AFMN BIOMEDICINE

ORIGINAL ARTICLE

PARAMETERS OF OXIDATIVE STRESS IN PATIENTS WITH BENIGN PROSTATE HYPERPLASIA, CHRONIC PROSTATITIS, AND PROSTATE CANCER

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Benign prostatic hyperplasia (BPH), chronic prostatitis (CP), and prostate cancer (PC) are frequently occurring conditions that affect the prostate gland, with overlapping clinical features and potentially shared pathogenetic mechanisms. A growing body of research indicates that oxidative stress (OS) is a critical factor in both the onset and advancement of these disorders. Xanthine oxidase (XO) is a known enzymatic source of reactive oxygen species (ROS); however, its involvement in prostate disease pathogenesis remains underexplored.

The study included 17 patients with CP, 10 with BPH, and 15 with PC. Ten healthy individuals served as controls. Serum samples were collected for the BPH and CP groups, while PC samples were obtained from surgical tissues. OS was assessed by measuring thiobarbituric acid-reactive substances (TBARS) and advanced oxidation protein products (AOPP). XO activity was determined spectrophotometrically in plasma and tissue homogenates.

Serum concentrations of TBARS and AOPP were markedly higher in individuals diagnosed with BPH and CP relative to those in the healthy control group ($p < 0.001$). Similarly, XO activity was markedly increased in these groups. In PC tissue, both TBARS and AOPP concentrations, as well as XO activity, were significantly higher than in non-tumor prostate tissue ($p < 0.001$), indicating local OS and enzymatic ROS production.

These findings confirm that systemic and tissue-level OS is elevated in BPH, CP, and PC. XO may represent a shared mechanism linking inflammation and carcinogenesis. The study supports further investigation into the therapeutic potential of antioxidants and XO inhibitors as adjunct strategies in prostate disease management.

Keywords: benign prostate hyperplasia, chronic prostatitis, prostate cancer, oxidative stress

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INTRODUCTION

Prostatic disorders rank among the most prevalent health issues observed in older male populations. The onset of these diseases typically begins around the age of 40. Starting at approximately 50% in 60-year-olds, the occurrence increases substantially, reaching up to 90% by the age of 85 (1). Benign prostatic hyperplasia (BPH) is a condition associated with high morbidity but a very low mortality rate (2). In recent years, chronic prostatitis (CP) has emerged as a major issue in urology (3). Around 90% of men exhibiting symptoms of prostatitis are classified as having chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), or category III, characterized by a symptom duration of at least three months and the lack of a detectable urinary tract infection (4).

Prostate cancer (PC) represents the second most frequently diagnosed malignancy in the male population (5). Although the exact mechanisms underlying prostate tumor development are not fully understood, a strong association has been documented between oxidative stress (OS) and increased cancer risk. A growing body of evidence indicates that OS contributes significantly to both the initiation and advancement of PC (6). The imbalance caused by excessive reactive oxygen species (ROS) and insufficient antioxidant protection is recognized as a major contributor to the pathogenesis of several prostate-related conditions. Chronic inflammatory processes in the prostate have been linked to age-associated hormonal fluctuations and infections (7). Such sustained inflammation within prostatic tissue facilitates the formation of free radicals, contributing to OS. At sites of inflammation, injury, or infection, immune cells are known to stimulate the production of free radicals. Accordingly, OS in these patients may significantly contribute to disease progression. OS may stem from bacterial infections and/or the body's inflammatory reaction to these pathogens (8).

The inflammatory process can initiate proliferation and induce DNA modifications in prostate tissue caused by OS. Repeated injury to tissue, along with the presence of OS, can initiate compensatory mechanisms that drive increased cellular division, thereby elevating the likelihood of abnormal tissue growth or the formation of neoplastic lesions (9). Damage to DNA in this context may disrupt normal transcriptional and replication processes, activating multiple intracellular signalling pathways and ultimately contributing to genomic instability, a hallmark feature in the development of cancer (10).

Among the harmful effects exerted by ROS, lipid peroxidation is particularly damaging, resulting in permanent impairment of cellular membrane structure and function. Thiobarbituric acid-reactive substances (TBARS) are recognized as terminal products and dependable biomarkers of lipid peroxidation activity (11).

Proteins are also susceptible to oxidative modifications caused by free radicals. Research indicates that plasma levels of advanced oxidation protein products (AOPP) are markedly higher in individuals with urinary tract disorders (12). The release of these oxidative markers may be associated with inflammatory processes or a reduction in the body's antioxidant capacity. OS contributes to urinary tract injury through direct cellular toxicity, potentially by disrupting vascular function or acting as a key regulator of various pathological mechanisms.

One recognized pathway for ROS generation involves the enzyme xanthine oxidase (XO). XO produces uric acid, which is the end product of adenine nucleotide breakdown (13). This enzyme is widely present in various tissues across multiple animal species, where it facilitates the oxidation of both endogenous and exogenous compounds. In mammals, XO exists in two interchangeable forms: xanthine dehydrogenase and XO. Specifically, XO is the isoform responsible for generating oxidative radicals. Under certain pathological conditions, xanthine oxidase becomes a major contributor to the production of superoxide anion radicals (O_2^-) (14,15).

An important question is whether XO activity may represent a key factor contributing to the onset and progression of the BPH, CP, and prostate carcinogenesis.

The purpose of this research was to evaluate the extent of OS in individuals diagnosed with BPH, chronic prostatitis, and PC, as indicated by the concentrations of TBARS and AOPP. Furthermore, our study sought to assess XO activity as a possible contributor to ROS generation in the plasma of men with prostate disorders, compared to healthy controls. The overarching objective was to explore the therapeutic potential of XO inhibitors and antioxidants in managing these diseases.

METHODS

Patients

The study included 17 patients with CP treated at the Clinical Center Kragujevac and the Health Center Knić, 10 patients with BPH and 15 patients with PC treated at the University Clinical Center Niš. Serum samples were

collected from patients with BPH and CP, while tissue samples were obtained for the examination of PC.
All patients underwent routine diagnostic procedures. CP was diagnosed through microbiological and biochemical analysis of prostatic fluid. Carcinomas were diagnosed via biopsy and confirmed pathohistologically following radical prostatectomy.
Participants were categorized into three clinical groups according to their specific disease diagnosis.
Group I—17 patients with CP;
Group II—10 patients with BPH;
Group III—15 patients with PC.
The control group consisted of 10 healthy individuals, selected in relation to the clinical groups, where the absence of disease was confirmed by the concentration of prostate-specific antigen (PSA). Control subjects had no acute or chronic illnesses or hypertension. The participants were matched based on age and gender.
Blood samples from patients with BPH, CP, and the control group were collected, then centrifuged at 3000 rpm to isolate plasma, which was subsequently stored at -20°C until further analysis. After radical prostatectomy, tissue specimens from PC patients were obtained by a pathologist, after which they were homogenized and used for analysis. The control tissue was the prostate tissue most distant from the cancerous region.
Informed consent was obtained from all participants prior to their inclusion in the study. The research adhered to the principles of the Declaration of Helsinki and received approval from the Ethics Committee of the Medical Faculty in Niš (Decision No. 12-8818-2/8) on September 23, 2020.

Lipid peroxidation products quantification
Lipid peroxidation products in plasma and tissue were quantified by a slightly adapted version of the method described by Nabavi et al. (16). The levels of TBA-reactive lipid peroxidation products were measured spectrophotometrically at 532 nm against a blank, with results expressed in µmol/L and µmol/mg.

AOPP concentration quantification
Plasma and tissue concentrations of advanced oxidation protein products (AOPP) were assessed spectrophotometrically following the procedure outlined by Vitko et al. (12). AOPP levels were reported as µmol/L chloramine T equivalents.

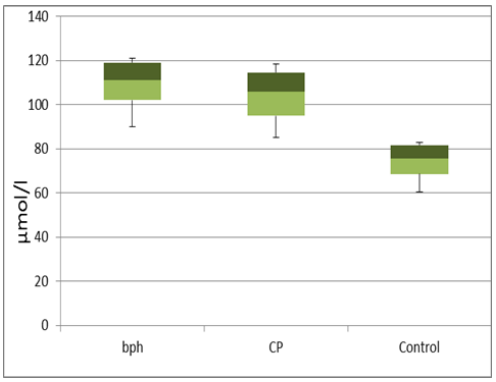
XO activity assessment
XO activity was determined spectrophotometrically using xanthine as a substrate. The assay measured uric acid production over a set time in the absence of NADH, where molecular oxygen acted as the sole electron acceptor. Uric acid formation was monitored at 293 nm, and XO activity was expressed as units per mg of tissue protein in the homogenate (17).

Determination of protein concentration
The amount of protein in cancer and healthy tissue was measured following the procedure outlined by Popović et al. (18), with results expressed as mg of protein per liter.

Statistical analysis
Data were presented as mean ± standard deviation (SD). A p-value less than 0.05 was considered statistically significant. For comparisons between two independent groups, a Student's t-test was used, and the following parameters were reported: t-value and degrees of freedom. For more than two groups, a one-way analysis of variance (ANOVA) was performed, including the presentation of the F-value, between-group and within-group degrees of freedom and corresponding p-values. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows, version 11.0 (Chicago, Illinois, USA).

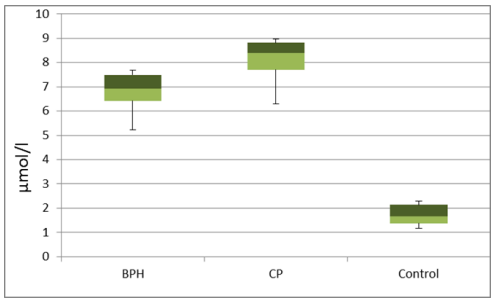
RESULTS

In the serum of the patients with BPH, CP, and healthy controls, we determined the level of lipid peroxides in the form of TBARS (Figure 1). Serum TBARS levels were significantly elevated in patients with BPH and CP compared to the control group ($p < 0.001$). However, no statistically significant differences were observed between the patient groups.
Next, we measured the level of oxidation of proteins, via AOPP concentration (Figure 2). Serum AOPP levels were significantly higher in patients with BPH and CP compared to the control group ($p < 0.001$), with no notable differences observed between the patient groups.
Then, we assessed XO enzyme activity (Figure 3) as a potential contributor to OS in patients with BPH and CP. The plasma XO activity was significantly elevated in both patient groups compared to the controls ($p < 0.001$). In the subsequent phase of our study, we quantified OS markers in PC tissue. As the control, we used healthy tissue located outside of the tumor site.



Group	Mean	St.dev	P value
BPH	111.42	12.46	< 0.001 vs control
CP	105.02	19.42	< 0.001 vs control
Control	73.96	12.73	

Figure 1. *Vertical boxplot for TBARS values in patients with BPH, CP, and controls*



Group	Mean	St.dev	P value
BPH	6.82	1.46	< 0.001 vs control
CP	8.39	4.42	< 0.001 vs control
Control	1.78	0.53	

Figure 2. *Vertical boxplot for AOPP values in patients with BPH, CP and controls*

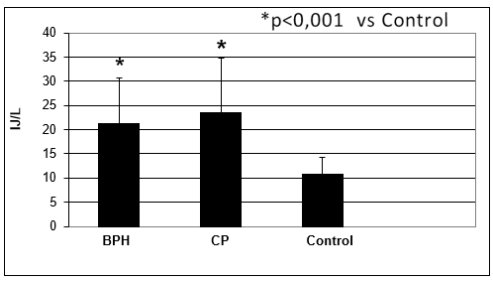
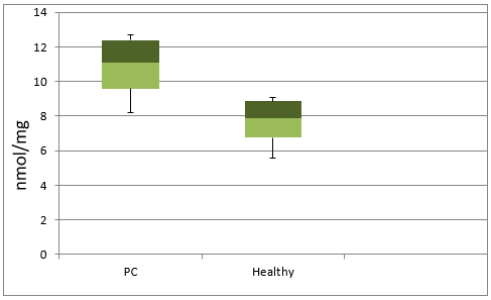


Figure 3. *Xanthine oxidase activity in patients with BPH, CP, and controls*

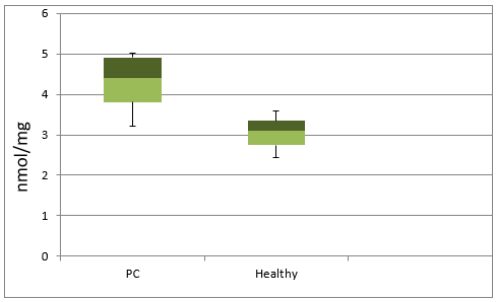
Next, we found the significantly increased level of TBARS in PC tissue when compared to control healthy tissue ($p < 0.001$) (Figure 4).



Group	Mean	St.dev	P value
PC	11.1	1.95	< 0.001 vs healthy
Healthy	7.96	0.75	

Figure 4. *Vertical boxplot for TBARS values in PC tissue and healthy prostate tissue*

Figure 5 illustrates the concentration of AOPP in PC and healthy control prostate tissue. We observed the significantly increased level of AOPP in PC tissue when compared to control tissue ($p < 0.001$). (Figure 5).



Group	Mean	St.dev	P value
PC	4.45	0.62	< 0.001 vs Healthy
Healthy	3.16	0.34	

Figure 5. *Vertical boxplot for AOPP values in PC tissue and control tissue*

Assessing XO enzyme activity as a potential contributor to OS in PC, we found that XO activity was significantly higher compared to healthy prostate tissue (Figure 6).

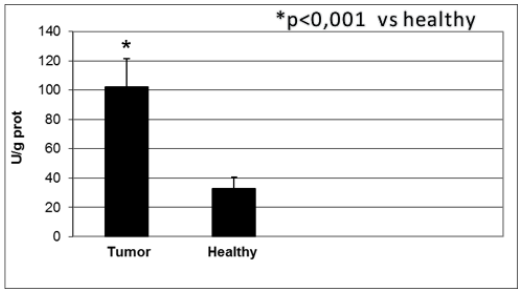


Figure 6. *XO values in tissue of the patients with PC and control tissue*

DISCUSSION

Benign prostatic hyperplasia (BPH), as well as chronic prostatitis (CP), remain diseases with an insufficiently understood etiopathogenesis, where the therapeutic approach is not yet fully defined. As one of the most common benign tumors, BPH is treated based on the severity of symptoms throughout a patient's lifetime (19). A large number of patients suffer from prostatitis, which ranks among the most common conditions encountered in urology (20). Prostatitis poses a particular diagnostic and therapeutic challenge when there is no confirmed bacterial colonization in prostatic tissue, yet inflammatory infiltrates are present. A key question is whether the pathogenetic mechanisms connect these benign conditions to PC, a tumor commonly diagnosed in men over 50 years of age (21). Is there a potential association between these three diseases and increased OS levels?

The prostate gland is very sensitive to free radicals due to the high lipid content of its cellular membranes and glandular capsule. The assessment of lipid peroxidation is commonly performed by measuring TBARS, which serve both as toxic molecules and biomarkers of OS (22). Our findings demonstrate that patients with BPH have significantly elevated TBARS levels compared to healthy controls (Figure 1), supporting the involvement of OS in BPH progression (23,24). It has been proposed that BPH might represent an immune-mediated condition characterized by pronounced inflammation (25,26). Chronic inflammation within the prostate contributes to disruptions in sex steroid hormone balance. Furthermore, infections can promote infiltration of immune cells, including macrophages and neutrophils, into prostatic tissue. These immune cells produce reactive oxygen and nitrogen species, which can overwhelm antioxidant defences and trigger OS. Chronic oxidative damage to prostatic tissue initiates compensatory cell proliferation, which eventually results in hyperplastic growth and the development of prostatic adenoma (27,28).

The most significant indicator of OS's systemic effect and prostate injury is likely the level of AOPPs. Our study demonstrated that AOPP concentration is higher in the serum of patients with BPH when compared to healthy individuals (Figure 2). Hong Yan Li et al. (29) demonstrated that in a remnant kidney model, elevated levels of AOPPs were associated with accelerated renal injury progression, as indicated by significant increases in tubular fibrosis and glomerulosclerosis. The direct toxic effect of AOPP was further supported by experiments showing that its administration raised urinary protein excretion in sham-operated rats (30). Moreover, chronic exposure to AOPP in this kidney model was found to elevate TBARS levels and diminish antioxidant defences (29). Free radicals can also lead to direct damage to DNA and accelerate apoptosis, processes that may contribute to cellular hyperplasia (31).

In our study, we also included patients with CP type III, characterized by inflammation in prostate fluid without the presence of bacteria. Disruptions in redox balance trigger numerous oxidative-reductive reactions that are fundamental to the pathophysiology of inflammation. Multiple studies have shown that OS plays a significant role in the onset and progression of chronic inflammation, contributing to the pathogenesis of various chronic conditions, including chronic prostatitis (32,33). Our findings indicated that serum levels of both TBARS and AOPP were significantly elevated in patients with chronic prostatitis (CP) compared to healthy individuals (Figure 1 and 2). ROS can also be generated by inflammatory cells in CP (34). The superoxide anion radical, released by phagocytes recruited to inflammatory sites, is considered a primary radical in the process of the cellular and tissue injury in these regions. This process can also lead to apoptosis dysregulation in many chronic inflammatory diseases (35). A possible mechanism underlying the increased OS levels in non-bacterial inflammatory prostatitis (category IIIa) is that inflammatory reactions can trigger inflammatory cells to generate and release numerous inflammatory mediators, such as inflammatory cytokines, cytochrome P450, and NADPH cytochrome P450. These factors may contribute to metabolic disturbances in the hypoxanthine-xanthine oxidase system, leading to the production of free radicals. Xanthine oxidoreductase (XOR), a pivotal enzyme in this system, can convert between its dehydrogenase and oxidase forms, catalysing the transformation of hypoxanthine and xanthine into uric acid while producing highly reactive superoxide anion radicals (O^{2-}) (36).

Therefore, XO activity is considered a significant source of free radical generation. The role of XO-induced ROS production has been implicated in the pathogenesis of ischemic injuries affecting the intestines, liver, and kidneys (37). XOR is essential for urate biosynthesis, and our previous research demonstrated that XO activity substantially contributes to ROS production in experimental renal injury (38). XO has been linked to both ischemic damage and fibrotic processes (39). In our investigation, we noticed a statistically significant elevation of XO activity in the serum of patients with CP and benign BPH when compared to healthy controls (Figure 3). Additionally, inflammatory cells can stimulate enzymes and factors such as cyclooxygenase-2 (40), nuclear factor kappa B (NF-κB) (41), inducible nitric oxide synthase, as well as various oxidants and pro-inflammatory cytokines, leading to increased generation of free radicals including superoxide anion ($^{02-}$), hydroxyl radicals (OH), nitric oxide (NO), and hydrogen peroxide (H2O2) (42). Our results are in accordance with the results of Person et al. (43), who, in a parallel double-blind controlled study, demonstrated increased XO activity in prostatic fluid. They also found that administering allopurinol to patients for 240 days led to a decrease in subjective symptoms and a reduction in prostatic secretion of xanthine and urate.

In our previous article, we reported a high level of XO activity and OS in samples of PC (44). In this investigation, the results are similar. Concentrations of TBARS and AOPP are higher when compared to healthy prostate tissue (Figure 4 and 5), and prostate tissue exhibits higher XO activity (Figure 6). We can associate enhanced XO activity with the transformation of XO from its dehydrogenase form to its oxidase form, a process driven by the reversible oxidation of thiol groups. An additional potential mechanism involves irreversible proteolytic damage triggered by increased peroxynitrite levels (45).

To explore the impact of XO activity on increased OS, we measured the levels of prooxidants and the degree of oxidative modifications in lipids and proteins. TBARS, as end products of lipid peroxidation, are highly electrophilic molecules capable of reacting with cellular nucleophiles to form DNA adducts and oligomers. They also bind to nucleic acids, creating adducts with deoxyguanosine, deoxyadenosine, and deoxycytidine (46). TBARS-DNA oxidation products have been reported to exert pro-mutagenic effects, inducing genetic changes in oncogenes and tumor suppressor genes within human tumors (47). In the present study, TBARS concentrations were significantly elevated in the serum of patients with BPH and CP, as well as in cancerous tissue compared to healthy controls. These results are consistent with findings by Yilmaz et al. (48), who observed increased lipid peroxidation. Furthermore, protein oxidation levels were higher in PC tissue relative to healthy tissue. AOPPs may arise through the oxidation of specific amino acid side chains by aldehydes generated during lipid peroxidation, serving as early and reversible markers of protein oxidation. Pande et al. (49) also reported elevated AOPP levels in PC patients compared to healthy individuals. These results suggest a strong connection between overall OS in the body and the localized prooxidant conditions within tumor tissue, reinforcing the idea that the male reproductive system preserves a redox-controlled microenvironment essential for maintaining redox balance. OS may represent a common pathogenic mechanism linking BPH, CP, and PC. Despite these results, certain limitations of the study should be recognized. The redox parameters assessed can only be deemed meaningful after excluding other conditions linked with OS. OS is undoubtedly only one of several mechanisms contributing to tumor development. Our research provides a foundation for larger clinical trials aimed at exploring the role of redox biomarkers in a wider cohort of patients with prostate disorders. Future studies should also evaluate the potential therapeutic benefits of antioxidant treatments across the spectrum of prostate diseases, from BPH to cancer.

CONCLUSION

The findings of this study demonstrate that the levels of lipid peroxides and AOPP are markedly increased in patients with BPH, CP, and PC, implying that systemic OS contributes to the development of these diseases. XO activity appears to be a potential producer of ROS in the prostate and may serve as a link between inflammation and carcinogenesis. These findings support the potential therapeutic role of XO inhibitors and antioxidants as adjuvant treatments for prostate diseases.

Acknowledgements

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Statement of Ethics

The research adhered to the principles of the Declaration of Helsinki and received approval from the Ethics Committee of the Medical Faculty in Niš (Decision No. 12-8818-2/8) on September 23, 2020.

Competing Interest

The authors declare no relevant conflicts of interest.

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