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Role of oxidative stress in pathology of chronic prostatitis/chronic pelvic pain syndrome and male infertility and antioxidants function in ameliorating oxidative stress

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ABSTRACT

Oxidative stress (OS) is a result of the imbalance between reactive oxygen species (ROS) and antioxidants in the body that can cause tissue damage. Oxidative stress has a significant involvement in the pathogenesis of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and male infertility. CP/CPPS is a major risk factor for male infertility due to generation of excessive ROS that damage sperm DNA, lipids, and proteins, resulting in compromised vitality and decreased sperm motility. Here we present a comprehensive review of oxidative stress relevance in CP/CPPS and male infertility, and embody the protective effects of antioxidants against ROS. An online literature was searched using the following keywords/terms: oxidative stress, ROS, Oxidative stress and chronic prostatitis, oxidative stress and male infertility and antioxidants. Original and review articles, clinical trials, and case reports of human and animal studies published till 2017 were searched using the PubMed and MEDLINE.

1. Oxidative stress

Cells are protected against potentialcytotoxicity due to the critical balance between production and degradation of reactive oxygen species (ROS). Reactive oxygen species have the significant role in the cell signaling and homeostasis in normal state; however, the imbalanced ROS interact with lipids, proteins, carbohydrates, and nucleic acids [1,2]. Oxidative stress arises when there is an imbalance between reactive oxygen species and antioxidants, in favor of ROS. Reactive oxygen species include free oxygen radicals, such as superoxide ($O_2\cdot^-$), hydroxyl radical (OH), peroxyl radical (ROO) and hydrogen peroxide (H_2O_2), which is non-radical. The non-radicals are either oxidizing agents or easily transformed into the radicals.

ROS or free radical is defined as an oxygen molecule containing one or more unpaired electrons in atomic or molecular orbitals. For example, the addition of one electron to dioxygen (O_2) forms the superoxide anion radical ($O_2\cdot^-$), the primary form of ROS. This superoxide anion can then be directly or indirectly (enzymatic, metal catalyzed) converted to secondary ROS such as the hydroxyl radical (OH), peroxyl radical (ROO) or hydrogen peroxide (H_2O_2) [3]. Although, free radical and ROS are interchangeable terms, it should be noted that all ROS are not free radicals [4]. For example, hydrogen peroxide (H_2O_2) is

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considered a ROS but it is not a free radical since it does not contain unpaired electrons. ROS react with molecules in immediate surroundings and have short lifespans that range from Nanoseconds to milliseconds [5].

Superoxide is the major ROS produced by biological machinery [5]. In the aerobic organism, most of the oxygen is reduced to water in the mitochondrial respiratory chain. However, a small proportion of the oxygen molecules (1%–2%) is converted to superoxide anion radical [6,7].

Hydrogen peroxide (H_2O_2) is the most stable intermediate of oxygen reduction in the cell membranes under physiological pH and temperature in the absence of metal ions [8]. Superoxide and hydrogen peroxide produce reactive hydroxyl radical via cellular transformations by reduction of ferric (Fe3+) to ferrous ion (Fe2+) in the presence of superoxide, follows by the H_2O_2 transformation to hydroxyl radical [9].

Hydroxyl radical (·OH), the most reactive and dangerous radical, is formed from superoxide anion and H2O2 in the presence of metal ions [10]. In vivo, primarily hydroxyl radicals emerge from the metal-catalyzed breakdown of H2O2, through Fenton reaction [11].

Establishing the participation of free radicals in the disease pathogenesis is particularly difficult due to the short lifetimes of free radicals and lack of sensitive technologies to identify them in biological tissues. Therefore, it is still unclear, whether free radicals are the sole cause of the injury or generated after disease induction. However, accumulating evidence for the participation of oxidative stress in diseases such as aging, atherosclerosis, reperfusion injury, arthritis, connective tissue disorders, toxin exposure, infection, neurologic and dermatologic diseases, chronic inflammation, and cancer has been widely acknowledged [12–15].

Oxidative stress has also a significant correlation with chronic prostatitis/ Chronic pelvic pain syndrome (CP/CPPS) and male infertility. Prostatic inflammation results in activation of inflammatory cells within the prostate and enhances ROS production, thus damaging sperm protein, DNA and membrane integrity. Therefore, the controlled exogenous and endogenous ROS production is of paramount importance to assure normal sperm function. On the other hand, low levels of ROS are vital for the spermatozoon to attain fertilizing capability [16,17]. Superoxide ($O2\cdot^-$), hydrogen peroxide (H2O2), and nitric oxide (NO·) are released by mammalian spermatozoa under capacitating conditions and elicit phosphorylation events that culminate with the ability to induce the acrosome reaction upon particular physiological stimuli [18–21].

We present a review concerning the pathological association of ROS with CP/CPPS and male infertility and role of anti-oxidants in minimizing deleterious effects of ROS.

2. ROS contribution in chronic prostatitis/chronic pelvic pain syndrome and male infertility

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) or category III prostatitis is the complex and poorly understood disease of the prostate gland. This type of prostatitis may be inflammatory (IIIA) or noninflammatory (IIIB) based on the presence or absence of leukocytes in the prostatic fluid [22]. The current knowledge of CP/CPPS is limited in several ways: the exact etiology of CP/CPPS is still elusive, and no unified diagnostic and treatment criteria have been established yet [22–25]. Suggested causes for CP/CPP include infection [26], autoimmunity [27], inflammation [28], and neurological disturbances [23,29]. Multiple treatments are available to treat chronic prostatitis that include antibiotics, anti-inflammatories, α-blockers, pollen extracts with B vitamins [30], prostate massage, anti-depressants, and acupuncture [31–34].

CP/CPPS is usually characterized by inflammation and increased infiltration of cytokines, secreted by inflammatory cells, which are the major biomarkers [35,36]. Interleukin 1 beta (IL-1β) is an important proinflammatory cytokine in the pathogenesis of Prostatitis because of its close association with inflammation. Tumor necrosis factor alpha (TNF-α) is synthesized by monocytes and macrophages and recent studies indicated its key role in infection and chronic inflammation [36]. CP/CPPS patients had higher TNF-α and IL-1β level in their semen as demonstrated by Alexander and Co-worker [35,37].

Hidden prostatic bacterial infection is also one of the etiological agent and biomarker for CP/CPPS disease [38]. In one study, it was demonstrated that the hidden bacterial infection e.g. ureaplasma urealyticum [39] is the possible causes of chronic abacterial prostatitis. These findings provide evidence that cytokines and bacteria are the pathological agents in CP/CPPS progression. These biomarkers lead to excessive ROS production and initiation of a vicious circle in the prostate tissue.

Recently, Oxidative stress involvement in CP/CPPS has come under scrutiny and multiple studies indicate the role of oxidative stress in chronic prostatitis patients, regardless of the etiological basis of CP/CPP [14,40–44]. Chronic prostatitis patients acquire oxidative stress because inflammation in tissue is always accompanied by OxS [45]. Category IIIA patients are characterized by the enhanced level of OxS at both local and systemic level, e.g., blood, urine [46].

Chronic prostatitis either bacterial or non-bacterial leads to stromal or epithelial cell damage causing inflammation in a majority of cases [47]. The continual exposure of prostate tissue to the inflammation can lead to the intense release of ROS, causing changes in protein structure and function, and DNA modifications [48]. Inflammatory cells, particularly macrophages migrate to the site of inflammation in CP/CPPS and increase the concentration of hydroxyl radicals, superoxides and peroxides in the semen [49]. Multiple studies also identified the production of ROS in the semen by activated leukocytes in response to inflammation [42,50,51]. The increased oxidative stress due to leukocytospermia may modulate the level of pro-inflammatory cytokines. Infiltration of TNF-α and interleukin-1β pro-inflammatory cytokines in the seminal fluid [52] intensifies the oxidative stress status [53]. They effect T-cells proliferation in CP/CPPS patients and stimulate chemotaxis of granulocytes, which contribute to tremendous amount of ROS in seminal plasma [42]. Migration of activated granulocytes in the prostate or seminal vesicles during genital tract inflammation induces ROS production and impairs the sperm function [42,54].

Ureaplasma urealyticum, also known as T-strain mycoplasma, is the smallest free-living microbe and causes urinary infections, such as prostatitis [55] and pelvic inflammatory diseases. Elevated ROS level among prostatitis patients with positive ureaplasma urealyticum cultures was observed. Seminal cultures, semen analysis, and ROS measurement were evaluated in 50 patients with NIH Category III prostatitis. Seventeen of the patients had positive ureaplasma urealyticum semen cultures [42]. Therefore, oxidative stress in expressed prostate secretions (EPS) or semen mirrors the inflammatory reaction or bacterial involvement [14,56]. These factors link chronic prostatitis with male infertility via different pathways including changes in the prostate's biochemical environment, the production of ROS by inflammatory pathways, and changes via seminal leukocytosis.

Several investigators have detected the same oxidative stress levels among chronic prostatitis and infertility patients. Potts regarded chronic prostatitis as a major risk factor for fertility as the chronicity and relapses of the syndrome may have toxic effects on the male reproductive system [42]. Increased infiltration of inflammatory cells in CP/CPPS induces peroxidative damage to the sperm plasma membrane [57] and male reproductive organs leading to infertility [52,58,59]. ROS level was also found higher in prostatitis patients accompanied with leucocytospermia or varicocele and tended to be more prone to infertility [45]. An elevated level of TNF-α, macrophages, and IL-1β in CP/CPPS adversely effects the sperm parameters [60]. Interleukin-1 produces due to inflammation or tissue damage [61] causes activation of interleukin 6 and proliferation of first-line defense immune cells, i.e., neutrophils and macrophages that in turn produce reactive oxygen species. ROS cause a potential decrease of spermatozoa polyunsaturated