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Review Article

Oxidative stress in prostate cancer patients: A systematic review of case control studies

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ABSTRACT

Background: Prostate cancer (PCa) is the most common cancer in men in Western countries. *In-vitro and in-vivo* studies suggest that oxidative stress (OS) and antioxidants play a key role in the pathogenesis of chronic diseases including PCa, which is promoted by the production of reactive oxygen species and impaired antioxidant defense mechanisms. This study evaluates the association between OS and men with PCa.

Methods: A literature search was carried out on Medline, PubMed, and ScienceDirect databases, as well as manual searches from inception up to August 2015 using the keywords "Oxidative stress" or "Reactive oxygen species" or "Lipid peroxidation" AND "Prostate cancer." All studies including data on the measurement of OS biomarkers in PCa were included.

Results: Twenty-three case control studies were retrieved with sample sizes ranging from 15 to 3,613 (6,439 participants in total). Markers of OS were significantly higher in patients with PCa compared with control groups in 21 studies. Two self-controlled case studies comparing OS between PCa cells and non-PCa cells in tissue biopsies found OS to be statistically higher in PCa cancer cells. Results on markers of antioxidant capacity (superoxide dismutase, catalase, glutathione, glutathione reductase, glutathione peroxidase, uric acid, lutein, lycopene, beta carotein, vitamin A, vitamin C, vitamin E, and total antioxidants) were not completely consistent in their association with PCa.

Conclusions: Upregulated OS profiles and impairment of antioxidant defense systems may play a role in men with PCa. To confirm these findings, robust clinical trials utilizing a personalized approach which monitors both OS and antioxidant markers during therapy are warranted.

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1. Introduction

Prostate cancer (PCa) is the most common malignancy and the second leading cause of cancer-related mortality in men in the Western world including Australia and the USA.[1] PCa is a multifocal neoplasm, which forms solid tumors of glandular origin. The risk of PCa increases with age but the etiology and pathogenesis are poorly understood.[2] Clinically localized PCa is managed with observation, surgery, or radiation treatment; the latter may be combined with androgen-deprivation therapy (ADT). Men with metastatic disease[3] are managed almost exclusively with ADT and chemotherapy. The natural history of untreated PCa is still poorly understood, with a wide variation in outcomes in patients with apparently similar cancers based on standard staging and pathological grading.[4] Being able to risk stratify individuals with regard to clinical risk is therefore necessary in order to personalize therapeutic strategies, with the aim of minimizing harm to those at low risk, and maximizing the therapeutic armament to those at highest risk. The most widely used biomarker to detect and monitor PCa is prostate-specific antigen. However, strong clinical and preclinical evidence for the role of elevated cellular reactive oxygen species (ROS) and impaired protective mechanisms as a driver of PCa susceptibility[4,5] points to the potential clinical utility of these markers. The term oxidative stress has been used to refer to the imbalance between levels of ROS and the protective "antioxidant" mechanisms, resulting in an accumulation of molecular damage in DNA, proteins, and lipids.[5]

Several clinical studies have demonstrated that increased OS is related to PCa and that some antioxidants have the potential to protect men from PCa.[6–8] Multiple *in-vitro* and *in-vivo* studies have attempted to elucidate the mechanisms of initiation and progression of PCa in relation to OS.[9] Oxidative free radicals caused by multiple factors such as modulation of androgens, inflammation, vitamin D, tumor suppressor protein (p53), antioxidants, and age-related OS may initiate PCa.[10] More specifically, in men with PCa it has been suggested that serum androgens promote ROS production and accumulation in PCa cells.[10] Androgen-associated redox homeostasis is involved in the signal transduction network of multimeric redox-sensitive transcription factors, enzymes, and epigenetic modifications. Androgens have been shown to promote cancer by increasing reactive oxygen derivatives in tissue.[11] Androgen-induced ROS levels in prostate epithelial cells play a critical role in PCa development, progression, and recurrence.[12] Further, studies demonstrate that castration or estrogen therapy can lead to the regression of cancer in patients with metastatic PCa.[13] Hence, it may be proposed that ADT combined with antioxidant agents may inhibit the progression of PCa.[14]

To date, no robust randomized controlled trials have been conducted to determine the impact of OS on the risk of developing PCa. A number of studies have attempted to examine the effect of exogenous antioxidants in preventing cancer recurrence and reducing the risk of developing cancer. These studies include lung,[15] breast,[16,17] colorectal,[18] gastrointestinal,[19] head and neck,[20] leukemia,[21] bladder cancer,[22] and PCa,[23,24] and findings have been inconsistent. Further, there have been reported risks of antioxidants instead of their protective effects. The major limitation of these studies is the lack of consideration of the redox imbalance between oxidation and antioxidants, and the double-edged effect of exogenous antioxidants. Supplementation of exogenous antioxidants in the long-term without monitoring the redox balance can result in beneficial as well as harmful effects depending on the concentration of ROS and the required amounts to maintain or re-establish redox homeostasis in each individual patient.[25] Studies suggest that high doses of exogenous antioxidants could paradoxically act as a pro-oxidant by disrupting the redox balance. Thus, the balance between oxidation and antioxidants is a critical issue to consider in an individual patient when assessing the anticancer effect of antioxidants. To our knowledge, there have been no literature reviews examining the association between OS and men with PCa. Furthermore, none of the aforementioned studies have examined the effect of the redox balance in men with PCa. Thus, we conducted a systemic review to clarify the association between OS and men with PCa.

2. Materials and methods

2.1. Search strategy

A literature search was carried out on Medline, PubMed, and ScienceDirect databases from inception up to August 2015 using the keywords "Oxidative stress" or "Reactive oxygen species" or "Free radical" or "Lipid peroxidation" AND "Prostate cancer." A manual search was also conducted from the retrieved articles. Inclusion criteria were articles that presented data on OS biomarkers, with the full article published in English. Acceptable study designs were case control, nested case control, prospective cohort, or randomized control trials. We excluded articles based on animal and cell models.

2.2. Quality assessment

The quality of each article included in this review was assessed using the Newcastle–Ottawa Scale following the Cochrane Collaboration recommendation.[26,27] The Newcastle–Ottawa Scale was developed jointly by the University of Newcastle (Australia) and the University of Ottawa (Canada) to assess the quality of nonrandomized studies to be included in systematic reviews.[27] It has been widely used since at least 2004,[28] and the results from several validation studies have been published.[29,30] The total score ranges from 0 to 9, with a higher score indicating greater quality.

2.3. Data extraction

A review template was developed specifying the key information about each study (Tables 1 and 2). Two reviewers (B.O. and S.L.) independently applied the inclusion and quality assessment criteria. The two reviewers compared results and resolved any discrepancies in the published articles.

2.4. Statistical analysis for meta-analysis

The meta-analysis was conducted using a random-effects model, which assumes that the effect size has a distribution rather than a fixed value, i.e., the effect size varies within the population. The summary statistic of interest is the standardized mean difference; specifically, the difference in mean for PCa patients compared with healthy controls, divided by the standard deviation pooled across these groups. For each effect size we calculated a 95% confidence interval (CI). Restricted maximum likelihood estimation was used to estimate the model. Analyses were conducted using the metafor package in R 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The relevant studies covered a range of oxidation and antioxidants, but these were dominated by malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), so to allow for comparisons of sufficient size and homogeneity, and to avoid the complication of including multiple outcomes per study, we chose to analyze only MDA, SOD, and GSH-Px. The results presented are an overall effect size and CI, as well as a forest plot. Heterogeneity of effects for each outcome was reported using I^2, which represents

Table 1
The characteristics of the studies involving oxidative stress and antioxidants.

Author, y, country	Study population	Study design	Sample size Mean age	Control group	Sample collection	Outcome measurement & method	Clinical variables	Results & conclusion
Klotz et al[33] 1988 Germany	PCa and benign BPH	Case control study 2 arms	Total $N = 26$ Case ($n = 16$) 66 y Control BPH ($n = 10$)	BPH	Tissue specimens	Nitric oxide: iNOS iNOS immunostaining	Age, clinical diagnosis	• Positive iNOS immunostaining was detected in all sections from patients with prostate carcinoma. The malignant epithelial cells were highly positive. However, round cells in benign tissue stained negative for iNOS. • Prostate carcinoma tissue had high iNOS expression, whereas benign tissue did not. • Epithelial iNOS expression can be used as a specific immunohistochemical marker for prostate carcinoma.
Baltaci et al[34] 2001 Turkey	High-grade prostatic intraepithelial neoplasia (PIN)	Case control study 4 arms	Total $N = 80$ BPH ($n = 20$) Low-grade PIN: ($n = 20$) High-grade PIN ($n = 20$) Primary prostatic adenocarcinomas ($n = 20$)		Tissue samples	Nitric oxide: iNOS iNOS immunostaining		• Positive iNOS immunostaining was detected in all samples from all patients; iNOS was detected in both basal epithelial cells and secretory cells of the glandular epithelium. • High-grade PIN and prostatic carcinoma samples had more intense iNOS immunostaining than low-grade PIN and BPH samples. • In all samples, smooth muscle cells showed weak or moderate iNOS immunoreactivity and endothelial cells showed moderate immunostaining. • Nitric oxide generated by iNOS may be involved in prostate tumorigenesis and further studies with immunohistochemical and molecular biology are needed to determine the exact role of iNOS in the pathogenesis of prostatic carcinoma.
Camphausen et al[31] 2004 Sweden	PCa	Case control study 2 arms	Total $N = 15$ Case: ($n = 15$) Control: Historical data	Historical data	Urine sample	Oxidative stress: 8-iso-PGF2 and 15-keto-dihydro-PGF2 Student t test	ND	• No increase in either 8-iso-PGF2_ or 15-keto-dihydro-PGF2_ in the urine of patients with PCa compared with in historical normal controls. No increase in either of the eicosanoids during RT to the prostate gland.
Iynem et al[35] 2004 Turkey	Metastatic PCa patients	Prospective case control study 2 arms	Total $N = 41$ Case: Metastatic PCa ($n = 21$) 69 y Control ($n = 20$) 64 y	Healthy volunteer nonsmokers	Blood samples	Oxidative stress: MDA Antioxidant status: GSH, GSH-Px, GR, GST, and Vit E	ND	• Plasma MDA levels were significantly higher and plasma vitamin E levels were significantly lower in the patients compared with control patients ($P \leq 0.001$ and $P \leq 0.001$). • Erythrocyte GSH level, activities of erythrocyte GSH-Px and GR enzyme were significantly lower and erythrocyte GST enzyme activity was significantly higher in the patients compared to control patients. ($P < 0.01$, $P \leq 0.001$, $P < 0.05$ and $P \leq 0.001$, respectively). • Plasma MDA levels were found to be significantly decreased after antiandrogenic supplementation ($P < 0.05$). • There were no significant differences in erythrocyte GSH,GR, GSH-Px and plasma vitamin E levels before and after therapy.

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Table 1 (*continued*)

Author, y, country	Study population	Study design	Sample size Mean age	Control group	Sample collection	Outcome measurement & method	Clinical variables	Results & conclusion
Yilmaz et al[36] 2004 Turkey	Newly diagnosed PCa and Treated benign prostatic nodular hyperplasia (BPNH) patients	Case control study with 3 arms	Total $N = 121$ Case PCa ($n = 21$) 66 y BPNH ($n = 50$) 64 y Control ($n = 50$) 66 y	Age, sex, BMI matched healthy participants	Blood samples	Oxidative stress: MDA Antioxidant status: Cu, Zn, Cu-Zn SOD, and GSH-Px Data analysis: The Mann −Whitney *U*-test	PSA level, transrectal ultrasonography, and biopsy Gleason sum.	• Erythrocyte GST activity was found to be significantly elevated after therapy when compared with baseline ($P \leq 0.01$). • MDA levels were higher and the antioxidant activity and Zn levels lower in the PCa groups compared to healthy control and BPNH groups ($P \leq 0.001$). • MDA levels were higher in the advanced PCa group compared to localized PCa group ($P \leq 0.001$). • MDA and SOD were associated with Gleason score in PCa patients. • MDA levels can be used in the diagnosis and follow-up of PCa.
Miyake H[37] 2004 Japan	PCa limited to prostate stage (T1-T4)	Prospective case control study 2 arms	Total $N = 115$ Case ($n = 82$) Control ($n = 33$)	Age-matched healthy participants	Urine samples	Oxidative Stress: DNA damage: Urinary 8-OHdG and creatinine (Cr) Serum prostate Specific antigen (PSA) Data analysis: The Mann −Whitney *U*-test	Serum PSA, clinical stage, metastasis, biopsy, Gleason score	• The ratio of urinary 8-OHdG-to-Cr (8-OHdG/Cr) was significantly higher in patients with PCa compared to controls ($P < 0.05$). • Only age was significantly associated with 8-OHdG/Cr in PCa cases among several clinico-pathological factors including serum PSA, clinical T stage, metastasis and Gleason score. • No significant differences in urinary 8-OHdG/Cr in 42 patients before and after radical prostatectomy. • Urinary 8-OHdG/Cr in 40 patients was significantly lower ($P < 0.05$) after hormonal therapy compared with before hormonal therapy. • Changes in PSA after initial treatment were not related to changes in urinary 8-OHdG/Cr. • Oxidative stress may be involved in an early event in PCa development and androgen suppression without surgical removal of PCa is capable of decreasing oxidative DNA damage. • Androgen ablation therapy combined with antioxidant agents could be a novel therapeutic strategy for inhibiting the progression of PCa.
Srivastava[38] 2005 India	PCa and benign BPH	Case control study 3 arms	Total $N = 107$ Case ($n = 47$) 62 y BPH ($n = 55$) 60 y Control ($n = 25$) 61 y	Healthy men	Blood samples	Oxidative stress: MDA Antioxidant status: GST from serum, GSH-Px and GSH Data analysis: One-way ANOVA	ND	• Significantly higher levels of MDA and GSTs activities were observed in the serum ($P < 0.005$) of PCa and BPH cases compared to controls. • GSH concentration and GSH-Px activities were significantly lower in PCa compared with controls ($P < 0.05$).

						and Linear regression model		• Oxidant−antioxidant imbalance may be one of the major factors responsible for the development of PCa and benign prostate hyperplasia.
Almushatat et al[39] 2006 UK	BPH, localized and metastatic PCa	Case control study 4 arms	Total $N = 112$ Localized PCa ($n = 40$) 70 y Metastatic PCa ($n = 38$) 74 y BPH ($n = 20$) 67 y Control ($n = 14$) 64 y	Healthy subjects	Blood samples	Oxidative stress: MDA Antioxidant status: Plasma retinol, a-tocopherol, lutein, lycopene, α-carotene and β-carotene Inflammation biomarker: C-reactive protein (CRP) Data analysis: ANOVA (Kruskal−Wallis and Mann−Whitney U-test	Age, PSA, Gleason score, cholesterol	• PCa patients had higher concentrations of MDA ($P < 0.05$) and lower circulating concentrations of lutein ($P < 0.05$), lycopene ($P < 0.001$) and β-carotene ($P < 0.05$). • Patients with metastatic PCa, when compared to patients with localized disease, had a higher Gleason score ($P < 0.01$) and more hormonal treatment, but lower concentrations of PSA ($P < 0.05$), a-tocopherol ($P < 0.05$), retinol ($p < 0.01$), lutein ($P < 0.05$), and lycopene ($P < 0.01$). • PCa PSA correlated with the concentrations of the lipid peroxidation product, MDA ($rs = 0.353$, $P < 0.002$) in PCa cases • CRP was not correlated with the vitamin antioxidants or MDA. • In contrast, there was a negative correlation between MDA concentrations and both lutein ($rs = -0.263$, $P < 0.020$) and lycopene ($rs = -0.269$, $P < 0.017$). • The lower concentrations of carotenoids, in particular lycopene, reflect disease progression rather than the systemic inflammatory response in patients with PCa.
Aydin et al[40] 2006 Turkey	Newly diagnosed PCa patients and benign prostatic hyperplasia (BPH) patients	Case control study 3 arms	Total $N = 85$ Case Nonmetastatic PCa ($n = 25$) 68 y BPH ($n = 36$) 64 y Control ($n = 24$) 65 y	Sex-matched healthy volunteers	Blood samples	Oxidative stress: MDA Antioxidant status: SOD, GSH-Px, CAT, Cu-Zn SOD Data analysis: ANOVA tests followed by Tukey−Kramer's multiple comparisons test a posteriori	ND	• Increased lipid peroxidation (TBARS) with a concomitant decrease in GSH-Px and CuZn-SOD activities in the PCa patients versus controls ($P < 0.001$) and versus BPH patients ($P < 0.05$). Zn levels were lower in PCa patients versus controls ($P < 0.01$) with no significant changes between BPH and the cancer group. • No significant differences were observed in the erythrocyte CAT and Cu levels among any of the studied groups.
Ozmen et al[41] 2006 Turkey	PCa	Case control study 2 arms	Total $N = 41$ Case ($n = 20$) 72 y Control ($n = 21$) 66 y	Healthy men	Blood samples	Oxidative stress: MDA Antioxidant status: Vitamin A,C,E and selenium in serum Fe and trace element (Ni, Zn, Co, and Cu)	ND	• Vitamin A, C, and E levels were significantly lower and MDA levels significantly higher ($P < 0.001$) in patients with PCa compared with controls. • Se and Zn levels were significantly lower, and levels of Ni, Co, and Cu were higher ($P < 0.001$) in patients with PCa compared with controls.

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Table 1 (*continued*)

Author, y, country	Study population	Study design	Sample size Mean age	Control group	Sample collection	Outcome measurement & method	Clinical variables	Results & conclusion
						Data analysis: Student *t* test		• Fe levels were not significantly different in patients compared with controls. • The administration of vitamins A, C, and E, and Se and Zn may be beneficial in the prevention and treatment of human PCa.
Surapanenet al[42] 2006 India	PCa	Case control study 2 arms	Total $N = 60$ Case ($n = 30$) Control ($n = 30$)	Healthy men	Blood samples	Oxidative stress: MDA Antioxidant status: GSH, SOD, and GST Data analysis: unpaired t-test	ND	• Erythrocyte MDA & SOD levels were significantly higher in patients with carcinoma of prostate compared with controls ($P < 0.01$ and $P < 0.001$ respectively). • GSH levels were significantly lower in patients with carcinoma of prostate compared with controls ($P < 0.01$). • No significant change was observed in GST compared with controls. • Oxidative stress may be involved in PCa as evidenced by higher MDA levels and lower GSH levels. • Increased activity of antioxidant enzyme may be a compensatory regulation in response to oxidative stress.
Yossepowitch[43] 2007 Israel	PCa completed either radical prostatectomy or receiving androgen deprivation therapy	Case control study 4 arms	Total $N = 104$ Case: ($n = 79$) Localized undergoing radical prostatectomy ($N = 42$) 63 y Metastatic disease receiving androgen deprivation therapy ($n = 37$) HSPC ($n = 15$) HRPC ($n = 22$) 63 y Control ($n = 25$) 72 y	Age matched healthy men	12-h fasting blood sample	Oxidative stress: MDA Antioxidant status: Uric acid, vitamin E (α-tocopherol), copper induced peroxidation ($CucCL_2$), nd Vmax (OD_{246}) $OD_{max.}$ Data analysis: ANOVA on log transformed data. Univariate binary logistic regression analyses Ordinal logistic regression model	PSA, biopsy, Gleason score, age, smoking history, vitamin supplements, and lipid profiles	• Compared to control subjects, patients with localized PCa had no difference in oxidative stress indexes, whereas those with metastatic disease had a shorter lag preceding oxidation and increased MDA ($P < 0.05$), each reflecting a state of high oxidative stress. • In patients with PCa, the probability of disease progression from localized to advanced state increased with a shorter lag preceding oxidation ($P < 0.001$), increased MDA ($P < 0.03$) and decreased uric acid ($P < 0.04$). • Patients with advanced PCa had higher circulating markers of oxidative stress compared with controls, as determined by increased susceptibility of serum lipids to peroxidation. This association was not detected in patients with localized cancer and is not attributable to altered levels of α-tocopherol.
	PCa and BPH	Case control study 3 arms	Total $N = 30$ Case ($n = 15$)	Healthy males of similar age	Blood sample	Oxidative stress: MDA		• Plasma MDA levels were significantly higher in patients with both BPH and carcinoma of

Kotrikadze et al[44] 2008 Georgea			BPH ($n = 15$) Control ($n = 15$)			Antioxidant status: SOD, CAT, Ceruloplasmin (Cp), GSH, GSH-Px, and glutathione-reductase (GR) Data analysis: Means of standard variation statistics MINITAB (basic statistic),		prostate compared to controls ($P < 0.001$ and $P < 0.001$ respectively). • SOD activity in blood erythrocytes showed that increase in SOD activity was sharply manifested in BPH (~1.3 times, $P < 0.001$), compared with the control group, while in PCa, activity of the enzyme decreases versus control group (~1.6 times, $P < 0.0001$). • CAT activity remained unaltered in BPH and was slightly declined in PCa (0.01). • Cp was increased in both kind of tumors, especially in PCa (0.0001), as well as GSH (0.0001) and GR (0.0001). • GSH-Px was sharply increased in BPH and reduced in PCa (0.0001). • The development of BPH reflects relatively weakly on blood system as activity and content of antioxidant enzymes do not reveal marked changes. in contrast to PCa, which show the reduced functional state of blood antioxidant enzyme system.
Akinloye et al[45] 2009 Nigeria	PCa	Case control study 4 arms	Total $N = 170$ Case ($n = 120$) Low-grade PSA (5−10 ng/mL) ($n = 33$), Medium-grade PSA (11−20 ng/mL) ($n = 45$) High-grade PSA (> 20 ng/mL) ($n = 42$) Control ($n = 20$)	Healthy volunteers PSA concentration < 3.0 ng/mL	Blood samples	Oxidative stress: Microsomal membrane Antioxidant status: SOD, CAT, reduced GSH, Uric acid and Vitamin C and E. Data was analysis: One-way ANOVA followed by the post-hoc Duncan multiple range test for analysis of biochemical data	PSA, ALT, AST, Total bilirubin	• Serum LPO, total bilirubin and alkaline phosphatase (ALP) were significantly elevated ($P < 0.05$) in patients 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 patients with PSA ≥20 ng/mL, respectively. • SOD and CAT activities were lower ($P < 0.05$) in all cancer patients. • Subjects with a PSA level of 11−20 ng/mL and PSA >20 ng/mL had significantly lower uric acid and GSH 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. • Depletion of antioxidants was found in PCa patients, and an inverse relationship between antioxidants and PSA values.
Arsova-Sarafinovsk et al[46]	PCa and BPH	Case control study 3 arms	Total $N = 312$ Cases	Healthy volunteers	Blood sample	Oxidative stress: MDA and 8-OHdG		• A similar pattern of alteration in the oxidative/ nitrosative stress-related

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Table 1 (*continued*)

Author, y, country	Study population	Study design	Sample size Mean age	Control group	Sample collection	Outcome measurement & method	Clinical variables	Results & conclusion
2009 Turkey			Case ($n = 107$) BPH ($n = 167$) Control ($n = 38$)			NO2−/NO3− and cGMP Antioxidant status: CuZn-SOD, GSH-Px, and CAT Data analysis: ANOVA and Tukey−Kramer multiple comparisons test a posteriori or Kruskal−Wallis nonparametric test, Dunn's multiple comparisons test	Smoking, family history of cancer, Gleason score and PSA	parameters was found in both, Macedonian and Turkish studied samples: higher MDA concentrations in PCa patients versus controls and BPH Groups ($P < 0.001$) and lower GSH-Px ($P < 0.001$) and CuZn-SOD ($P < 0.01$) activities in PCa patients versus controls and BPH groups. • CAT activity ($P < 0.01$) was decreased in the PCa patients versus controls in the Turkish studied sample. • PCa patients had increased plasma NO2−/NO3− ($P < 0.01$) and cGMP levels ($P < 0.01$) versus controls and BPH groups in both studied samples. • An imbalance in the oxidative stress and antioxidant status and an altered nitrosative status were present in PCa patients.
Hoque et al[32] 2010 USA	PCa	Nested case-control design 2 arms	Total $n = 3,613$ Case ($n = 1,808$) 64 years Control ($n = 1,805$) 64 y	Biopsy negative	Biopsy and blood samples	Oxidative stress: Carbonyl Data analysis χ^2 test for categorical variables and t test for continuous variables and multiple logistic regression analysis	Age, race, education, physical activity, smoking, fruit intake, vegetable intake, and family history of PCa, and BMI	• No significant associations between PCa risk nor its aggressiveness and serum levels of oxidized protein as measured by protein carbonyls.
Battisit et al[47] 2011 Brazil	PCa	Case control study 3 arms	Total $N = 110$ Case ($n = 55$) Metastatic ($n = 23$) Non-metastatic ($n = 32$) Control ($n = 55$)	Age matched-healthy men	Blood sample	Oxidative stress: MDA and carbonylation Antioxidant status: CAT,SOD, Vitamin C and vitamin E Data analysis: One-way ANOVA followed by the Duncan's multiple test.	Metastasis, standard treatment, Gleason score, family history, smoking and alcohol intake	• TBARS levels and serum protein carbonylation were higher ($P < 0.005$) in PCa patients than in controls. • CAT activity was decreased ($P < 0.005$) and SOD ($P < 0.005$) activity was higher in PCa patients when compared with controls. Nonprotein thiol levels were increased, however, serum vitamin C and vitamin E content were reduced ($P < 0.05$) in PCa patients when compared with controls. • Different parameters analyzed in PCa patients based on metastasis, treatment and Gleason score showed changes in oxidative stress biomarkers and antioxidant defenses. This may indicate an imbalance in the oxidant/antioxidant status, supporting the idea that oxidative stress plays a role in PCa, moreover, the oxidative profile appear to be modified by bone metastasis, treatment and Gleason score.
	Patients with high grade prostatic	Case control study 3 arms	Total $N = 500$ HGPIN ($n = 140$)	Confirmed biopsy negative	Urine and biopsy	Oxidative stress: F2IP	BMI race, health history, family	• Adjusted geometric mean F2-isoprostane levels were higher in patients with PCa

Barocas et al[48] 2011 USA	intraepithelial neoplasia (HGPIN) and PCa		66 y PCa ($n = 200$) 68 y Control ($n = 160$) 67 y			Data analysis: Multivariable linear and logistic regression was used	history and other risk factors (smoke), biopsy, DRE results, current use of NSAIDs and statins, and transrectal ultrasound prostate volume.	(1.82, 95% CI 1.66−2.00) or high grade prostatic intraepithelial neoplasia (1.82, 95% CI 1.68−1.96) than in controls (1.63, 95% CI 1.49 −1.78, $P < 0.001$), but were similar across Gleason scores ($P < 0.511$). • The adjusted odds of high grade prostatic intraepithelial neoplasia and PCa increased with increasing F2-isoprostane quartile (p-trend = 0.015 and 0.047, respectively) and the highest F2-isoprostane quartile was associated with significantly increased odds of PCa (OR 2.44, 95% CI 1.17−5.09, $P = 0.017$). • Urinary F2-isoprostane provides a biomarker for the role for oxidative stress in prostate carcinogenesis. F2-isoprostanes may also serve to estimate the efficacy of interventions targeting oxidative stress mechanisms in PCa prevention or treatment.
Wozniak et al[49] 2012 Poland	PCa limited to prostate gland (T1ABCN0M0, T2ABCN0M0Gx, and T1ABCN0M0Gx)	Prospective case control study 2 arms	Total $N = 90$ Case ($n = 60$) 67 y Control ($n = 30$) 62 y	Healthy men.	Blood sample	Oxidative stress: TBARS Antioxidant status: GSH-Px, CAT, and SOD Data analysis: ANOVA	Age, PSA, Gleason score, TNM, hemoglobin	• Erythrocyte GSH-Px in the patients was lower than in healthy subjects by 34% ($P < 0.001$), 50% ($P < 0.001$), 30% ($P < 0.05$), and 61% ($P < 0.001$), respectively, at all periods. • No significant differences were found by comparing SOD and CAT in PCa patients with that of controls. • After 2 y of treatment, the activity of studied enzymes demonstrated a decreasing tendency versus before therapy. • Blood plasma TBARS concentration was higher than in controls at all periods, while erythrocyte TBARS decreased after 2 y compared with control levels. • An imbalance of oxidant-antioxidant processes occurs in the course of PCa. • The therapy did not alter the levels of oxidative stress markers, which may prove its applicability. Two y is too short a period to restore the oxidant−antioxidant balance.
	PCa	Case control study 2 arms	Total $N = 537$ Case ($n = 304$)	Healthy individuals	Blood and urine samples.	Oxidative stress: 8-isoPGF2a	Age, PSA, Gleason score, TNM,	

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Table 1 (*continued*)

Author, y, country	Study population	Study design	Sample size Mean age	Control group	Sample collection	Outcome measurement & method	Clinical variables	Results & conclusion
Brys et al[50] 2013 Poland			61 y Control ($n = 233$) 65 y			Antioxidant status: Uric acid and glucose Data analysis: Q-Dixon test, Mann−Whitney and Cox regression analysis	hemoglobin, Prostate volume	• A statistically increased level of isoprostanes was present in urine of patients with PCa compared with control group ($P < 0.001$). • The concentration of tested antioxidants (uric acid and glucose) in blood from patients with PCa was also higher than in healthy volunteers ($P < 0.001$). • The correlation between increased amount of UA and lipid peroxidation exists in PCa patients (in all tested groups) ($P < 0.001$). • Correlation between PCa risk and urinary isoprostanes level was analyzed, and a positive association was found (relative risk for highest vs. lowest quartile of urinary isoprostanes = 1.6; 95% confidence interval 1.2−2.4; p for trend = 0.03). • Reactive oxygen species induce peroxidation of unsaturated fatty acid in patients with PCa, and the level of isoprostanes may be used as a noninvasive marker for determination of oxidative stress.
Pande et al[51] 2013 India	Newly diagnosed PCa patients Stage (1-4) Metastatic (n = 16), non-metastatic ($n = 24$)	Case control study 2 arms	Total $N = 80$ Case ($n = 40$) 64 y Control ($n = 40$) 68 y	Age-matched healthy individuals	Venous blood collection, and the serum was used for various biochemical and hematologic investigations	Oxidative stress: 8-OHdG, carbonyls and MDA Antioxidant status: Total antioxidant status Angiogenesis: VEGF levels Data analysis: Student t test, One-way ANOVA, Pearson's correlation coefficient	PSA level at diagnosis, transrectal ultrasound, and biopsy Gleason score	• Serum VEGF, cell proliferation, and oxidative stress levels were significantly higher in patients with prostate carcinoma compared with controls • Levels of 8-OHdG, protein carbonyls, and MDA were found to be significantly increased with the progression of disease as depicted by increased level in advanced PSA, stage, spread, and Gleason score ($P < 0.0001$). • Serum VEGF level and cell proliferation index were significantly associated with PSA, stage, spread and Gleason score. • VEGF and cell proliferation index correlated with increase in levels of oxidative stress markers. • All indexes of oxidative stress, angiogenesis, and cell proliferation share a significant negative correlation with total antioxidant status.
Kosova et al[52] 2014 Turkey	PCa and BPH	Prospective case control study 2 arms	Total $N = 40$ Case ($n = 20$) Control ($n = 20$)	Age matched BPH	Blood sample	Oxidative stress: 8-OHdG and MDA Caspase-3 Data analysis Mann−Whitney U test, Wilcoxon test	Age, sex, weight, and height	• In PCa patients, MDA and DNA damage levels were significantly higher but caspase-3 levels were significantly lower compared to levels in benign prostate hyperplasia ($P < 0.05$). • Altered pro-oxidant, DNA damage levels may lead to an increase in oxidative damage and may consequently play an important role in prostate carcinogenesis.

Yang et al[53] 2015 USA	PCa	Prospective nested case control study 2 arms	Total $N = 48$ Case ($n = 24$) 60 y Control ($n = 24$) 60 y	Age-matched healthy subjects	Blood and urine samples	Oxidative stress; Urine F2-isoprostanes FlOPs Carboxymethyl-lysine (CML) Data analysis: Conditional logistic regression model. transformed the variables into a logarithmic scale	Age, BMI, smoking status (current and past smoker, or never smoked), family history of PCa, history of benign prostatic hyperplasia, history of hypertension, history of diabetes, and other demographic characteristics	• At baseline, cases had similar age, body mass index, proportion of family history of PCa, history of benign prostatic hyperplasia, history of hypertension, history of diabetes, no. of smokers, and plasma glucose levels compared with controls. Levels of plasma CML were significantly higher in cases compared with controls (182 vs. 152 mg/mL, $P < .05$). • In the conditional logistic regression model, an increase in CML equivalent to 1 standard deviation was associated with an increased risk of incident PCa (relative risk, 1.79; 95% confidence interval, 1.00–3.21) and accounted for approximately 8% variance of PCa liability. • Urine F2-isoprostanes and plasma fluorescent oxidation products were not associated with PCa incidence. • Higher levels of plasma CML were associated with increased risk of PCa.

ABTS, 2,2′-azino-di-(3-ethylbenzthiazoline sulfonate); AGE, advanced glycation end products; BMI, body mass index; BPH, benign prostate hyperplasia; CAT, catalase; cGMP, cyclic guanosine monophosphate; CI, confidence interval; CML, carboxymethyl-lysine; DNPH, 2,4-dinitrophenyl hydrazine; DRE, Digital rectal examination; FAD, flavin adenine dinucleotide; FIGO, International Federation of Gynecology and Obstetrics; FlOPs, fluorescent oxidation products (lipid, protein and DNA); F2IP, F2-isoprostane; FRAP, ferric reducing antioxidant power; GSH, glutathione; GSH-Px, glutathione peroxidase; GR, glutathione reductase; GST, glutathione S-transferase; HNSCC, head and neck squamous cell carcinoma; HRPC, hormone refractory prostate cancer; HSPC, hormone sensitive prostate; MDA, malondialdehyde; NADPH, reduced nicotine amide adenine dinucleotide; ND, not described; NSAID, nonsteroidal anti-inflammatory drug; OSCC, oral squamous cell carcinoma; SOD, superoxide dismutase; TBARS, thiobarbituric acid; 8-isoPGF2, 4-HNE, 4-hydroxy-2-nonenal.

the percentage of variability due to heterogeneity rather than chance.

3. Results

3.1. Study characteristics

Twenty-three case control studies were identified (Fig. 1). In 23 studies, the total number of participants was 6,377 of which 3,558 were PCa cases. Seven studies were undertaken in Turkey; three studies each in India and USA; two studies in Poland; one study each in Brazil, Georgia, Germany, Japan, Nigeria, Sweden, and the UK. All study participants were recruited from urology clinics. Sample sizes ranged from 15 to 3,163.[31,32] The mean age of participants ranged from 60 years to 74 years. Twenty-three studies were conducted using a case control study design, 19 were case control studies, two were prospective, one was nested, and one was a subset of the Nashville Men's Health study.

Comparative and control groups varied. Two self-controlled case studies compared oxidation status with the biopsy specimens of PCa cells and non-PCa cells[33,34]. Twenty-one case control studies compared oxidation status between patients with PCa and healthy volunteers. Studies included two arms ($n = 11$), three arms ($n = 7$), or four arms ($n = 3$). One study used historical data as the control group, two studies used men with benign prostate hyperplasia as the comparator, two studies used a negative biopsy, and 18 studies used age-matched healthy men as the control group.

3.2. Oxidative stress and antioxidant status in PCa

Of 23 studies, 21 studies reported at least one of the markers of OS to be significantly higher in patients compared with controls while two studies reported no significant difference. OS was analyzed on biopsy ($n = 2$), urine ($n = 2$), blood ($n = 16$), and both urine and blood ($n = 3$) samples of participants (Tables 1 and 2). Fifteen studies measured both OS and antioxidant values whilst eight studies measured OS only. OS value was measured based on lipid peroxidation ($n = 19$), protein oxidation ($n = 9$), or both lipid and protein peroxidation ($n = 5$). Eight OS biomarkers were identified among 23 studies. Most studies ($n = 14$) measured MDA while nine studies used different biomarkers including 8-hydroxy-2' -deoxyguanosine (8-OHdg; $n = 4$), isoprostanes ($n = 4$), inducible nitric oxide synthase ($n = 3$), carbonylation ($n = 2$), glycation ($n = 2$), microsomal membrane ($n = 1$), and cyclic guanosine monophosphate ($n = 1$).

Markers of antioxidant capacity assessed in the studies (Table 2) can be categorized as endogenous [catalase (CAT; $n = 6$); glutathione (GSH; $n = 6$); glutathione reductase (GR; $n = 2$); GSH-Px; $n = 7$; glutathione S-transferase (GST; $n = 3$); SOD; $n = 8$; uric acid ($n = 3$); bilirubin ($n = 1$)]; and exogenous [i.e., markers reflecting dietary intake such as (lutein ($n = 1$); lycopene ($n = 1$); β-carotein ($n = 1$); vitamin A ($n = 1$); vitamin C ($n = 3$); vitamin E ($n = 4$); and total antioxidants ($n = 1$)]. Twelve studies measured antioxidant values based on more than two indicators. Three studies measured antioxidant values based on only one indicator. Seven studies reported GSH-Px values to be low in patients with PCa. The values of six other antioxidant indicators (CAT, GSH, GR, SOD, uric acid, and vitamin E) were more variable, but tended to be lower in patients compared with the control group. Conversely, two antioxidant indicator values (GST and bilirubin) were higher in patients.

Table 2
Oxidative stress and antioxidant profiles in prostate cancer patients.

	Oxidative biomarkers							Antioxidant indicators											
	Lipid peroxidation			Protein peroxidation				Endogenous antioxidant								Exogenous antioxidant			
	MDA	Microsomal membrane	Isoprostanes	NO^2-/NO^3-/iNOS/cGMP	DNA damage 8-OHdg	Carbonylation	Glycation (CML)	CAT	GSH	GR	GSH-Px	GST	SOD	Bilirubin	Uric acid	Lutein, Lycopen, β-carotein	Vit A	Vit C	Vit E	Total antioxidant (TAS)
Klotz et al 1988				+																
Baltaci et al 2001				+																
Camphausen et al 2004			NS																	
Iynem et al 2004	+								−	−	−	+							−	
Yilmaz et al 2004	+										−		−							
Miyake H 2004					+															
Srivastava et al 2005	+								−		−	+								
Almushatat et al 2006	+															−				
Aydin A et al 2006	+							NS			−		−							
Ozmen et al 2006	+																−	−	−	
Surapaneni et al 2006	+								−			NS	+							
Yossepowitch et al 2007	+														−				+	
Kotrikadzet al 2008	+							−	+	+	−		−							
Akinloye et al 2009		+						−	−				−	+	−			−	−	
Arsova-Sarafinovsk et al 2009	+			+	NS			−			−		−							
Hoque et al 2010							NS													
Battisit et al 2011	+					+		−	+				+					−	−	
Barocas DA et al 2011			+																	
Wozniak et al 2012	+							NS			−		NS							
Brys et al 2013			+												+					
Pande et al 2013	+				+	+														−
Kosova et al 2014	+				+															
Yang et al 2015			NS				+													

+, significant increase in prostate cancer; −, significant decrease in prostate cancer; CAT, catalase; cGMP, cyclic guanosine monophosphate; CML, carboxymethyl-lysine; GR, glutathione reductase; GSH, glutathione; GSH-Px, glutathione peroxidase; GST, glutathione S-transferase; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; NS, not significant; SOD, superoxide dismutase; Vit, vitamin; 8-isoPGF2, 4-HNE, 4-hydroxy-2-nonenal.

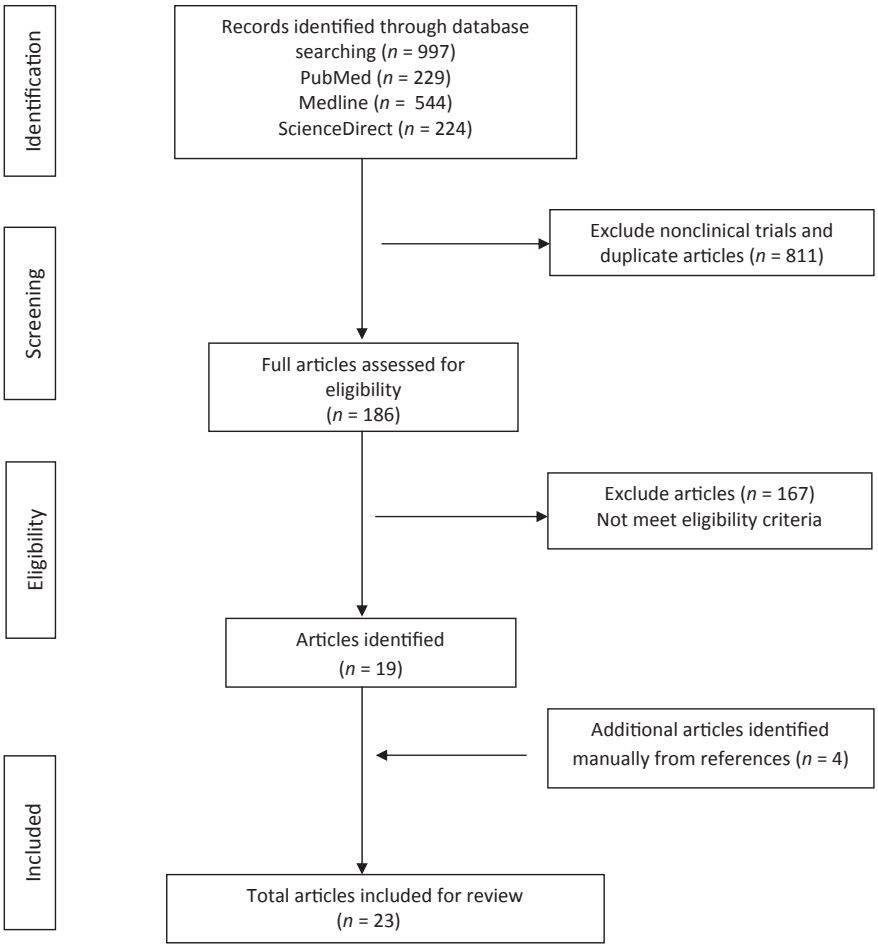

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses.

3.3. Result of meta-analysis

Studies that reported data of sample size, mean value of OS, mean value of antioxidant, and standard deviation were included in the meta-analysis (Figs. 2–4). In studies included in this review, MDA, SOD, and GSX-Px were the most commonly used indicator for OS and antioxidants, respectively.

For the comparison of MDA ($n = 9$), the mean effect size was 2.47 [95% CI (1.42, 3.52)] indicating that MDA levels were significantly higher for PCa patients than controls. Heterogeneity for this outcome was high ($I^2 = 96\%$). For the comparison of SOD ($n = 13$), the mean effect size was −0.62 [95%, CI (−1.73, 0.50)], indicating no differences between PCa patients and controls. Heterogeneity for this outcome was high ($I^2 = 96\%$). For GSX-Px ($n = 8$), the mean effect size was −1.01 [95%, CI (−1.22, −0.80)], indicating GSX-Px levels were lower for PCa patients than controls. Heterogeneity for this outcome, as measured by I^2, was 0%.

3.4. Study quality

The overall quality of the studies included in this review, assessed using the Newcastle–Ottawa Scale, was moderate with an average score of 6.83 (standard deviation = 1.19, range, 4–8) on a nine-point scale. The main areas where quality was lacking were comparability of cases and controls on the basis of the design and analysis. Nonreporting of the nonresponse rates was a major factor for low scores in the provision of well-defined outcome measures.

4. Discussion

Over the last decades, epidemiological, experimental, and clinical studies have demonstrated that markers of OS are associated with the development and progression of cancer.[9] The present study seeks to evaluate the association between PCa and OS and antioxidants. Overall, results of our review confirm that markers of OS are increased in PCa patients compared with healthy controls, with the strongest and most consistent circulating biomarker being MDA. To our knowledge, this is the first systemic review conducted to examine the association between OS and antioxidants in men with PCa.

The present study found that most OS biomarkers were significantly higher in patients with PCa than the control group. Of 23 studies, 21 studies reported at least one marker of OS to be higher in men with PCa, whereas two studies did not detect any significant differences between the two groups. These results are consistent with recent studies examining the correlation of OS and the risk of cancer in various tumor groups which reported significantly increased lipid peroxidation and DNA damage in breast,[54,55] brain,[56] colorectal,[57] lung,[58] liver,[59] head and neck[60] cancers, and oral squamous cell[61] carcinoma.

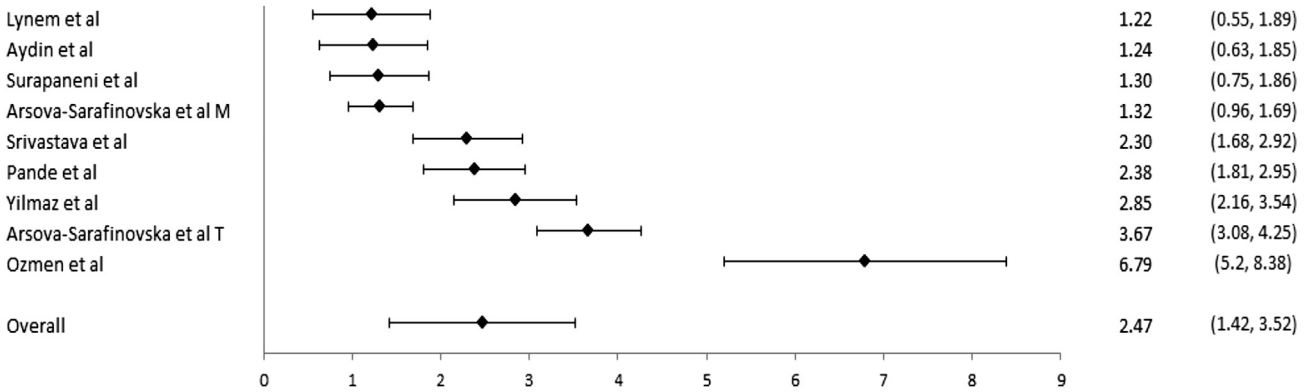

Fig. 2. Forest plot for malondialdehyde. For each study, the marker indicates the effect size and the error bars are 95% confidence intervals. For Arsova-Sarafinovska et al, "M" indicates Macedonian patients and "T" indicates Turkish patients.

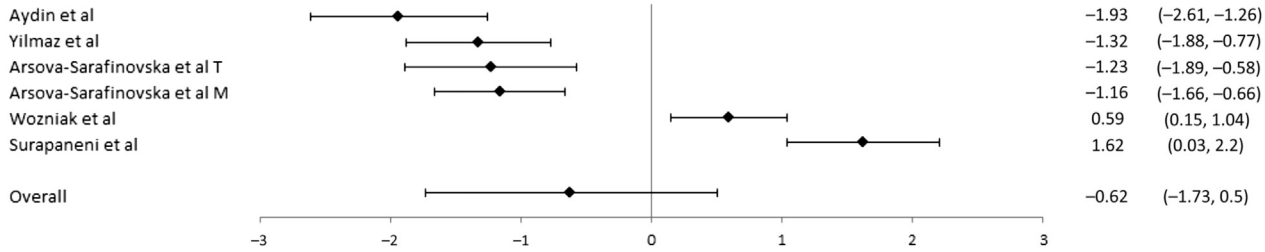

Fig. 3. Forest plot for superoxide dismutase. For each study, the marker indicates the effect size and the error bars are 95% confidence intervals. For Arsova-Sarafinovska et al, "M" indicates Macedonian patients and "T" indicates Turkish patients.

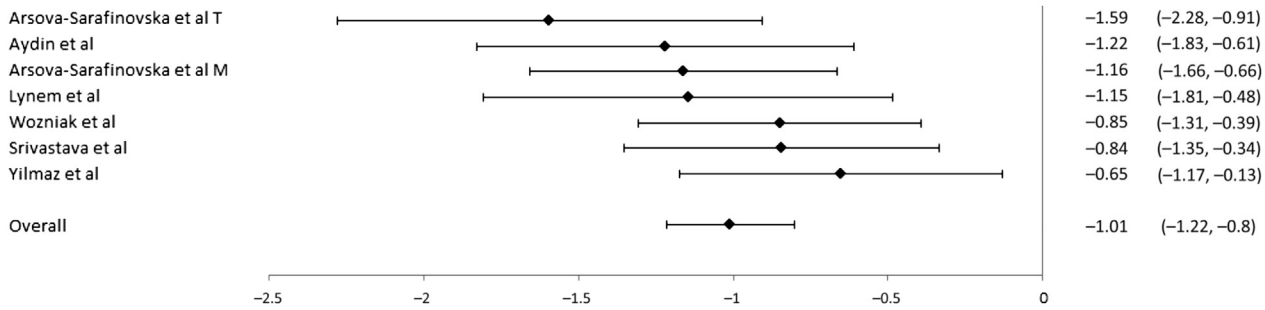

Fig. 4. Forest plot for glutathione peroxidase. For each study, the marker indicates the effect size and the error bars are 95% confidence intervals. For Arsova-Sarafinovska et al, "M" indicates Macedonian patients and "T" indicates Turkish patients.

The oxidation of lipid or lipid peroxidation is one of the most commonly reported indices of OS which is recognized as a pathological factor contributing to chronic disease including cancer and aging.[62,63] The most frequently studied markers of lipid peroxidation are MDA and isoprostanes.[64] Of 23 studies, 14 studies measured OS with MDA and reported OS to be associated with PCa. In those studies, high levels of OS in PCa were consistent, although, MDA was measured using different methods such as thiobarbituric acid test, thiobarbituric acid-reactive substances test, and chromatographic assays (high performance liquid chromatography-diode array detection-fluoro and Liquid chromatography–mass spectrometry- diode array detection). One study reported that MDA levels correlated with the Gleason score and progression of disease.[36] However, another study[43] observed an association between OS and advanced PCa but not localized PCa. To confirm this result will require further studies with an adequate sample size.

Four studies measured lipid peroxidation with isoprostanes, which are prostaglandin-like compounds formed from the free radical catalyzed peroxidation of arachidonic acid. Two studies[48,50] reported urine F2-isoprostane generated by lipid peroxidation to be associated with PCa whilst two other studies did not.[31,53] These two studies[31,53] were likely hampered by the limitation of small sample sizes. Further, differences in study populations may also be a cause of divergent findings. One study[53] was conducted in diabetic and hypoglycemia patients while the former two studies were conducted in nondiabetic patients.

To measure outcomes of protein oxidation, DNA damage with 8-OHdG and with NO_2^- or NO_{3-} are commonly used in cancer

research.[64] Three studies reported a difference of 8-OHdG between two groups while one study did not observe a difference. The latter study suggested that there was a need to improve the validated analytical procedure of measuring 8-OHdG using plasma or serum samples. The results of these three studies are similar to previous studies which demonstrated that higher DNA damage correlated with the risk of PCa.[65,66]

Three studies which measured protein oxidation with NO_2^- or NO_{3-} showed OS to be consistently higher in PCa. These findings are in agreement with previous studies which suggested that ROS, including oxygen and nitrogen-free radicals, may cause specific oxidative DNA damage and play a leading role in initiation and promotion of carcinogenesis.[67]

CAT, SOD, and GSH related enzymes are considered primary endogenous antioxidants while vitamins C, E, and A (converted from beta-carotene) are considered exogenous antioxidants as they are directly involved in elimination of ROS.[46,68] Both endogenous and exogenous antioxidants protect cells against ROS induced during metabolism in living organisms.[46] For example, GSH-Px removes both H_2O_2 and lipid peroxides using GSH. SOD metabolizes and protects the cells against O_2^-, mediated by lipid peroxidation, and CAT acts on H_2O_2 and decomposes it to H_2O and OH^-. The exogenous antioxidants (vitamins A, C, and E) at the molecular and cellular level are also considered to be effective in eliminating free radicals and prevent chronic diseases including cancer.[68] Thus, our review further evaluated the relationship between antioxidants and men with PCa, in addition to OS.

Fifteen studies measured antioxidant indicators. SOD was measured in eight studies with erythrocytes or whole blood. Five studies reported low SOD levels in patients while two studies[42,47] reported contrasting results, and one study[49] found no differences. CAT was measured on erythrocytes and whole blood samples in six studies. Four studies[44–47] reported lower CAT levels in patients and two studies[40,49] found no differences. The main reason for the inconsistency in SOD and CAT values could be attributed to the progression of disease.[49] This hypothesis is consistent with Battisit et al[47] who observed that an alteration in CAT and SOD values existed between patients with localized disease and those with bone metastases.

Further, four studies reported lower GSH levels in patients whereas two studies reported conflicting results.[44,47] All seven studies that measured GSH-Px showed GSH-Px values to be lower in patients. In contrast, GST values were higher in men with PCa. Overall, the GSH-dependent enzyme levels were either decreased or increased or unchanged. The reason for the inconsistency of GSH-dependent enzyme activities could be influenced by the prostate-specific antigen values, as suggested by several studies.[45,51] Furthermore, GSH and GSH-dependent enzymes have been known to be of central importance in the detoxification of peroxides, hydroperoxides, xenobiotics, and drugs.[69] Hence, modification of GSH-dependent enzyme activities can be explained by the interdependence and dynamics of the GSH enzyme family pathway. GSH is turned to gluthathione disulfide by GSH-Px. Glutathione disulfide is reduced again by GR using nicotinamide adenine dinucleotide phosphate as a cofactor. GSH has the ability to directly scavenge cellular ROS nonenzymatically as well as serving as a cofactor for GSH-Px in the reduction of H_2O_2 and other peroxide species.[70] GSH-Px is also responsible for detoxifying other lipid peroxides to the corresponding alcohol.[70] GST catalyzes the conjugation of GSH to a wide variety of endogenous and exogenous electrophilic compounds. GSH conjugation is the first step in the mercapturic acids pathway that leads to the elimination of toxic compounds.[71]

Six studies measured exogenous antioxidant substances.[35,39,41,43,45,47,51] Both vitamin A (including beta-carotene, lycopen, leutin) and vitamin C were found to be lower in patients with PCa. With regard to vitamin E, four studies found lower levels in patients whereas one study[43] reported contrasting results. The authors[43] attributed this difference to different study populations. Patients participating in this study received ADT whilst most other studies included patients who did not receive anticancer treatment. ADT may alter vitamin E levels. Future studies are needed to confirm this.

A major limitation of this review is the inability to control for potential confounding factors. It is possible that the risk of PCa is influenced by multiple factors such as radiation, pollution, alcohol, diet, smoking, anxiety and stress, inflammation, drugs, and chronic diseases, which can all modulate OS levels. Most papers included in this review did not report these variables. Despite this limitation, our results suggest that redox imbalance is more common in men with PCa which may be useful for designing future randomized controlled trials.

In conclusion, the results of our review suggest that dysregulation of redox balance occurs in patients with PCa. OS biomarkers MDA and 8OH-dg as well as antioxidant parameters SOD, CAT, GSH enzyme family, and vitamins C and E may be potentially predictive biomarkers of PCa. Robust studies are required to elucidate whether reduced antioxidant enzyme levels are caused by the counteraction to OS or enhanced oxidation, which occurs as a result of depleted antioxidants over a prolonged period of time.

Conflicts of interest

The authors declare no conflicts of interest.

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