduction ($p < 0.05$) in plasma vitamin C and E levels was observed in these patients. The levels of vitamins C and E decreased by 27% and 77% in subjects with PSA >20 ng/ml, and by 25% and 47% in subjects with a PSA level of 11–20 ng/ml, respectively. Serum total bilirubin, alkaline phosphatase (ALP) and LPO were significantly ($p < 0.05$) elevated in subjects with PSA >11 ng/ml. More specifically, total bilirubin, ALP and LPO levels were elevated by 75%, 66% and 107% in subjects with PSA at 11–20 ng/ml, and by 167%, 105%, 98% in subjects with PSA ≥ 20 ng/ml, respectively. Moreover, superoxide dismutase and catalase activities were lower ($p < 0.05$) in all cancer patients.

CONCLUSIONS The results confirmed the depletion of antioxidants in PCa patients, and an inverse relationship between antioxidants and PSA values in this group.

INTRODUCTION Cancer is a major cause of mortality worldwide, and in the United States, it is second only to heart disease.¹ Prostate cancer (PCa) is the most common type of cancer among men, with an incidence rate of one in six men.² Furthermore, because androgens may play a role in smooth muscle proliferation associated with the development of PCa, men at an increased risk of PCa may also display heightened risk of cardiac disease.³ As many as one in four men >60 years old have symptoms of benign prostate enlargement, and therefore have an increased risk of PCa.^{3,4} Moreover, although prostate

specific-antigen (PSA) concentration of ≥ 4.0 ng/ml ($4.0 \mu\text{g/l}$) is often used in screening for PCa, more than 20% of men diagnosed as having PCa have PSA levels below this cut-off value.⁵ Thus, recent work has focused on using free PSA expressed as a percentage in combination with total PSA to improve the specificity of diagnosis and decrease false-positives.⁵ Since PCa affects many men, there is a need for affordable and practical preventive options that target this disease. The exact cause of PCa is largely unknown.⁶ However, several risk factors that increase the risk of developing this disease have been identified.

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These include age, racial differences, family history, dietary habits, lifestyle, and environmental factors.⁷⁻¹¹ Epidemiological studies suggest that a diet rich in fruit and vegetables is associated with a reduced risk of developing cancers, including PCa.¹² Because such diets are abundant sources of phytochemicals, it has been suggested that a relatively low risk of developing PCa among Asian men may be attributed in part to high phytochemical consumption.^{13,14} Likewise, several in vitro studies confirmed the role of exogenous antioxidants in inhibiting the proliferation and growth of different PCa cells. For example, Hahm and Singh¹⁵ reported that Honokiol, a constituent of the oriental herb, *Magnolia officinalis*, caused G₀-G₁ cell cycle arrest in human LNCaP PCa cells. Moreover, silibinin and mixtures of flavonolignans (isolated from the dried fruits of milk thistle, *Silybum marianum*), resveratrol and epigallocatechin-3-gallate obtained from red wine and green tea, respectively, and anthocyanins from potato extracts showed beneficial effects on different PCa cells via induction of p21/Cip1 and p27/Kip1, G₁ arrest, induction of apoptosis, and scavenging of reactive species in vitro.¹⁶⁻¹⁸ In view of the above observations, it might be suggested that prostate carcinogenesis may promote free radical generation, underlying the effectiveness of antioxidant-rich diet intervention^{10,15}, and exogenous antioxidants in inhibiting the growth of PCa cells.^{17,18} This statement was supported by Miyake et al.¹⁹, who reported that oxidative stress may be involved in early events in PCa development, and androgen suppression is capable of decreasing stress. In this study, we have investigated the pattern of antioxidants (enzymatic and nonenzymatic) and lipid peroxidation (LPO) in the blood of PCa patients relative to their respective PSA values.

PATIENTS AND METHODS **Patients** A total of 170 participants, aged 24–73 years and resident in south-western Nigeria, were recruited from the Cancer Screening Unit, University College Hospital, Ibadan. One hundred twenty participants had PSA in the range of 5.0–43.8 ng/ml; specifically, they were grouped into low-grade PSA (5–10 ng/ml) (n = 33), medium-grade PSA

(11–20 ng/ml) (n = 45), and high-grade PSA (>20 ng/ml) (n = 42). Likewise, 50 apparently healthy subjects were recruited as controls and had a PSA concentration <3.0 ng/ml. Exclusion criteria included abstinence from hormonal and/or radiation therapy, use of prescription and nonprescription preparations known to alter PSA (e.g., Saw Palmetto, Finasteride), hormone levels and blood pressure. Eligible subjects were invited, screened and their blood samples collected. Written informed consent was obtained from each participant, and the Human Ethical Committee at the Oyo State Ministry of Health, Ibadan, Nigeria, approved the study.

Sample collection Blood samples were drawn from antecubital veins of subjects into tubes containing EDTA and another portion into plain centrifuge tubes. All sample collection procedures were conducted with minimum light exposure. The samples in plastic centrifuge tubes were allowed to clot, and spun at 3000 × g for 15 min in an MSC bench centrifuge to obtain serum which was used for the determination of PSA, alanine and aspartate aminotransferases (ALT and AST), alkaline phosphatase, LPO and total bilirubin. The blood samples in the EDTA tubes were divided into two portions. One portion of the whole blood was used for the determination of antioxidant profile (superoxide dismutase, catalase and glutathione levels). The second portion was centrifuged at 3000 × g for 15 min to obtain plasma which was used to estimate uric acid and vitamins C and E.

Laboratory and clinical methods We measured PSA in serum using electrochemiluminescence immunoassays from Roche Diagnostics in combination with a Roche/Hitachi MODULAR ANALYTICS device. Whole blood superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) were determined by colorimetric assays at wavelengths of 560 nm, 240 nm and 412 nm according to the laboratory methods described by McCord and Fridovich²⁰, Aebi²¹, and Moron et al.²², respectively. Furthermore, serum ALT and AST activities were determined using combined methods of Mohun and Cook²³

TABLE Changes in total bilirubin, uric acid and reduced glutathione levels in prostate cancer patients

Grouping	Subjects			
	PSA			
	<3 (normal) (n = 50)	5–10 (n = 33)	11–20 (n = 45)	>20 (n = 42)
total bilirubin(mg/dl)	0.52 ±0.21	0.58 ±0.13	0.91 ±0.43 ^a	1.39 ±0.50 ^a
uric acid (mg/dl)	3.62 ±0.88	3.80 ±1.06	2.18 ±0.77 ^a	2.33 ±0.41 ^a
reduced (μg/ml) glutathione	3.79 ±0.75	3.38 ±0.58	1.39 ±0.81 ^a	1.54 ±0.39 ^a

Values are means ± standard deviation

^a Significantly different from normal at p <0.05

Abbreviations: PSA – prostate-specific antigen

FIGURE 1 Changes in alanine and aspartate aminotransferases activities in prostate cancer patients
a significantly different from normal and other PSA groups at $p < 0.05$
 Abbreviations: ALT – alanine aminotransferase, AST – aspartate aminotransferase, prostate-specific antigen (ng/ml), PSA – prostate-specific antigen

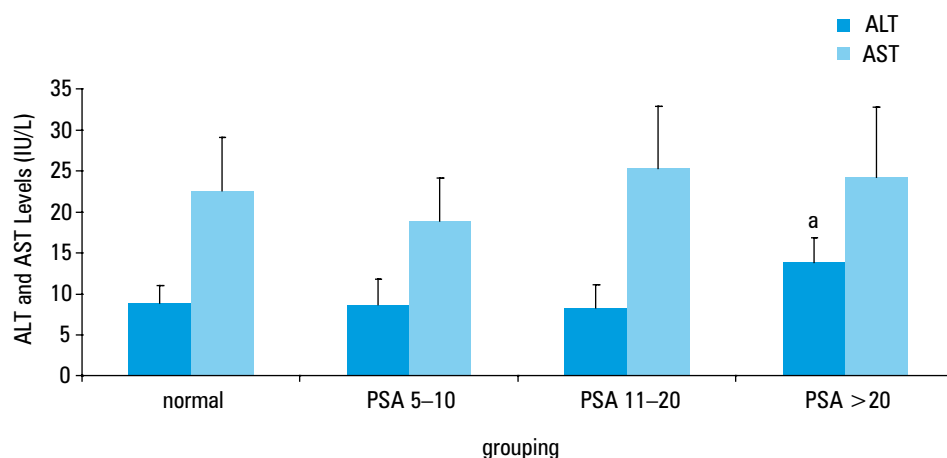


FIGURE 2 Changes in serum alkaline phosphatase activities in prostate cancer patients
a significantly different from normal and PSA 5-10 at $p < 0.05$
 Abbreviations: see FIGURE 1

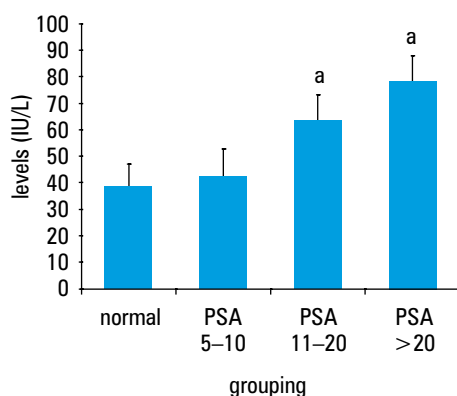
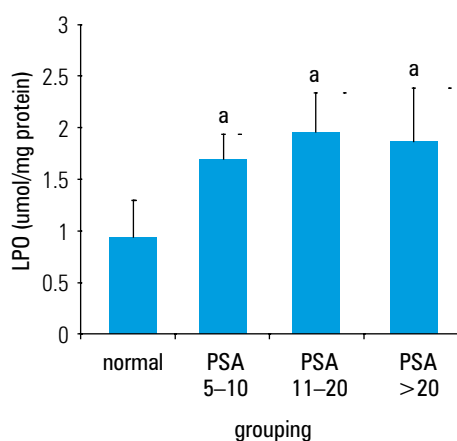


FIGURE 3 Changes in the levels of lipid peroxidation products in prostate cancer patients
a significantly different from normal at $p < 0.05$
 Abbreviations: LPO – lipid peroxidation, others – see FIGURE 1



as well as Reitman and Frankel²⁴, respectively. Likewise, the estimation of serum alkaline phosphatase (ALP) activity was based on the Williamson spectrophotometric method.²⁵ Serum protein levels were determined according to the laboratory procedure described by Lowry et al.²⁶, using bovine serum albumin as standard, while the extent of LPO was estimated by spectrophotometry as described by Buege and Aust.²⁷ Total bilirubin levels were determined colorimetrically using the assay by Rutkowski and DeBaare.²⁸ Plasma uric acid level was determined by the laboratory procedure of Kyaw²⁹, while plasma vitamins C and E were estimated spectrophotometrically by the procedure of Sauberlich³⁰, and Meshali et al.³¹, respectively.

Statistical analysis All values were expressed as the mean \pm standard deviation ($n > 30$ in all groups). Data was analyzed using one-way ANOVA followed by the post-hoc Duncan multiple range test for analysis of biochemical data using SPSS version 11 (SPSS Inc Chicago, Illinois). Values were considered statistically significant at $p < 0.05$.

RESULTS Plasma uric acid and whole blood GSH levels were significantly lower in known PCa patients (PSA > 20 ng/ml) and subjects with PSA 11–20 ng/ml ($p < 0.05$). The levels of uric acid decreased by 36% and 40%, while GSH levels decreased by 59% and 63%, in subjects with PSA > 20 ng/ml and PSA of 11–20 ng/ml, respectively (TABLE). Furthermore, serum total bilirubin levels were elevated by 167% and 75% in subjects with PSA > 20 ng/ml and PSA of 11–20 ng/ml, respectively. In FIGURE 1, there were no significant differences ($p > 0.05$) in the activities of serum ALT and AST of subjects with PSA < 3.0 ng/ml when compared to other groups, except for ALT activity of known PCa patients (PSA > 20 ng/ml) which was elevated by 56% when compared to subjects with PSA < 3.0 ng/ml. FIGURES 2 and 3 revealed that the levels of serum ALP and LPO were significantly higher in PCa patients with PSA > 20 ng/ml and PSA of 11–20 ng/ml. ALP and LPO levels were elevated by 105% and 66% in subjects with PSA > 20 ng/ml, and by 98% and 107% in subjects with PSA of 11–20 ng/ml, respectively. In FIGURE 4, plasma vitamin C and E levels showed an inverse relationship with PSA values of subjects. Vitamin C and E levels were significantly reduced in known PCa patients (PSA > 20 ng/ml) by 27% and 77%, and subjects with PSA of 11–20 ng/ml by 25% and 47%, respectively. The depletion of vitamin E seems more pronounced than vitamin C, and could be observed in subjects with PSA of 5–10 ng/ml. Enzymatic antioxidants (SOD and CAT) were significantly reduced ($p < 0.05$) in subjects with PSA 11–20 ng/ml and PSA > 20 ng/ml. Furthermore, SOD activity decreased by 67%, 71% and 81% in subjects with PSA of 5–10 ng/ml, PSA of 11–20 ng/ml and PSA > 20 ng/ml, respectively, while CAT activity also decreased by 55%

FIGURE 4 Changes in plasma vitamin C and E levels in prostate cancer patients

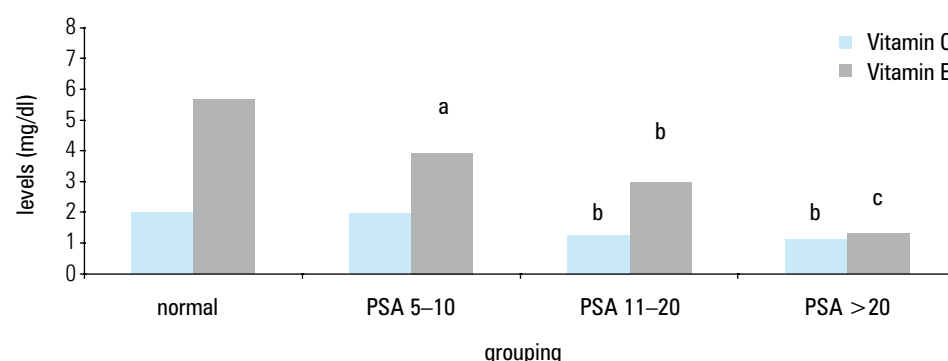
a significantly different from normal at $p < 0.05$

b significantly different from normal and PSA 5–10 at $p < 0.05$

c significantly different from normal, PSA 5–10 and PSA 11–20 at $p < 0.05$

Abbreviations: see

FIGURE 1



and 58% in subjects with PSA of 11–20 ng/ml and PSA >20 ng/ml, respectively.

DISCUSSION The major finding of this study was that antioxidant levels, both enzymatic and non-enzymatic, were significantly reduced in subjects with high PSA values. The inverse relationship points to the fact that oxidative stress in subjects correlates positively with PSA values.

Free radicals, oxidative stress and antioxidants have become common terms in modern research on pathologic mechanisms.³² Nonetheless, free radical production occurs as a consequence of normal endogenous reactions and plays an important role in physiological cell function. It is important to note that the ingestion of exogenous substances and environmental factors can also promote free radical formation, thereby leading to the depletion of cellular antioxidants.³³ Reactive oxygen species (ROS) have physiological functions, including activation and modulation of signal transduction pathways³⁴, alteration of activities of redox-sensitive transcription factors³⁵, and regulation of mitochondrial enzyme activities.³⁶ Levels of ROS are reduced by antioxidant defense, but increased by transition metals such as iron or copper and by exogenous agents such as ionizing radiation or ozone. To protect against toxic effects of ROS and to modulate physiological effects of ROS, the cell has developed an intricately regulated and a very complex antioxidant defense system. It is composed of small molecular weight antioxidant compounds (vitamins E, C, A, uric acid, and so forth), primary (SOD, catalase, glutathione peroxidase) and secondary

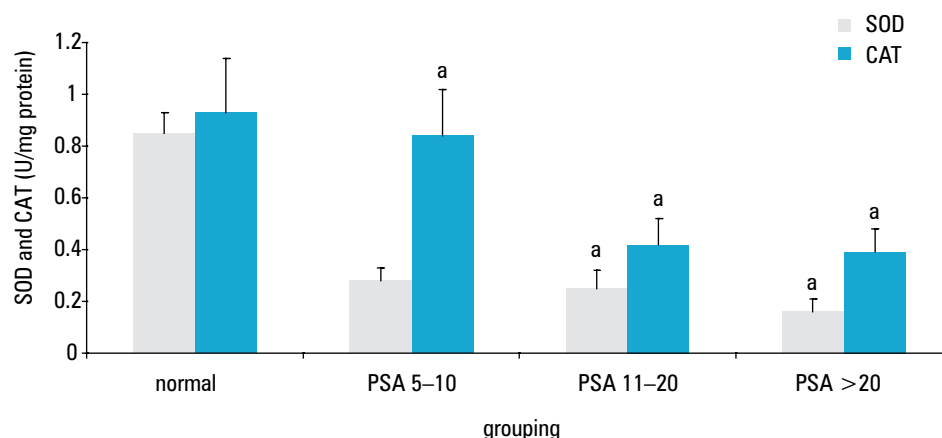
antioxidant enzymes (glutathione reductase and glucose-6-phosphate dehydrogenase), and the glutathione³⁷, glutaredoxin and thioredoxin systems³⁸. Protein and DNA repair enzymes may be considered part of the antioxidant system.³⁹ In the present study, the activities of the antioxidant enzymes (SOD and CAT) decreased significantly in known PCa patients (PSA >20 ng/ml) when compared to normal (PSA <3.0 ng/ml). This observation is consistent with most in vivo and in vitro studies which demonstrated that the levels of antioxidant enzymes are altered in cancer.⁴⁰ The most consistent findings in biochemical studies have been that of SOD which is lowered in most types of primary cancers and cancer cell lines.⁴¹ Studies on antioxidant enzymes in human lung, renal and prostate cancers^{42–44} confirmed the reduced levels of this enzyme in various cancers. Furthermore, immunoperoxidase studies demonstrated low levels of antioxidant enzymes in primary tumors, although small groups of cancer cells, often on the invading edge of the tumor, did occasionally show strong positivity. These results agree with the well-developed paradigm from numerous biochemical studies that SOD levels are low in PCa.⁴⁵ In contrast, some studies have shown that significantly elevated levels of SOD are possible in metastatic PCa.⁴⁶ In all cases, after comparison with normal tissue controls, SOD has been shown to be altered (elevated or depressed) in primary cancers. One possible explanation of this fluctuation is that primary PCa cells undergo a selection process, with those cells destined for metastasis having high levels of SOD.⁴⁶ Furthermore, polymorphisms

FIGURE 5 Changes in whole blood superoxide dismutase (SOD) and catalase (CAT) activities among prostate cancer patients

a significantly different from normal at $p < 0.05$

Abbreviations: see

FIGURE 1



in the leader sequence of the SOD gene have been correlated with abnormal regulation.⁴⁷ In the present study, the levels of plasma uric acid and whole blood GSH of known PCa patients were significantly lower compared to normal. These biochemical indices measured the nonenzymatic antioxidant levels, and together with the elevated malondialdehyde (MDA) (index of lipid peroxidation) reflect the altered cellular redox status of the subjects.⁴⁸ Several laboratories have analyzed changes in cell redox state in cancer. Okamoto et al.⁴⁹ demonstrated with biochemical techniques that renal cell carcinomas showed higher levels of DNA oxidation compared with corresponding normal tissue controls, as determined by measurements of 8-hydroxy-2-deoxyguanosine. Likewise, Badjatia et al.⁵⁰ reported significantly higher serum MDA, and lower vitamin C and E levels in patients with urothelial bladder carcinoma. This trend was also confirmed in the present study. The notion that ascorbate is involved in resistance to neoplasms was introduced and advocated by Linus Pauling.⁵¹ This notion was based on the demonstration of low ascorbate reserves in cancer patients, and later on the results of clinical trials where the survival time of cancer patients was prolonged by ascorbate supplementation.^{52,53} It is well known that transition metals can interact with and destroy ascorbate.⁵⁴ The role of ascorbate as an antioxidant molecule has been appreciated for years, but only recently ascorbate has been found to play a crucial role in hydroxylation reactions that determine interactions and functioning of thousands of cellular proteins. Hydroxylation is catalyzed by a variety of nonheme iron containing dioxygenases, including prolyl, asparaginyl, and lysyl hydroxylases^{55,56} and novel DNA repairing enzymes, human ABH2 and ABH3 proteins⁵⁷, which require α -ketoglutarate as cofactor. In view of the lower plasma vitamin C levels observed in this study, it is logical that these essential functions of ascorbate are impaired or hindered in cancer patients. Furthermore, vitamin E (α -tocopherol) levels were significantly lower in subjects with PSA of 5–10 ng/ml, PSA of 11–20 ng/ml and PSA >20 ng/ml when compared to controls. This observation is consistent with the findings of Liang et al.⁵⁸, who linked a significant increase in bladder cancer risk to the decreasing plasma α -tocopherol level of study subjects. Vitamin E is a fat-soluble antioxidant, which is known to inhibit the proliferation of PCa cell lines in vitro by arresting DNA synthesis, or by stimulating transforming growth factor β .⁵⁹ However, detailed mechanisms by which vitamin E prevents PCa cell proliferation remain largely unknown. Also, vitamin E breaks free radical chain reactions as a result of their ability to transfer phenolic hydrogen to a peroxy free radical of a peroxidized polyunsaturated fatty acid (PUFA), and thereby preventing peroxidation of PUFA contained in cellular and subcellular membrane phospholipids.⁶⁰ Therefore, depletion of vitamin E levels accounts for

the elevation of MDA (higher lipid peroxidation) observed in this study. It is obvious that a notable decrease in antioxidant status occurred as the PSA values of the subjects increased. Similarly, the low levels of antioxidants in PCa patients could result from increased oxidative damage or it could be that low values of these antioxidants aggravated free radical damage and increased the chance of developing PCa in study subjects, indicating the essential role of antioxidants in disease prevention. The limitations of this study are due to the fact that our data did not reflect the dietary habits and lifestyles of the subjects which may affect the prostate.

In summary, our results may contribute to current knowledge on the relationship between antioxidant status and PSA values of PCa patients, which may help to design a more efficacious therapeutic treatment.

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Zmiany stężenia przeciwutleniaczy oraz peroksydacji lipidów u nigeryjskich pacjentów z rakiem gruczołu krokowego

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SŁOWA KLUCZOWE

Nigeryjczyk, peroksydacja lipidów, antyoksydant, rak gruczołu krokowego, antygen swoisty dla prostaty (PSA)

STRESZCZENIE

WPROWADZENIE Stres oksydacyjny uczestniczy w powstawaniu szeregu patologii u człowieka.

CELE Badanie zaplanowano w celu oceny stężenia antyoksydantów i peroksydacji lipidów (*lipid peroxidation* – LPO) w zależności od poziomu we krwi antygenu swoistego dla prostaty (*prostate-specific antigen* – PSA) u pochodzących z Nigerii pacjentów z rakiem gruczołu krokowego (*prostate cancer* – PCa).

PACJENCI I METODY 120 pacjentów z PCa podzielono na 3 grupy – grupa 1 (niski poziom) ze stężeniem PSA wynoszącym 5–10 ng/ml ($n = 33$), grupa 2 (pośredni poziom) z PSA wynoszącym 11–20 ng/ml ($n = 45$) oraz grupa 3 (wysoki poziom) z PSA >20 ng/ml ($n = 42$). Grupa kontrolna składała się z 50 zdrowych osób z PSA $<3,0$ ng/ml.

WYNIKI U pacjentów z poziomem PSA wynoszącym 11–20 ng/ml i PSA >20 ng/ml stwierdzono istotnie statystycznie mniejsze stężenia kwasu moczowego i zredukowanego glutationu ($p < 0,05$). U tych pacjentów zaobserwowano również znaczne zmniejszenie ($p < 0,05$) poziomów witaminy C i E w surowicy. Stężenie witamin C i E zmniejszyło się odpowiednio o 27% i 77% u pacjentów z PSA >20 ng/ml oraz o 25% i 47% u pacjentów z poziomem PSA 11–20 ng/ml. Poziomy bilirubiny całkowitej, fosfatazy alkalicznej (*alkaline phosphatase* – ALP) oraz LPO w surowicy były większe u pacjentów z PSA >11 ng/ml ($p < 0,05$). Poziomy bilirubiny całkowitej, ALP i LPO były zwiększone odpowiednio o 75%, 66% i 107% u pacjentów ze stężeniami PSA wynoszącymi 11–20 ng/ml, oraz o 167%, 105% i 98% u pacjentów z PSA >20 ng/ml. Także aktywność dysmutazy ponadtlenkowej i katalazy była mniejsza u wszystkich chorych pacjentów ($p < 0,05$).

WNIOSKI Wyniki potwierdziły niedobór przeciwutleniaczy u pacjentów z PCa, a także odwrotną zależność pomiędzy poziomami przeciwutleniaczy a stężeniami PSA.

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