Accepted that free radicals play a role in carcinogenesis and that BPH should be considered a premalignant condition which may evolve into prostate cancer. High OS parameters and low antioxidant activity are more prominent in prostate cancer patients compared with BPH and controls.

Conclusions: Further studies are needed to clarify the potential role of antioxidants in BPH also in view of preventing the progression to prostate cancer. © 2014 S. Karger AG, Basel

Introduction

Benign prostatic hyperplasia (BPH) is a prevalent and chronic progressive disease that may be correctly defined as prostate gland enlargement secondary to hyperproliferation of stromal and glandular cells, with predominance of mesenchymal cells [1]. It is an extremely common disease of ageing men and carries a distressingly high morbidity because of its irritative and obstructive symptoms. The etiology and pathogenesis of BPH are not well understood [2].
Several parameters including inflammatory mediators, hormones, dietary factors, inflammatory genes, and oxidative stress (OS) have been considered to play a role in the development of BPH, but there is no consensus as to which is the primary one. To date, these multifactorial and chronic conditions have been studied to prevent BPH progression. In the last few years, a relationship between prostatic inflammation and lower urinary tract symptoms related to BPH has been suggested [3]. Today, even though it is not yet known exactly when and why chronic inflammation occurs, it has been hypothesized that BPH is an immune-mediated inflammatory disease and inflammation may directly contribute to prostate growth [3].

OS is an imbalance between the production and detoxification of reactive oxygen species (ROS) that can cause tissue damage. Leukocytes are the major source of ROS, and in the case of inflammation, the production of ROS is very much elevated and can exhaust the antioxidative protection system [4]. Therefore, OS can result from either an excess in oxidant production or depletion of antioxidant defenses.

**Literature Review**

We present a comprehensive collection of up-to-date systematic reviews and other important publications on the complex association of OS and BPH. We describe important developments and perspectives based on a systematic analysis of the most cited research in this field.

We searched MEDLINE for articles in English published up to March 2014 using the key words ‘oxidative stress’, ‘antioxidants’ and ‘benign prostatic hyperplasia’. All the studies showing data about the measurement of OS in BPH were included.

**Role of Oxidant Production (table 1)**

Prostate tissue damage and OS may lead to compensatory cellular proliferation with the resulting hyperplastic growth. Prostatic inflammation can cause the generation of free radicals/OS such as inducible nitric oxide (iNOS), reactive nitric species and ROS [5]. Both macrophages and neutrophils provide a source of free radicals that can induce hyperplastic transformations through OS to tissue and DNA [6].

OS can induce vascular tissue damage, protein structure and function damage, genomic damage and cause posttranslational modifications including those involved in DNA repair and apoptosis [7]. These can lead to oxidative DNA damage in point mutations, deletions, or rearrangements and reduce DNA repair. OS also alters the stem cell population. Genomic alterations in cellular DNA result in the modulation of an imbalance between cell proliferation and cell death. A change in the normal regulation of programmed cell death leads to hyperplastic or precancerous transformation [5].

Human prostate tissue is vulnerable to oxidative DNA damage due to more rapid cell turnover and fewer DNA repair enzymes. OS then can activate the transcription factor NF-κB by the TNF-α/AP-1 transduction pathway and the NF-κB-inducing kinase (NIK) transduction pathway. NF-κB is known as a master inflammatory transcriptional regulator; its targets include genes regulating immune response, inflammation, cell proliferation, cell migration, and apoptosis. The nuclear translocation of NF-κB can activate target genes involved in carcinogenesis. Dysregulation of NF-κB has been proposed to be one putative molecular mechanism leading to chronic inflammation and cancer [5]. Exposure of prostate epithelial cells to proinflammatory soluble mediators directly activates NF-κB and induces local production of proinflammatory cytokines in the prostate epithelial cells [8].

In normal prostate, the transduction pathway from NIK to NF-κB seems to be inactive. In BPH, there was increasing TNF-α/AP-1 transduction pathway also followed by increasing apoptotic pathway to inhibit uncontrolled cell proliferation [5]. Another study demonstrated a novel link between OS and loss of imprinting, showing that OS, measured by increased NF-κB activity, induces loss of imprinting of insulin-like growth factor 2 in both cancerous and noncancerous human prostate cells. This loss during aging is important in tumorigenesis. Therefore, modulating NF-κB may prevent age-related alteration in the epigenome [9].

In all the inflammatory cells that arrive in the prostate, iNOS activates reactive nitrogen that can damage cells [10]. iNOS is not detected in normal prostate, while it is expressed in the prostate of all BPH patients, even in the absence of prostatitis or systemic signs of an inflammatory condition. This suggests that sex hormones may be involved in iNOS induction and that there may be a role for NO in the pathogenesis of BPH [11].

NO and cyclooxygenase (COX) activity may play an important role in determining the association between inflammation and prostate growth. Inflammatory cells that are present in the prostate and iNOS are the principal factors activating reactive nitrogens that can damage cells. NOS expression in human prostate tissue has been characterized by increased immunostaining in the epi-
## Table 1. Summary of considered studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study description</th>
<th>Patients</th>
<th>Methods</th>
</tr>
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<tbody>
<tr>
<td>Olinski et al. [32]</td>
<td>Comparison of endogenous level of OH radicals in BPH tissue and in healthy tissue</td>
<td>15 patients with BPH</td>
<td>Isolation of chromatin and measures of enzymes through gas chromatography</td>
</tr>
<tr>
<td>Doğru-Abbasoğlu et al. [30]</td>
<td>Comparison of antioxidant enzyme activities and lipid peroxides in the plasma of patients with BPH or PCa</td>
<td>24 patients with BPH, 19 patients with PCa</td>
<td>Lipid peroxide activities Total sulfhydryl contents and activities of SOD, GPX, and CAT</td>
</tr>
<tr>
<td>Merendino et al. [23]</td>
<td>Evaluation of MDA levels in BPH</td>
<td>22 healthy subjects, 22 patients with BPH</td>
<td>MDA in plasma PSA plasma level</td>
</tr>
<tr>
<td>Zachara et al. [38]</td>
<td>Measurement of blood and tissue Se concentration and GPX activities in patients with PCa and BPH</td>
<td>32 patients with PCa, 40 patients with BPH, 39 healthy subjects</td>
<td>Selenoenzyme GPX (GSH-Px) measurement in red cells, plasma and prostate tissue</td>
</tr>
<tr>
<td>Almushatat et al. [26]</td>
<td>Comparison of concentration of vitamin antioxidants, lipid peroxidation and the systemic inflammatory response in BPH, cancer and healthy tissues</td>
<td>14 healthy subjects, 20 patients with BPH, 38 patients with metastatic PCa</td>
<td>Assessment of plasma concentration of retinol, α-tocopherol, lutein, lycopene, α-carotene and β-carotene concentrations with HPLC MDA in plasma C-reactive protein in plasma</td>
</tr>
<tr>
<td>Srivastava and Mittal [24]</td>
<td>Comparison of oxidative activity between BPH patients and healthy subjects</td>
<td>47 patients with BPH, 55 patients with PCa, 25 healthy subjects</td>
<td>GST activity GSH Lipid peroxidation in serum or hemolysates</td>
</tr>
<tr>
<td>Aydin et al. [21]</td>
<td>Evaluation of OS and antioxidant status in nonmetastatic PCa and BPH</td>
<td>25 patients with nonmetastatic PCa, 36 patients with BPH, 24 healthy subjects</td>
<td>Thiobarbituric acid reactive substances SOD activity GPX CAT Cu Zn</td>
</tr>
<tr>
<td>Aryal et al. [25]</td>
<td>Comparison of concentration of vitamin antioxidants and antioxidant response in BPH and healthy subjects</td>
<td>48 patients with BPH, 46 healthy subjects</td>
<td>MDA in plasma α-Tocopherol and ascorbic acid level</td>
</tr>
<tr>
<td>Goswami et al. [22]</td>
<td>Comparison of serum protein-bound sialic acid in benign and malignant prostatic growth</td>
<td>10 patients with BPH, 10 healthy subjects</td>
<td>Carbonylation of proteins Lipid peroxidation products, PSA and protein-bound sialic acid</td>
</tr>
<tr>
<td>Arsova-Sarafinovska et al. [17]</td>
<td>Comparison of the oxidative/ nitrosative stress status in PCa and BPH</td>
<td>163 patients from Macedonia (73 PCa patients, 67 BPH patients and 23 healthy subjects), 149 patients from Turkey (34 PCa patients, 100 patients with BPH and 15 healthy subjects)</td>
<td>Erythrocyte MDA levels Erythrocyte activities of superoxide dismutase (CuZn-SOD) GPX CAT Plasma nitrite/nitrate cGMP and 8-hydroxy-2′-deoxyguanosine levels</td>
</tr>
<tr>
<td>Savas et al. [28]</td>
<td>Comparison of oxidative activity between BPH patients and healthy subjects</td>
<td>74 patients with BPH, 62 healthy subjects</td>
<td>Antioxidative status of plasma Total antioxidant capacity Oxidative status of plasma</td>
</tr>
<tr>
<td>Kullisaar et al. [4]</td>
<td>Evaluation of systemic OS levels in the case of noncancer prostate-associated disorders</td>
<td>21 asymptomatic inflammatory (NIH category IV) prostateitis patients, 48 noninflammatory (NIH category IIIb) chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) patients, 44 inflammatory (NIH category IIIa) CP/CPPS patients, 33 patients with BPH, 22 patients with BPH and NIH IV category prostatitis, 28 healthy subjects</td>
<td>Determination of 8-EPI in urine by competitive enzyme-linked immunoassay</td>
</tr>
<tr>
<td>Eichholzer et al. [37]</td>
<td>Evaluation of the association between the risk of BPH and Se status</td>
<td>111 patients with BPH, 214 healthy subjects</td>
<td>Serum Se and selenoprotein P concentrations and GPX activity</td>
</tr>
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</table>

HPLC = High-performance liquid chromatography; PCa = prostate cancer.
the epithelial cells of cases with BPH when compared with normal tissue [12]. NO also enhances COX activity. COX-2 activity has been detected in all inflammatory cells in the epithelium and interstitial spaces of human prostate tissue, and it is increased in proliferative inflammatory lesions, generating proinflammatory prostaglandins [13, 14]. Moreover, COX-2 has shown to upregulate prostaglandins [14] and one of its important breakdown products, isoprostanoids, is detected in BPH patients compared with controls [12]. Moreover, COX-2 inhibition has been shown to induce prostate cell apoptotic activity [16].

Another nitrosative stress-related parameter, plasma nitrite/nitrate, was found elevated in BPH patients compared with controls [17].

ROS may also indirectly cause the formation of DNA adducts by initiating autocatalytic lipid peroxidation, which generates a large variety of potential genotoxic breakdown products, including alkoxyl radicals, peroxyl radicals, and aldehydes, such as malondialdehyde (MDA) [18, 19].

High plasma peroxide levels were found in BPH patients compared with controls [20].

Lipid peroxidation, estimated by measurement of thiobarbituric acid reactive substances was found to be increased in BPH patients compared with controls [21, 22].

MDA is an end product derived from peroxidation of polyunsaturated fatty acids and related esters. In contrast to free radicals, aldehydes are relatively stable and therefore able to diffuse within or out of the cell and to attack targets distant from the site of original free radical-initiated events. Furthermore, MDA does not just reflect lipid peroxidation, but is also a by-product of cyclooxygenase activity in platelets, and persistent platelet activation is a common feature of many clinical syndromes associated with enhanced lipid peroxidation. Thus, measurement of MDA levels in plasma or serum provides a convenient in vivo index of lipid peroxidation and represents a noninvasive biomarker of OS often clinically employed to investigate radical-mediated physiological and pathological conditions [19].

Circulating MDA levels were found to be significantly higher in BPH patients than in healthy donors [17, 23–25] and strongly correlated with prostate-specific antigen levels [23]. However, other works found circulating MDA levels in BPH patients similar to those in controls [26].

Lipid peroxidation can also trigger prostaglandin synthesis via activating COX-2 [14].

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Another product of lipid peroxidation, 8-epi-prostaglandin F2α (8-EPI), is an isoprostane produced by the nonenzymatic peroxidation of arachidonic acid by ROS. In urine, it is a reliable approach to assess systemic OS in vivo [27]. 8-EPI urinary levels were found elevated in BPH patients in comparison with controls [4]. However, other studies found no significant changes in total oxidative status [28], lipid peroxidation or NOX2 expression [29] in BPH patients compared to controls [30].

Role of Depletion of Antioxidant Activity

Normally, highly oxidative stresses are removed by natural protective mechanism, the superoxide dismutase (SOD) enzyme system, such as SOD, glutathione peroxidase (GPX) and catalase (CAT) enzyme, as well as vitaminic antioxidants like α-tocopherol and ascorbate.

The extent of ROS-induced oxidative damage can be exacerbated by a decreased efficiency of antioxidant defense mechanisms. Balance between OS and the antioxidant component of the cells has also a role in developing prostate disease [31]. There are increases in OS and decreased antioxidant mechanisms in prostate diseases reported in several studies; however, the data are not univocal.

Lower activity of SOD and CAT and increased endogenous levels of DNA base products were found in the majority of BPH tissues compared to the surrounding disease-free prostate tissue [32]. Moreover, when both CAT and SOD had decreased activity in BPH tissues than in normal tissues, the increase in DNA base products was more prominent. When only SOD activity was decreased in BPH tissues and CAT activity was similar in both tissues types, the increase in levels of DNA base products was less pronounced. In the case of similar SOD and CAT activity in both tissues types, no changes in levels of DNA products were observed. Therefore, these results suggested a possible association between antioxidant enzyme activity and levels of DNA base lesions in BPH tissues [32].

Decreased total equivalent antioxidant capacity levels were found in patients affected by BPH compared with controls, and an inverse correlation between plasma peroxides and total equivalent antioxidant capacity was observed in those patients. However, no statistically significant modifications were observed as concerns SOD activity [20].

Glutathione S-transferases (GSTs) are a family of phase II xenobiotic metabolizing enzymes, protecting the body from oxidative insults by conjugating glutathione (GSH) with various electrophilic compounds generated after activation by phase I enzymes [33]. Deletion of GSTM1 and GSTT1 genes, which are important isoenzymes of GST, leads to a complete lack of activity of their enzymes. Absence of these enzymes due to homozygous...
deletions is implicated in poor elimination of carcinogenic substances, making individuals with these deletions susceptible to oxidative injury [34]. A study has reported a positive association of GSTM1 or GSTT1 polymorphism with increased risk of BPH [35]. In individuals with BPH and with double deletions GSTM1/GSTT1, significantly higher MDA levels were observed compared to GSTM1+/GSTT1+ [34]. Significantly higher MDA levels were also present in BPH subjects amongst GSTM1+/GSTT1+ groups compared to GSTM1+/GSTT1+ genotypes. A study reported the GSTM1 null genotype to be associated with increased risk of BPH [33]. Therefore, the presence of the GSTTI genotype and/or absence of the GSTM1 genotype might have significance in the possible development of OS in BPH patients [36].

Lower activities of SOD [17, 21], GPX [17, 23] and reduced GSH concentration [24] versus corresponding controls have been shown in BPH patients; however, one of these studies [17] reported different results between patients from Macedonia and Turkey, the latter showing a decreased activity only in GPX.

The study of Srivastava and Mittal [24] also showed higher GST activity in BPH patients, and a positive correlation between serum MDA level and GSH, GST and GPX in BPH patients. This suggested a cause-and-effect relationship, i.e. if OS developed, an increase in the level of antioxidant would try to nullify the effect [24].

Selenium (Se) is a key component of GPX; it not only increases the activity and/or concentration of GPX, but also the concentration of selenoproteins [37]. Se concentration in whole blood and plasma and red cell GPX activity of BPH patients were lower compared with controls [38]. In another work, the risk of BPH was found significantly decreased with an increased serum Se concentration. However, no significant association between serum selenoprotein P concentration or GPX activity and risk of BPH was found [37].

α-Tocopherol and ascorbate act in synergy in the membrane and cytosol of the cell. α-Tocopherol scavenges lipid peroxy free radicals and interrupts the chain reaction of lipid peroxidation becoming oxidized itself in the process. Ascorbate present in the aqueous compartments acts as a water-soluble chain-breaking antioxidant, converts the tocopheroxyl radical back to active α-tocopherol, thereby replenishing antioxidant activity of α-tocopherol [39]. Decreased levels of α-tocopherol and ascorbate were found in BPH patients; moreover, a significant inverse correlation between ascorbate and MDA was found, but the correlation between α-tocopherol and MDA was not statistically significant [25].

Other studies found no significant difference in total antioxidant capacity between BPH patients and controls [29].

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**Conclusion**

Several studies demonstrated the presence of OS in BPH. OS can be due to an overproduction of oxidant molecules or to a deficiency in the antioxidant system, or both. In BPH, both mechanisms are present.

Growing evidence indicates that the cumulative production of ROS and reactive nitric species through either endogenous or exogenous insults plays a major role in the aging process and age-related diseases.

It is generally accepted that free radicals play a role in the early phases of carcinogenesis and that prostate hyperplasia should be considered a sort of premalignant condition which may evolve into prostate cancer, even though experimental and clinical lines of evidence are still controversial in relation to this last suggestion [20].

Data from the literature show that high OS parameters and low antioxidant activity are more prominent in prostate cancer patients compared with BPH and controls [17, 20, 21]. Whether the presence of OS-related parameters could be used to make differential diagnosis or to predict prognosis in patients with prostate cancer and BPH is a question which requires further, larger studies for a better management of disease in such patients. Moreover, prospective studies and well-structured research are obviously needed to better clarify the potential role of antioxidants in BPH also in view of preventing the progression to prostate cancer.

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**References**


Review


