

# Inflammatory mechanisms and oxidative stress in prostatitis: the possible role of antioxidant therapy

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**Abstract:** This article focuses on the role that oxidative stress plays in chronic prostatitis, not only with respect to the known impact on symptoms and fertility but also especially in relation to possible prostate cancer development. Prostatitis is the most common urologic disease in adult males younger than 50 years and the third most common urologic diagnosis in males older than 50 years. If the germ-causing acute prostatitis is not eliminated, the inflammatory process becomes chronic. Persistent inflammation causes ongoing production of large quantities of pro-inflammatory cytokines and both oxygen and nitrogen reactive species, with consequent activation of transcription factor nuclear factor-kappa B (NF-κB) and genes encoding for further production of pro-inflammatory cytokines, chemotactic factors, and growth factors. Confirming the role of oxidative stress in chronic prostatitis, several studies have demonstrated the presence of oxidative stress markers in the genital secretions of patients suffering from the disease. Antioxidants can therefore play an essential role in the treatment of chronic bacterial and non-bacterial prostatitis; in the case of bacterial inflammation, they can be associated with antibiotic therapy. Moreover, due to their anti-inflammatory properties, antioxidants hinder the progression of inflammation and the possible development of prostate cancer.

**Keywords:** chronic prostatitis, chronic prostatitis treatment, radical oxygen species, nitrosative stress, antioxidant therapy

## Introduction

Prostatitis is the most common urologic disease in adult males younger than 50 years and the third most frequent urologic diagnosis in men older than 50 years.<sup>1</sup> In the literature, prevalence of the disease varies between 1.8% and 8.2%; in the United States, prostatitis contributes to about 8% of urologist visits and 1% of all general practitioner visits.<sup>2,3</sup> It has been estimated that about 50% of men experience symptoms of prostatitis during their lifetime.<sup>4</sup> Patients with a previous diagnosis of prostatitis have a 20%–50% risk of developing recurrence.<sup>5</sup> About 5%–12% of infertile men have a history of genital inflammation, including prostatitis, epididymitis, and orchitis.<sup>6</sup> Although a rarer asymptomatic form is possible, prostatitis symptoms can vary widely and include high fever (only in acute forms or new flares), flu-like symptoms (malaise, arthralgia, and myalgia), dysuria, stinging sensation when urinating, urethral burning (even at rest), strangury, difficulty in voiding, urinary urgency, frequent urination, urethral discharge, pain in one or several areas (urethra, penis, hypogastrium, groin, epididymis and testicle, perineum, anorectal and sacral region, and pelvis), hematospermia, ejaculatory disorders (premature ejaculation, peri- and/or post-orgasmic penile, and/

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or scrotal pain), very often emotional distress and negative impact on quality of life, and more rarely erectile dysfunction. The cause of prostatic infection, in most cases, is bacterial, and the most common germs are Gram-negative bacteria, particularly *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Serratia*, *Pseudomonas*, and *Proteus species*, but Gram-positive bacteria, particularly *Enterococcus*, can also be responsible for prostatic infection. Microorganisms responsible for sexually transmitted diseases can also cause prostatic infection; these include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Trichomonas vaginalis*, and *Gardnerella vaginalis*.<sup>7-9</sup> The risk factors for prostatic infection are intraprostatic ductal reflux, endourethral diagnostic and surgical procedures, urethral catheterization, unprotected anal intercourse, and phimosis.<sup>7</sup>

Prostatitis has been classified into the following categories: type I, acute bacterial prostatitis; type II, chronic bacterial prostatitis; type III, chronic non-bacterial prostatitis, also known as chronic pelvic pain syndrome (CPPS), which may be “inflammatory” (category III A) or “non-inflammatory” (category III B); and type IV, asymptomatic inflammatory prostatitis.<sup>10</sup>

In about 5% of patients with acute bacterial prostatitis, the inflammation can become chronic.<sup>7</sup> Recently, the chemical processes involved in oxidative stress have been shown to play an essential role in the pathophysiology of inflammation.<sup>11</sup> In the literature, several authors have proven the presence of oxidative stress in chronic prostatic inflammation.<sup>12-17</sup> This article focuses on the role that oxidative stress plays in chronic prostatitis, not only with respect to the known impact on symptoms and fertility but also especially in relation to possible prostate cancer development. High concentrations of free radicals are produced in the tissues during chronic prostatitis, leading to marked tissue damage and DNA fragmentation; excessive epithelial proliferation may then occur, with possible development of prostate cancer. Our interest in this topic was reinforced by a number of recent studies which, besides pointing to an increase in risk of developing prostate cancer in men with a history of chronic prostatitis, demonstrated that oxidative stress is associated with the development and progression of prostate cancer.<sup>18-27</sup>

## Oxidative stress and prostatic inflammation

### Oxidative stress

In many of our organism's cellular processes, there is a physiological balance between production and elimination of reactive oxygen species (ROS) (redox homeostasis). This

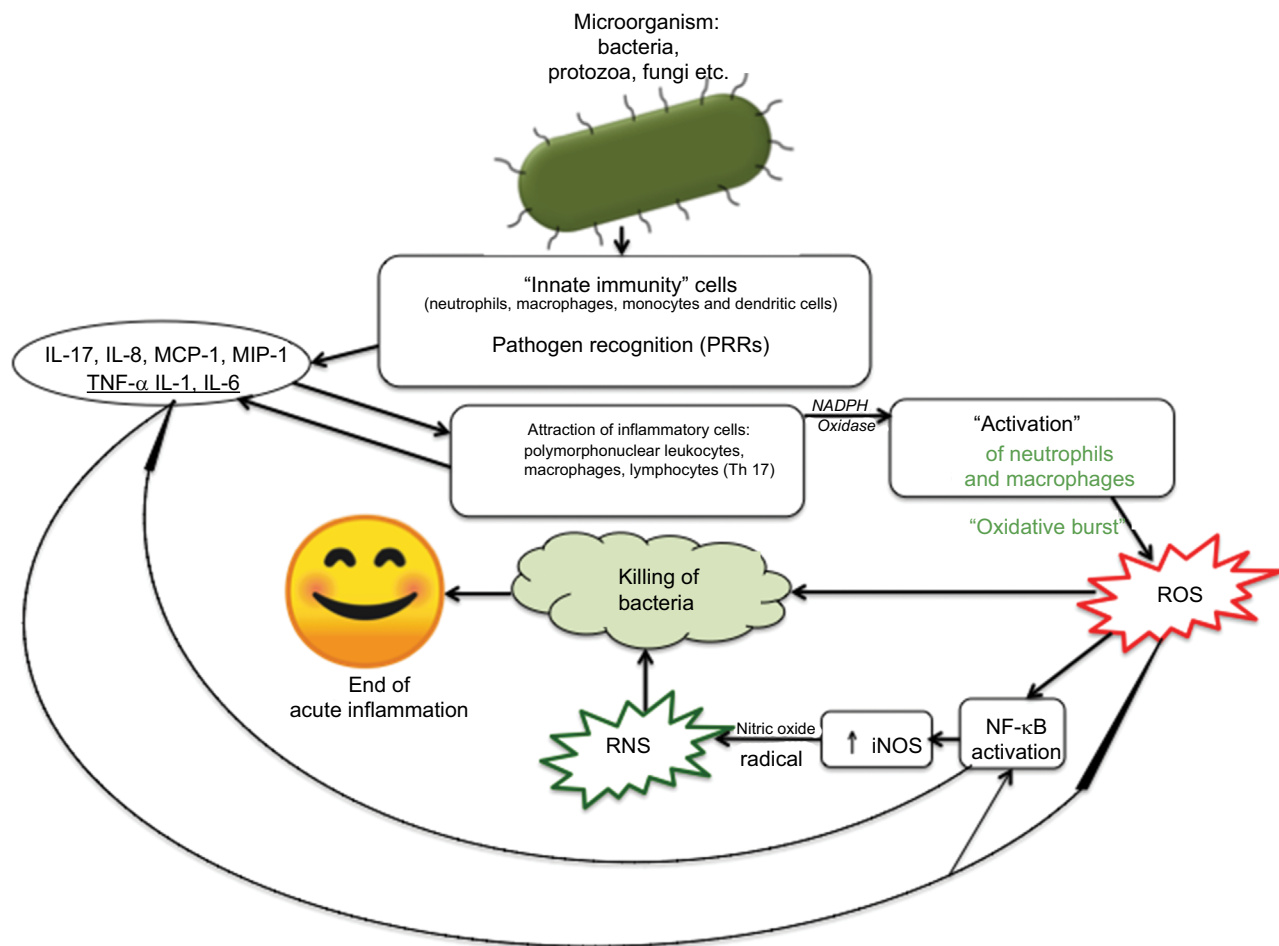
balance is preserved by protective endogenous antioxidant mechanisms. However, redox homeostasis is altered when there is an excessive production of reactive species, leading to the development of a state of oxidative stress.<sup>11</sup> Alteration of redox homeostasis causes a series of chemical reactions that play an essential role in the pathophysiology of inflammation. As a proof of this, several studies have shown that oxidative stress can cause the maintenance and progression of chronic inflammation, contributing to the pathophysiology of many chronic diseases, including chronic prostatitis and prostate cancer.<sup>11-17,21</sup>

Although in moderate concentrations, reactive species ensure that cell processes run normally, in high concentrations, they cause pathological changes in intracellular substances such as proteins, lipids, and DNA.<sup>11</sup> Therefore, certain excessive oxidative stress conditions, for instance, inflammation, including prostatitis, can cause cellular death and damage to the extracellular matrix (ECM) with consequent tissue damage and fibrosis.<sup>28</sup>

### Acute inflammation of prostate

When microbial pathogens (bacteria, viruses, fungi, etc) are detected by pattern recognition receptors (PRRs), the immune system produces an acute inflammatory response (Figure 1) aimed at eradicating the infectious agents.<sup>29,30</sup> This first defense line of the body is known as innate immunity (or non-specific immune system or natural immunity). PRRs are expressed by various innate immunity cells (neutrophils, macrophages, monocytes, and dendritic cells) and are able to recognize pathogen-associated molecular patterns (PAMPs), as well as patterns of the external cell walls of bacteria such as the lipopolysaccharides (LPSs) of Gram-negative bacteria (Figure 1) and the lipoteichoic acids and peptidoglycans of Gram-positive bacteria.<sup>29-31</sup> After the body has recognized the germ and the innate immune system has been activated, an acute inflammatory response begins with the secretion of various cytokines (tumor necrosis factor alpha [TNF- $\alpha$ ] and interleukin [IL]-1) and chemokines (IL-8, monocyte chemoattractant protein-1 [MCP-1], and macrophage inflammatory protein-1-alpha [MIP-1- $\alpha$ ]), which stimulate the recruitment of inflammatory cells at the site of prostatic infection.<sup>32-35</sup>

MIP-1- $\alpha$  is a chemotactic agent for neutrophil granulocytes, monocytes, and macrophages. In particular, MCP-1 acts as a powerful chemotactic agent for circulating monocytes, which turn into macrophages once they have reached the site of inflammation; therefore, MCP-1 regulates the recruitment of monocytes and the formation of macrophage



**Figure 1** Schematic illustration of the fundamentals involved in the mechanisms of acute prostatitis.

**Abbreviations:** IL, interleukin; iNOS, inducible nitric oxide synthase; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; NF-κB, nuclear factor-kappa B; PRR, pattern-recognition receptor; RNS, reactive nitrogen species; ROS, reactive oxygen species; Th, T helper; TNF-α, tumor necrosis factor alpha.

infiltrate. MCP-1 is produced by many types of cells, both by natural gene expression and by growth factors, cytokines, and oxidative stress after induction.

During the inflammatory reaction induced by a bacterial infection, a high concentration of inflammatory cells immediately occurs at the infection site; these cells are mainly neutrocytes (within and around the prostatic acini), followed in time by a stromal infiltration formed by lymphocytes and macrophages; in the following days, the neutrocytes gather mainly in the stroma.<sup>36</sup>

In the pre-antibiotic era, evolution into prostatic abscess with acute prostatitis was very frequent, whereas this event is rarer today (6%) although it can develop in particular situations (urethral or prostatic obstruction, urethral procedures with catheterization, prostate biopsy procedures, presence of prostatic urethral implants, immunosuppressive conditions, diabetes, chronic kidney failure).<sup>37</sup>

After the receptors have recognized bacteria and/or viruses and have been “activated,” the cells of the infiltrate, in particular neutrophils and macrophages, undergo degranulation with the release of lysosomal enzymes, and at the same time, a “respiratory burst” occurs, which results in the rapid release of ROS: superoxide anion radical and hydrogen peroxide.<sup>11</sup> Leukocyte activation takes place due to the presence of the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the neutrophils and macrophages. NADPH oxidase, catalyzing the chemical reaction, causes formation of the superoxide anion ( $O_2^{\bullet-}$ ).

Production of high amounts of superoxide anion by the inflammatory cells leads to subsequent chemical reactions, with the production of further reactive species such as hydrogen peroxide, hydroxyl radical, hypochlorous acid, and singlet oxygen. In this phase, the production of ROS, mainly superoxide anion, hydroxyl radical, and hypochlorous acid,

is aimed at killing the bacteria responsible for the prostatic infection.<sup>11,38–40</sup>

The cells of the inflammatory infiltrate, in turn, produce the release of inflammatory mediators such as pro-inflammatory cytokines: TNF- $\alpha$ , IL-1, and IL-6. As a consequence, high amounts of the following are released: cyclooxygenase-2 (COX-2), transcription factor nuclear factor-kappa B (NF- $\kappa$ B), and inducible nitric oxide synthase (iNOS). The continuous production of iNOS causes high local concentrations of nitric oxide radical (NO $\bullet$ ), which is able to compete with the enzyme superoxide dismutase (SOD) by stealing a superoxide anion from it and causing the formation of peroxynitrite and a series of reactions that lead to the formation of some of its highly reactive and toxic metabolites and aiming to destroy the microorganism; these metabolites, together with the nitric oxide radical, are called reactive nitrogen species (RNS).<sup>11,30,38,41,42</sup>

SOD is a part of the endogenous antioxidant defenses and intervenes as primary cellular defense against the superoxide anion.

Besides neutrocytes and macrophages, lymphocytes are also known to be present among the cells of the inflammatory infiltrate.

Recently, it has been ascertained that some T cells (which are part of the adaptive immune system) also contribute to acute inflammation.<sup>43</sup> Among these T cells, the most important are T helper 17 (Th17) cells, a subgroup of T helper (Th) cells that produce IL-17, which is able to induce the production of chemokines IL-8 and MCP-1, whose function is to recruit other leukocytes to the inflammatory site.<sup>43</sup>

After recognition of the pathogen, due to the release of ROS and RNS and activation of redox-sensitive factor NF- $\kappa$ B by ROS and cytokines IL-1 and TNF- $\alpha$ , a process is triggered that causes transcriptional expression of numerous inflammatory mediators, which coordinate the elimination of pathogens and infected cells.<sup>11,29,38,44</sup>

Furthermore, a downregulation of prostate-specific transcription factor Nkx3-1 occurs during bacterial prostatitis.<sup>36</sup> It has been experimentally proven that the loss of factor Nkx3-1 not only leads to a reduction in the gene expression of several antioxidant enzymes but also leads to an increase in the production of pro-oxidant enzymes.<sup>36</sup> This results in further accumulation of ROS and consequent amplification of the inflammatory process, due to further activation of redox-sensitive transcription factor NF- $\kappa$ B.<sup>11,38</sup>

Among many free radicals produced when prostate inflammation is in progress, it is important to mention isoprostane 8-epi prostaglandin-F2 $\alpha$  (PGF2 $\alpha$ ). The production

of this isoprostane also increases in other conditions associated with oxidative stress (smoking, consumption of alcohol, diabetes, aging, etc.). Isoprostane 8-epi PGF2 $\alpha$  is also used as a urinary marker of oxidative stress in patients with prostatitis.<sup>17</sup> Isoprostane 8-epi PGF2 $\alpha$  can cause potent smooth muscle contraction, having important effects on bladder muscles, significantly affecting the symptoms of prostatitis (urinary urgency, frequent need to urinate, etc).<sup>17,45</sup>

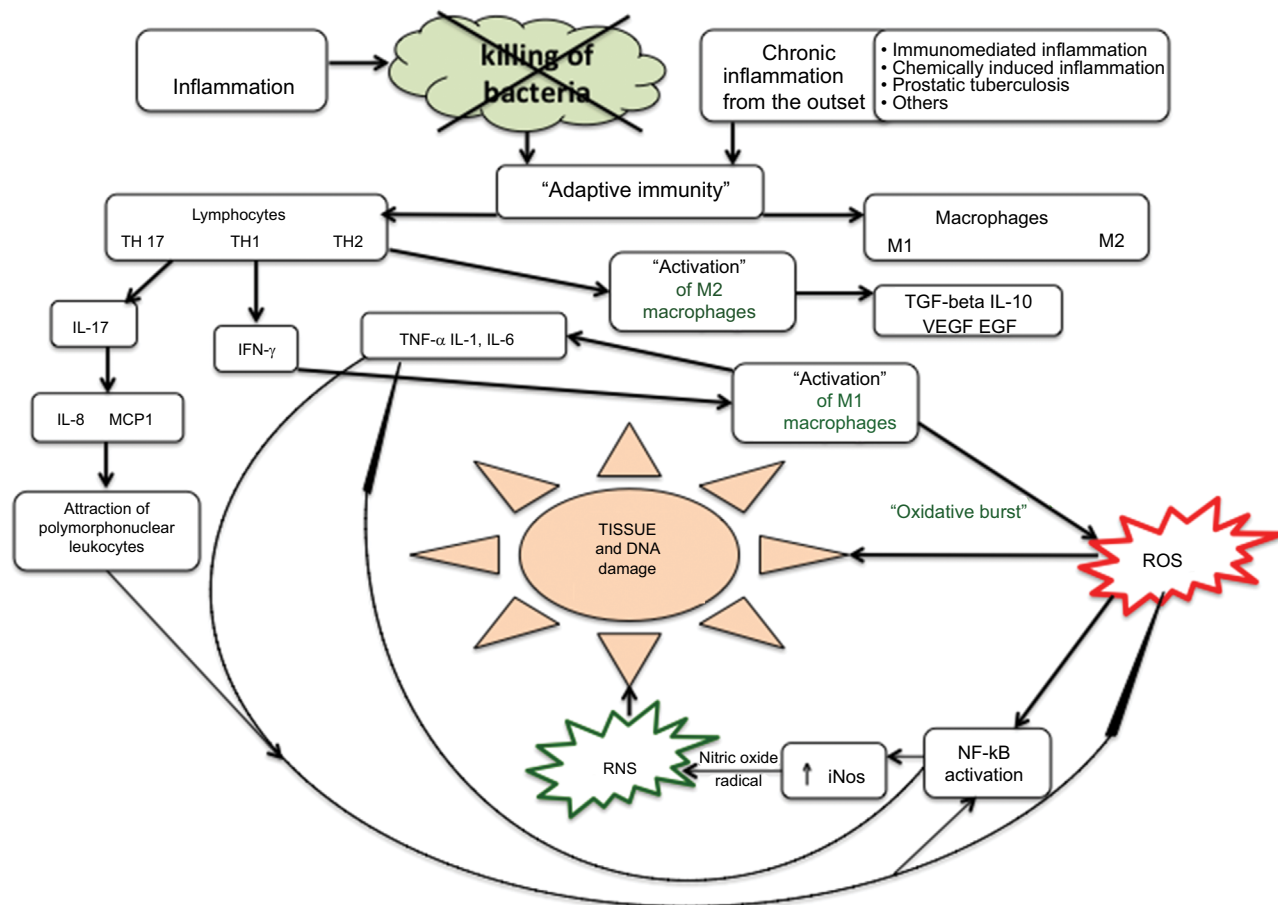
During the acute inflammatory process, inflammatory mediators (cytokines, ILs, chemokines, etc) are produced in waves, until the stimulus persists, and because they have a short half-life, they are degraded shortly after their release. Even neutrophils have a short half-life in tissues and die by apoptosis within a few hours. As the acute inflammation progresses, once the germs are eliminated, resolution of the inflammatory process occurs, due to a series of stop signals (arachidonic acid metabolites, IL-10, inhibition of the production of TNF- $\alpha$ , etc.), which lead to the end of the inflammatory reaction. The acute inflammatory process in acute prostatitis ends with the elimination of the germ.

## Chronic inflammation of prostate

If the germ is not eliminated, the inflammatory process turns chronic (Figure 2).<sup>11,38</sup> Adaptive (specific or acquired) immunity is then triggered, with activation of antigen-specific T and B cells.<sup>38</sup> Since the inflammatory process is not interrupted, the production of cytokines, ROS, and RNS persists, as the regulatory mechanisms that should have blocked the production and release were not activated, due to the persistence of the inflammation-causing agent. Thus, the prostatic inflammation becomes chronic.

More rarely, the inflammatory process can also insidiously present right from the start as a chronic inflammatory response, with no typical manifestation of acute inflammation. For example, this can occur with prostate tuberculosis and prostatic syphilis.

The histopathological profile of chronic prostatitis shows the presence of lymphocyte infiltration, more widely present in the stroma immediately adjacent to the prostatic acini and more scarcely present in the epithelium; macrophages are also present in significant numbers both within the glands and in the intervening stroma.<sup>7,46,47</sup> Macrophages have a dominant role in chronic inflammations as they contribute to the inflammatory reaction by secreting cytokines and growth factors and activating other cells, in particular T cells. During inflammation, macrophages can be activated both through the classic pathway (M1 macrophages) and through the alternative pathway (M2 macrophages). Macrophage activa-



**Figure 2** Schematic illustration of the fundamentals involved in the mechanisms of chronic prostatitis.

**Abbreviations:** EGF, epidermal growth factor; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP, monocyte chemoattractant protein; NF-κB, nuclear factor-kappa B; RNS, reactive nitrogen species; ROS, reactive oxygen species; TGF, transforming growth factor; Th, T helper; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

tion through the classic pathway can be caused by microbial endotoxins and cytokine interferon gamma (IFN-γ) produced by T helper 1 (Th1) cells. Alternative macrophage activation, instead, occurs following the action of cytokines IL-4, IL-5, and IL-13 produced by Th2 cells and other types of cells (mast cells, eosinophils, and T CD8+ cells). Macrophages must be divided into M1 and M2 macrophages; M1 macrophages are actively involved in the inflammatory reaction, whereas M2 macrophages suppress inflammation by producing cytokine IL-10 and contribute to tissue repair and remodeling by releasing transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF). M1 macrophages are inflammatory cells designed to eliminate pathogens and therefore release high amounts of ROS, which are highly cytotoxic; if the production of ROS is excessive and uncontrolled, it can cause

tissue damage. M1 macrophages also secrete TNF-α, IL-1, IL-6, and IL-12.<sup>38</sup> The T cells in the inflammatory infiltrate are both (cytotoxic) CD8+ T cells and CD4+ Th cells (also called CD4+ T cells or Th cells). In particular, CD4+ T cells 1 or simply Th1 cells produce IFN-γ, a cytokine that causes activation of M1 macrophages.

CD4+ T helper 2 (Th2) cells, besides producing cytokines IL-4, IL-5, and IL-13, cause activation of M2 macrophages. Th17 cells, which represent a subgroup of Th cells, produce IL-17, a cytokine that induces production (on the part of macrophages) of IL-8 and MCP-1, which have chemotactic effects on white blood cells.<sup>48,49</sup> In conclusion, there is an important interaction between macrophages and lymphocytes in chronic inflammation, because T cells produce cytokines that recruit macrophages and other cytokines, which activate the macrophages. In turn, the activated macrophages stimu-



late the response of T cells through cytokines such as IL-12 and IL-23.<sup>43</sup> In particular, cytokine IL-12 induces maturation of CD4+ cells toward Th1; IL-12 also stimulates the production of IFN- $\gamma$  by Th17 cells; cytokine IL-23 induces synthesis of pro-inflammatory cytokines (IL-17) by Th17 cells.<sup>43</sup>

Persistence of inflammation, therefore, causes ongoing production of high amounts of pro-inflammatory cytokines and hyperproduction of ROS and RNS, with consequent activation of NF- $\kappa$ B and the expression of genes encoding for fibroblast growth factor (FGF), TGF- $\beta$ , IFN- $\gamma$ , iNOS, and IL-17.<sup>11,15,16,38,47,50–52</sup>

The excessive production of iNOS leads to high local levels of ROS and RNS, which can cause cell and tissue damage, ECM damage, even through the lipidic peroxidation.<sup>11,15,16,28,53</sup>

Cellular death and ECM damage result in the release of several molecules originating from the cells (cytosolic or nuclear proteins, etc) and from ECM degradation. These damage-associated molecular patterns (DAMPs), or “alarmins,” are able to amplify and maintain the inflammatory response, since they are promptly detected by PRRs.<sup>11</sup> The inflammatory cascade is reactivated and boosted by the products of the damage caused by lipid peroxidation, thus favoring further progression of chronic inflammation.

Significant tissue damage is, therefore, a hallmark of chronic inflammation.<sup>15,16</sup> In prostatitis as in other inflammatory diseases, nitric oxide radical effects depend on its concentrations, so when local concentrations of the radical increase significantly, a high oxidation state occurs; in these conditions, the nitric oxide radical interferes with SOD, leading to high local concentrations of peroxynitrite.<sup>38,53</sup> Peroxynitrite is highly toxic and reactive and is capable of causing cell damage (by lipid peroxidation and DNA fragmentation), tissue damage, and depletion of plasma antioxidants. The high concentration of reactive species (ROS and RNS) that occurs during chronic prostatic inflammation is capable of causing direct DNA damage, with consequent sperm DNA fragmentation and its negative effects on fertility.<sup>15,16,54–57</sup> As in other forms of chronic inflammation, an important consequence of these abnormal inflammatory phenomena is the tissue damage due to oxidative stress and excessive induction of tissue repair mechanisms. Inflammation is an immunological response the main purpose of which is to eradicate pathogens and to repair damaged tissues, but if the natural response is not appropriate, excessive tissue repair (fibrosis, etc) and persistent oxidative stress can maintain and amplify the inflammatory response.<sup>11</sup> Thus, the abnormal inflammatory response becomes dysfunctional and capable of causing significant alterations in tissue and

organ functions; this occurs in chronic prostatitis and other more serious conditions, eg, atherosclerosis, chronic heart failure, neurodegenerative diseases, cancer, diabetes.<sup>11,58</sup> As in other chronic inflammatory diseases, tissue damage in chronic prostatitis essentially results in fibrosis and calcifications that cause lower urinary tract symptoms (LUTS), (at times obstructive) dysuria symptoms, and frequently recurring infections.<sup>59–62</sup> Moreover, the presence of bacteria within prostatic calcifications has been reported; therefore, calcifications represent a permanent receptacle for bacteria and cause bacterial persistence.<sup>63</sup>

Furthermore, a greater expression of cytokine TNF- $\alpha$  has been observed in patients with prostatic calcifications.<sup>64</sup> Considering the excessive inflammatory response occurring in chronic prostatitis, a number of authors have postulated that chronic inflammatory disease of the prostate is the result of an excessive adaptive immune response that can cause activation of an autoimmune process (autoimmune prostatitis).<sup>7,65–68</sup>

## Possible causes of the chronicization of prostatitis

Prostatitis may become chronic as a result of the following:

- failed recognition and diagnosis of the first episode of acute bacterial prostatitis, with consequent failure to treat;
- persistence of the germ in the prostate gland for various reasons (eg, presence of intra-prostatic calcifications), including the frequent possibility of antibiotic resistance;<sup>69,70</sup>
- insufficient duration of the antibiotic therapy (targeted treatment for 4–6 weeks is needed);<sup>7,71,72</sup>
- insufficient antibiotic concentration reached in the prostatic tissue;<sup>7,73</sup>
- asymptomatic prostatitis.<sup>7,10</sup>

## Antioxidants already studied and employed in the treatment of chronic prostatitis

Obviously, in the case of bacterial prostatitis, therapy must principally aim at eradication of the germ, with the use of antibiotics that should ideally be able to penetrate into the prostate and reach high tissue concentrations. Considering the long-term duration of antibiotic therapy, it is always advisable to associate prebiotic supplementation to avoid side effects on the resident’s intestinal microbiota. Antibiotic therapy should also be associated with anti-inflammatory and antioxidant substances, so as to limit the tissue damage and consequent symptoms as much as possible.

In the treatment of chronic prostatitis, several natural substances have been used, but scientific evidence and therapeutic rationale exist for only a few of them.

### **Serenoa repens**

*Serenoa repens* (SR), or saw palmetto, is very likely the most commonly used plant in the treatment of both prostatitis and benign prostatic hyperplasia. Despite widespread belief that SR acts through an antiandrogenic effect (inhibition of 5 $\alpha$ -reductase with consequent reduction in the production of dihydrotestosterone [DHT]), various studies in the literature have shown the antioxidant and anti-inflammatory properties of SR.<sup>74</sup>

In a 1997 study, Paubert-Braquet et al<sup>75</sup> proved that SR has anti-inflammatory effects as it is able to inhibit the production of 5-lipoxygenase metabolites and leukotrienes.

Colado-Velázquez et al<sup>76</sup> demonstrated the following effects of SR: antioxidant effect and significant reduction in the gene expression of pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 and growth factors FGFs and VEGFs.

Latil et al<sup>77</sup> proved that SR is able to inhibit gene expression of the pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) and the two chemotactic agents MCP-1 and IFN- $\gamma$ -induced protein 10 (IP-10).

Other studies have found significant positive effects of SR on inflammation biomarkers in biological samples of patients with prostatic inflammation.<sup>78,79</sup>

Furthermore, several in vitro studies have described the antioxidant and anti-inflammatory activity of most of its components.

Currently, available commercial SR extracts contain fatty acids and phytosterols.<sup>80-82</sup>

Capric acid is a saturated fatty acid (SFA), which has antioxidant and anti-inflammatory activities, inhibits the production of iNOS and nitric oxide radical, transcriptional activity of NF- $\kappa$ B, and COX-2 activity, and prevents the gene expression of chemotactic factor MCP-1.<sup>83-85</sup>

Even caprylic acid (SFA) has antioxidant action and also inhibits the production of chemokine IL-8.<sup>85,86</sup>

Lauric acid (SFA) also has antioxidant and anti-inflammatory action and is able to inhibit the COX-2 enzyme.<sup>85</sup>

Myristic acid (SFA) is a powerful scavenger of nitric oxide, superoxide, hydroxyl, and lipid peroxide.<sup>85,87</sup>

Palmitic acid (SFA) is capable of inhibiting the production of pro-inflammatory cytokine TNF- $\alpha$ .<sup>88</sup>

Oleic acid is an unsaturated fatty acid (UFA), and it is an antioxidant as it is able to inhibit the activation of transcription factor NF- $\kappa$ B, expression of the iNOS enzyme, and production of radical NO and ROS.<sup>86</sup> Oleic acid also

has anti-inflammatory action as it reduces the expression of COX-2 and prostaglandins E-2.<sup>89</sup>

Linoleic acid and linolenic acid are UFAs; they have antioxidant and anti-inflammatory activities, since they are able to reduce the gene expression of factor NF- $\kappa$ B and the production of iNOS, ROS, and RNS. In particular, linoleic acid also has anti-COX2 anti-inflammatory activity.<sup>90-92</sup>

Phytosterols campesterol, stigmasterol, and  $\beta$ -sitosterol are all antioxidants; in particular,  $\beta$ -sitosterol increases the activity of antioxidants SOD and glutathione peroxidase.<sup>93,94</sup>

Previous studies have also proven that other antioxidant substances are present in SR, including ferulic acid, vanillic acid, triterpenes, gallic acid, caffeic acid esters, flavonoids isoquercetin, avicularin, astragaloside, rutin, manghaslin, and kaempferol.<sup>82,95</sup>

### **Quercetin**

Quercetin is a flavonoid present in high concentrations in capers, red onion, lovage, and dill. It has been used successfully in the treatment of prostatitis, due to its antioxidant and anti-inflammatory properties; besides being an excellent scavenger of superoxide anion and nitric oxide radical, quercetin inhibits the production of ROS, IL-6, IL-8, TNF- $\alpha$ , and MCP-1 and blocks the activation of factor NF- $\kappa$ B.<sup>96-98</sup>

In a randomized, double-blind, placebo-controlled study, Shoskes et al<sup>99</sup> proved that quercetin (500 mg orally twice daily for 4 weeks) was able to significantly improve clinical symptoms in patients with chronic prostatitis.

### **Carnitine**

Carnitine is a molecule synthesized in the human body mainly in the liver and kidneys, whereas external natural sources are meat, milk, and codfish. Carnitine is a very powerful scavenger of superoxide anion, hydrogen peroxide, and peroxynitrite and also suppresses nitric oxide radical production and iNOS gene expression.<sup>100,101</sup> It also has anti-inflammatory property as it impairs the production of C-reactive protein (CRP), IL-1, IL-6, TNF- $\alpha$ , and TGF- $\beta$ 1.<sup>102,103</sup> Carnitine has been successfully used in the treatment of nonbacterial prostatovesiculopididymitis with leukocytospermia.<sup>104</sup>

### **Bee pollen extract**

Several studies have reported the successful use of pollen extract (PE) in the treatment of prostatitis.<sup>105-107</sup>

PE is a powerful scavenger of hydroxyl radicals, hydrogen peroxide, and superoxide anion.<sup>108,109</sup>

The main constituents of PE are fatty acids, phenols, and flavonoids. In particular, linolenic and linoleic acids are pres-

ent in high amounts, palmitic acid and oleic acid are present in slightly lower quantities; capric acid, eicosenoic acid, and arachidic acid are present in limited quantities; gallic acid and quercetin are also present.<sup>108,109</sup> Its fatty acid, quercetin, and gallic acid content give bee pollen antioxidant and anti-inflammatory properties.<sup>89–92,96–98,110</sup>

### Curcumin

A few positive experiences have been reported in the literature on the therapeutic effects of curcumin in chronic prostatitis.<sup>111,112</sup> Curcumin is a phenolic compound that is the main component of *Curcuma longa*, a plant widely used in the East as a spice, particularly in India as the main ingredient of curry. Curcumin has antioxidant scavenging activity against both ROS (superoxide anion and hydrogen peroxide) and RNS.<sup>113–115</sup> Since curcumin has antioxidant activity against peroxy radicals, it impairs lipid peroxidation and DNA fragmentation.<sup>116</sup>

Curcumin also has anti-inflammatory action, since it suppresses the activation of transcription factor NF- $\kappa$ B and is capable of inhibiting the production of cytokines TNF- $\alpha$ , IL-1, IL-2, IL-8, IL-12, and MCP-1; curcumin, furthermore, causes a downregulation of the enzymatic activity of COX-2, lipoxygenase, and iNOS.<sup>117,118</sup>

Moreover, curcumin has antifibrotic action, inhibiting the action of growth factors TGF- $\beta$ 1 and basic fibroblast growth factor (bFGF).<sup>119–121</sup>

Furthermore, curcumin has been shown to have a chemopreventive effect on the onset of prostate cancer, because it interferes with the proliferation of prostate cancer and the spreading of metastasis through downregulation of androgen receptors (ARs) and epidermal growth factor receptors (EGFRs) and promotion of cell cycle arrest.<sup>122</sup> Due to its properties, curcumin can play a very important role, especially in consideration of newly acquired knowledge indicating that chronic prostatitis favors the development of prostate cancer.<sup>18–25,27</sup>

### Resveratrol

Resveratrol is a natural phenol present in high concentrations in red grapes and grape-derived products (eg, red wine), blueberries, raspberries, apples, peanuts, plums, mulberry, pine trees (*Pinus* spp), legumes (*Cassia* spp, *Pterolobium hexapetalum*), etc. Resveratrol has antioxidant and anti-inflammatory properties; it has also been shown to have antifibrotic activity, since it can hinder the progression of chronic prostatitis by contrasting the effects of TGF- $\beta$  and converting fibroblasts back into myofibroblasts within the prostate.<sup>123</sup> A number of experimental studies have proven

the efficacy of this substance in the treatment of chronic prostatitis.<sup>124–126</sup>

### Monoterpenes

Monoterpenes are natural essential oils from plants that have antioxidant activities. A blend of these substances (Rowatinex® capsules; ROWA WAGNER GmbH & Co. KG, Bergisch Gladbach, Germany) was used to prove their efficacy in the treatment of chronic prostatitis patients.<sup>127</sup> Rowatinex contains the following: alpha-pinene, beta-pinene, camphene, borneol, fenchone, anethole, and cineol. These substances have antioxidant and anti-inflammatory properties; in particular, they are able to inhibit enzymes iNOS and myeloperoxidase (MPO), transcription factor NF- $\kappa$ B, production of 8-isoprostane, enzyme COX-2, and pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , IL-2, and IL-6.<sup>128–133</sup>

The formula containing the monoterpenes (Rowatinex capsules) was studied in a randomized controlled trial, and its therapeutic effects on 25 patients suffering from chronic prostatitis were compared with those obtained in another group of 25 patients who were treated with ibuprofen (a non-steroidal anti-inflammatory drug).<sup>127</sup> Therapeutic efficacy was assessed in the two treatment groups by evaluating the variations in the score of a specific questionnaire (NIH-CPSI) after 6 weeks of treatment. NIH-CPSI is a validated questionnaire that is used to assess the intensity of prostatitis symptoms (pain, urinary symptoms, and quality of life). After treatment, symptom improvement was significantly higher ( $P = 0.04$ ) in the group of patients treated with monoterpenes (Rowatinex) compared with those treated with ibuprofen.<sup>127</sup>

### Epilobium

*Epilobium* is a perennial herbaceous plant that includes various species; the species studied in relation to prostatitis are the following: *Epilobium parviflorum*, *Epilobium angustifolium*, and *Epilobium hirsutum*.

The properties of *Epilobium* are due to its high antioxidant content: myricetin, quercetin, and kaempferol (flavonoids), and oenothein B (a macrocyclic tannin). In particular, the extract of *Epilobium parviflorum* has been shown to have strong antioxidant activity (inhibition of enzyme MPO), anti-inflammatory activity (inhibition of enzymes cyclooxygenase-1 [COX-1] and COX-2), and antibacterial activity.<sup>134–136</sup> Moreover, oenothein B, which is present in *Epilobium* in high concentrations (20%–35%), was shown to powerfully inhibit cellular proliferation.<sup>136–138</sup> In particular, oenothein B hinders the progression of prostate cancer by inducing the production of neutral endopeptidase (NEP), an enzyme



that inactivates the neuropeptides that stimulate neoplastic cellular proliferation.<sup>138,139</sup>

### N-acetylcysteine (NAC)

NAC has also been observed in experimental studies that have proven its antioxidant and anti-inflammatory efficacy in prostatitis.<sup>140</sup> Its mechanism of actions are believed to consist in the inhibition of COX-2 and suppression of transcription factor NF- $\kappa$ B.<sup>140,141</sup>

Furthermore, NAC has been shown to have chemopreventive activity for prostate cancer, because it strongly suppresses the proliferation, migration, invasion, and adhesion of human prostate cancer cells.<sup>142,143</sup>

## Discussion and conclusion

It is evident that oxidative stress plays an important role at various levels in both acute and chronic inflammations. If inflammatory cells were not to release ROS, one of the key elements of the immune response could not take place, ie, neutralization and killing of the bacteria responsible for the infection. In the absence of reactive species (ROS and RNS), activation of factor NF- $\kappa$ B would not take place, along with the consequent production of pro-inflammatory cytokines, growth factors FGF and TGF- $\beta$ , and other inflammatory mediators such as COX-2 and lipoxygenase. Furthermore, by regulating the functions of T cells, ROS play an important role in the modulation of the immune response.<sup>144</sup> Oxidative stress is the most important cause of tissue damage in chronic prostatitis. As chronic prostatitis progresses, fibrotic and calcified areas are inevitably formed, which cause dysuria and reinfections.<sup>60–62</sup>

Confirming the role played by oxidative stress in chronic prostatic inflammation, several studies have proven the presence of oxidative stress markers in genital secretions or urine of patients suffering from the disease.<sup>12–14,17</sup> In conclusion, antioxidants can play an essential role in the treatment of chronic prostatitis. To date, a very few studies have analyzed the therapeutic effect of antioxidants in chronic prostatitis patients, although numerous studies have demonstrated the properties of the various antioxidants and pointed out their potential efficacy.<sup>79,99,104–107,111,112,127</sup>

Further randomized controlled studies on this topic are therefore needed, especially considering the enormous growth in interest in chronic prostatitis over the past few years, since excessive oxidative stress can favor the progression of inflammation and the development of prostate cancer.

## Disclosure

The author reports no conflicts of interest in this work.

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