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Review Article

Antioxidant status in patients with hyperplasia and prostate cancer

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Summary

This review aims to briefly describe and summarize data from various studies on the role and the link between serum Total Antioxidant Status (TAS) levels in patients with BPH and PC, as well as other more widely available endogenous antioxidants, the levels of markers of inflammation (CRP, Leuc.), as well as the link between the values of endogenous antioxidants and various harmful factors. Their levels and adequate assessment could help in the proper management of patients with BPH and PC, as well as in reducing morbidity.

Key words: Antioxidant status, inflammation, oncological diseases, oxidative stress, prostate cancer, prostatic hyperplasia

Introduction

One of the directions in searching for the reasons for the increase in the frequency of oncological diseases is the search for connection with possible disorders in the antioxidant status (AOS) in cancer patients. Studies in this direction aim to establish the levels of oxidative stress and inflammation in the body and what the link is between them in benign prostatic hyperplasia (BPH) and prostate cancer (PC). Prostate cancer is the second most common cancer in men worldwide, which defines it as a significant medico-social problem (Bray et al. 2018; Culp et al. 2020; Wang et al. 2022). BPH is a chronic disease in adult men and is a non-malignant increase in stromal and epithelial cells of the prostate. It is the most common condition in ageing men (Phua 2021).

The review aims to summarize the literature on the association between serum antioxidant status, significant markers of inflammation and various risk factors in patients with BPH and PC.

Materials and methods

We have made an initial review of the literature. We searched several databases (PubMed, Science Direct, and MEDLINE) for antioxidant status, oxidative stress, inflammation, prostate cancer, prostatic hyperplasia, and combinations of these. We found about 340 articles that fit the purpose of this review.

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Risk factors for the development of BPH and PC

BPH and PC are very important public health problems that tend to increase the incidence in the ageing population. The aetiology and risk factors are not fully analyzed, but some risk factors that are not subject to change are age, ethnicity, genetic predisposition and family history (Huynh-Le 2021; Phua 2021). Variable and impermanent factors are the environment, lifestyle and diet, which are also considered risks for developing BPH and PC (Shukla et al. 2020; Tan and Norhaizan 2021).

Family history has been found to increase the risk by two to three times. Environmental conditions and diet can accelerate the progression of latent tumours. A diet with a high intake of total calories and saturated fat, red meat, and more dairy products or calcium also causes an increased risk of disease progression. The intake of dietary antioxidants such as selenium, vit. E and lycopene have been linked to a reduced risk of prostate cancer. Anthropometric factors and physical activity are also of particular importance. High BMI is a risk factor - there is a specific interest in belly fat, which has metabolic effects (Harrison et al. 2020). Endogenous hormones also play a role in the aetiology of PC. The concentration of androgens is essential. The prostate gland needs them for its development, but data indicate that androgen blockade or lack of androgens leads to regression of the disease. There are still many studies on the levels of these hormones and the progression of prostate cancer. Another hormone hypothesis is related to the level of insulin-like growth factor-1 (IGF-1) - it mediates the action of growth hormone and is associated with the risk of prostate cancer. Conditions in the gland, such as BPH, are difficult to investigate as a risk factor for cancer because their existence is linked to diagnosing the patients later in time. Chronic inflammation of the prostate gland, accompanied by endogenous free radical formation, is very common. The oxidant/antioxidant balance is crucial (Gann 2002; La Vignera et al. 2016; Li et al. 2019).

Oxidative stress and antioxidant status

A large body of evidence suggests that oxidative stress (OS) and its effects on DNA damage have a major influence associated with the ageing and development of prostate cancer. The relationship of ageing to PC is undisputed, as is the relationship of ageing to oxidative stress (Kumar et al. 2008; Minelli et al. 2009). Ageing, also defined as a gradual decrease in the body's ability to resist stress, disability and disease, has been linked to the development of many diseases, such as cancer, diabetes, cardiovascular and neurodegenerative disorders (Liguori et al. 2018). OS is formed by the imbalance between reactive oxygen species (ROS) and the detoxification defence system, resulting in a ROS-rich environment and reduced body antioxidant defence (Bassey et al. 2020). There is a growing body of evidence that the lifespan of an organism can be increased by increasing antioxidant protection. Free oxygen radicals are formed endogenously from normal metabolic processes using oxygen and play an essential role in ageing (Minelli et al. 2009). Accumulating evidence suggests that the production of harmful oxidative damage molecules is important for age-related diseases such as BPH and PC (Bostwick et al. 2000). The wide variety of ROS and nitrogen species can attack DNA directly and lead to

mutations. ROS can also lead to lipid peroxidation that generates a wide variety of harmful radicals (Duru et al. 2014).

Endogenous defences against ROS include antioxidant enzymes such as glutathione peroxidase (GPX), catalase (CAT), and superoxide dismutase (SOD), as well as non-enzymatic. Lower levels of antioxidants in the blood have been found to be associated with an increased risk of cancer (Aydin et al. 2006). Non-enzymatic antioxidants are two subgroups: metabolic antioxidants and dietary antioxidants. Non-enzymatic metabolic antioxidants are bilirubin, melatonin, uric acid, albumin, coenzyme Q10, and glutathione (GSH). Non-enzymatic antioxidants, including vitamins A, E, and C, are commonly used as dietary supplements for general health. Given their benefits and a potential link with reduced cancer risk, they represent a good opportunity as preventive anticancer agents (Didier et al. 2023). Enzymatic and non-enzymatic antioxidants act together to dispose of the effects of OS and lipid peroxidation. This action can be measured with TAS, which is also one of the indicators of our study.

Lipid peroxidation products and levels of enzymatic and non-enzymatic antioxidants are used as markers of oxidative stress (Bhattacharyya et al. 2014). ROS molecules induce oxidative stress in feedback mechanisms involving many biological processes, such as apoptosis, necrosis, and autophagy. A growing body of evidence suggests that ROS are critical signalling molecules throughout the cell death pathway (Drozdz-Afelt et al. 2022). Their increased production can destroy the structure of biomolecules and organelles, leading to an inflammatory response, which in turn is a major mechanism for cancer development (Oberley et al. 2000; He et al. 2017). One of the hallmarks of cancer is the dysregulation of the cells' energetics, which allows tumour cells to survive in an environment in which normal cells most often die. Men are often attacked by many endogenous agents, such as inflammation and oxidative phosphorylation in the mitochondria, and exogenous ones, such as ultraviolet rays, drugs and cigarette smoke, which lead to oxidative stress and gradually to the development of BPH and finally to PC (White et al. 2020). Adequate assessment of antioxidant levels in patients with BPH and PC can help manage them properly and reduce morbidity. Antioxidant deficiency may be associated with greater cell degeneration, progression, cancer enlargement, and poor prognosis. Determination of TAS values in these two patient groups can complement PSA results in the diagnosis and treatment of these two groups of diseases (Duru et al. 2014). High levels of OS and reduced antioxidant defence of the body were more prominent in patients with PC compared to those with BPH and the control group. In recent years, a link has also been established between inflammation of the prostate and lower urinary tract symptoms associated with BPH (Minciullo et al. 2014). It has been suggested that chronic inflammation may directly contribute to gland growth.

Leukocytes are also one of the main sources of ROS. In inflammation, the production of ROS is very increased, which, in turn, exhausts the body's antioxidant defences (Mittal et al. 2014; Lloyd et al. 2019). Inflammatory markers such as CRP, Leuc., and PSA are expected to be elevated in patients with BPH and PC. These changes are important for the pathogenesis of prostate adenoma and gland cancer and are useful for assessing the condition of patients according to their stage. It is already known that the adverse effects of free radical processes are under the control of the antioxidant system present in the human body. TAS can be considered as two separate values - TAS for

slow-acting enzymatic antioxidants, such as GPX, SOD and other enzymes, and TAS for non-enzymatic fast-acting antioxidants, such as β-carotene, tocopherols, bioflavonoids, ascorbic acid, glutathione and albumin (Sawicka et al. 2020). Higher values of inflammatory markers are expected in patients with prostate carcinoma and in more advanced stages. Cancer cells themselves can produce inflammatory cytokines such as IL-1 and IL-6, which further stimulate the synthesis of CRP by the liver (Sawicka et al. 2020).

Endogenous antioxidants

Uric acid

Uric acid is a final product of the catabolism of the purine nucleosides adenosine and guanosine. They are excreted as uric acid and obtained from the breakdown of endogenous nucleic acids. A major regulator in this process is the enzyme xanthine oxidoreductase. It converts hypoxanthine into xanthine and, finally, xanthine into uric acid (Saito et al. 2021). Uric acid concentrations are also affected by exogenous food imports, especially from red meat, alcohol, and seafood. However, the diet does not generally have a major change in serum levels, and they do not tolerate large fluctuations, unlike hereditary and genetic predispositions (Major et al. 2018). Uric acid is synthesized endogenously mainly in the liver, muscles, intestine and vascular endothelium. Most of its excretion from the body occurs through the kidneys and a smaller part - through the gastrointestinal tract. Almost the entire amount is filtered by the glomeruli. Proximal tubules are the site of reabsorption and secretion of uric acid and about 90% is reabsorbed into the blood, suggesting their significant role (Maiuolo et al. 2016). In plasma, uric acid is found in the form of monosodium urate. At increased concentration, saturation of plasma levels occurs, followed by the formation of urate crystals and their deposition in tissues (hyperuricemia) (Kratzer et al. 2014). Elevated uric acid levels are involved in the pathogenesis of various diseases, such as gout, cardiovascular disease, hypertension, and chronic renal failure (Major et al. 2018). Chronic hyperuricemia is a major risk factor for gout, and the gender discrepancy in the prevalence of gout can be explained by different levels of serum urate in men and women. Women generally have significantly lower serum urate levels than men of the same age. The question of whether the male sex hormone directly affects uric acid levels, as well as the levels of female sex hormones, has not yet been fully analyzed (Park et al. 2018). Despite its involvement in developing certain diseases, it is the predominant antioxidant molecule in plasma, necessary to induce a type 2 immune response, which explains its protective potential for the body (Kratzer et al. 2014). In order to survive in an oxygen environment, aerobic organisms have many mechanisms to protect against oxygen radicals and singlet oxygen. One such protection mechanism is a direct extraction of harmful radicals, singlet oxygen and oxo-heme oxidants from uric acid (Davies et al. 1986). In humans, it takes up more than 50% of the antioxidant capacity of plasma (El Ridi and Tallima 2017). Urate levels in plasma in humans are significantly higher than those of ascorbate, making it one of the main antioxidants. Uric acid levels have evolutionarily increased significantly due to a series of mutations, resulting in prolonged life expectancy and reduced age-specific cancers (Ames et al. 1981).

Bilirubin

Bilirubin is a bile pigment, a major end product derived from the breakdown of heme, which is released when lysing erythrocytes. Its action is cytotoxic in high concentrations, but in normal concentrations, it has antioxidant effects, extracting ROS and decreasing OS (Maruhashi et al. 2019). At normal serum concentrations, unconjugated bilirubin cleanses singlet oxygen molecules, interrupts ROS chain reactions and acts as a strong antioxidant. Bilirubin in liposomes inhibits oxidation more than alpha-tocopherol, which is considered the best lipid peroxidation antioxidant. Many data support the idea that bilirubin is beneficial because it acts like an antioxidant. Recent studies have also identified it as a hormone that exerts its positive effects. In heart tissue, the production of reactive oxygen decreases; in liver tissue, hepatic steatosis decreases; in adipose tissue, its concentrations reduce abdominal obesity and hypertriglyceridemia. This role as a hormone or an antioxidant is still the subject of many studies. In addition to the consequences of pathologically elevated bilirubin levels, low concentration is also important. It has been proven that bilirubin also has an anti-inflammatory character. It also acts as an immune modulator. In some infections, it works together with the immune system. Moderately elevated concentrations may also lead to carcinogen degradation, which is still being studied (Creeden et al. 2021). More recent evidence suggests that slightly increased bilirubin levels are strongly associated with reduced prevalence of chronic disease, cancer, type 2 diabetes and reduced overall mortality (Wagner et al. 2015).

Albumin

Albumin is the main plasma protein in the human body. It accounts for about 60% of total plasma proteins. It is synthesized in the liver and is a negative acute-phase protein. It plays a major role in transporting various ions, neutral and electrically charged molecules, and in maintaining colloid-osmotic blood. It is associated with almost all medicines, food additives and toxic substances (Belinskaia et al. 2021). It is a major transporter of fatty acids, provides the metabolic modification of some ligands, neutralizes potential toxins, is responsible for most of the antioxidant capacity of human plasma and displays esterase, enolase, glucuronidase and pseudo-peroxidase enzyme activity. It is a major and predominant antioxidant in plasma, exerting more than 80% of the activity of serum to capture free radicals (De Simone et al. 2021). Thanks to the free thiol group, albumin can serve as a trap for reactive oxygen and nitrogen species and thus participate in redox processes. Albumin enhances the antioxidant status of the body by binding bilirubin and polyunsaturated fatty acids. Its antioxidant activity mainly reflects its metal-chelating properties (De Simone et al. 2021). Two albumin cysteine residues - Cys392 and Cys438, have a very important role in the antioxidant properties of albumin. Cys34 is one of the most important scavengers of ROS and contributes to its antioxidant properties. Its serum levels are a marker of the nutritional status of the body. The establishment of low levels (hypoalbuminemia) is increasingly being accepted as a risk factor and predictor of morbidity and mortality. The concentration of albumin in plasma plays a role in many diseases, such as infections,

cancer and even depression. Therefore, measuring its level in serum or plasma not only indicates the amount of one protein but also assesses the state of the whole organism (Belinskaia et al. 2021).

Importance of methods of treatment of BPH and PC

Many factors influence the outcome of patients diagnosed with cancer. Different treatment methods, such as surgery, therapy, and cytostatics, all lead to a systemic inflammatory reaction in the body. It is of physiological importance for the recovery of the patient. In some patients, inflammation persists for a long time, which is also due to other adverse risk factors that further aggravate the prognosis of the disease (Leimkuhler et al. 2020).

The method of treatment plays an essential role in the patient's condition. Minimally invasive techniques such as laparoscopy and robot-assisted surgery significantly reduce the risk of infectious complications and lead to faster recovery of the body. These surgical techniques have been established in practice worldwide and in the robotic surgery centres in Bulgaria. They also allow us to track changes in the antioxidant status of patients treated with various surgical methods (Liu et al. 2010). PSA, an organ-specific marker that reflects changes related to development, malignancy and staging, is well suited for monitoring the course of the disease. It is also used in patients from high-risk groups and those with BPH. Using the PSA combination, the Gleason biopsy assessment and the clinical T-stage showed better results in determining the pathological stage than each marker individually (Williamson and Song 2022). Large-volume surgery and advanced disease result in an immuno-inflammatory response, which is accompanied by the production of ROS at the site of injury. OS is supposed to play a triggering role in the development of organ failure. In situations of major surgery and advanced disease, a redistribution of antioxidants to the needy tissues and organs occurs. The redistribution of antioxidants, in turn, leads to a decrease in antioxidant stores, which can be harmful when the OS is long-lasting. In these cases, adding certain antioxidant amino acids and antioxidant trace elements may improve the treatment outcome. There is still little information about the effect of antioxidant supplementation in major surgery and the levels of antioxidant capacity and OS (van Stijn et al. 2008).

Conclusion

From all of the above, it becomes clear that the topic of antioxidant status and OS in these two socially significant diseases, such as BPH and PC, is relevant. Many more studies have yet to come on the impact of antioxidants on human health, the prevention of the development of malignant diseases, and the good management of patients with these diagnoses. The levels of TAS and the other endogenous antioxidants showed a significant decrease in subjects with high PSA values. Antioxidant deficiency may be associated with greater cell degeneration, progression, cancer enlargement and poor prognosis. Many studies have generally shown that extracellular antioxidant capacity is greatly reduced in selected groups of patients with BPH and PC. These results could also be the reason for the reduced overall survival in these patients, depending on the severity of the disease process and the stage in which they are.

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