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LITERATURE REVIEW

Oxidative stress-related pathophysiology in chronic rhinosinusitis with nasal polyps: research challenges

Ala Istratenco[1,2]

[1]Department of Otorhinolaryngology, "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

[2]Department of Laboratory Medicine, "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

ABSTRACT

Chronic rhinosinusitis with nasal polyps (CRSwNP) is considered a multifactorial pathology with negative impact on the quality of life and considerable socio-economic effects. The pathogenesis of CRSwNP has not yet been fully elucidated despite remarkable studies in this field. This limits the pathogenic treatment and, therefore, the pathological process is expressed by a greater tendency of recurrence. Patients with recurrent CRSwNP remain in a severe state and therapeutically uncontrolled. In recent studies, the involvement of oxidative stress (OS) in the pathogenesis of CRSwNP has been more frequently mentioned. CRSwNP is considered a response of the sinonasal tissue on the inflammatory state, associated with OS and production of reactive oxygen species, causing injury to sinonasal tissues. It was demonstrated that the amount of ROS in the nasal polyp tissue corresponds to the severity of CRSwNP.

A literature review on the role of OS in the pathogenesis of CRSwNP was undertaken. The relevant information was identified using a search of electronic databases. Keywords used to highlight relevant papers were a combination of *"chronic rhinosinusitis with nasal polyps"* and *"oxidative stress"*.

This review demonstrates that there is a strong relationship between OS and CRSwNP pathogenesis. It is hypothesized that antioxidants may have a preventive role in CRSwNP. Nevertheless, additional research is required to further evaluate the effectiveness of antioxidant therapy.

KEYWORDS: chronic rhinosinusitis with nasal polyps, oxidative stress, reactive oxygen species, free radical, oxidants, antioxidants.

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) or otherwise called nasal polyposis (NP) is a major health problem, frequently encountered in otorhinolaryngological practice. CRSwNP is a chronic inflammatory condition of the upper airway characterized by formation of nasal polyps, benign formations, often manifested by a high tendency of recurrent growth after surgery[1,2]. CRSwNP has a significant negative impact on the quality of life[3], resulting in enormous socio-economic effects. CRSwNP affects patients' quality of life more than other chronic pathologies, such as congestive heart failure, coronary artery disease, obstructive chronic bronchopneumopathy[4,5]. Patients with CRSwNP exhibit varying sleep disturbances in a high proportion (60-75%), which can lead to a considerable decline in quality of life, being responsible for the impairment of cognitive function and depression[6]. In the spectrum of otorhinolaryngological disorders, the prevalence of recurrent CRSwNP is near 20-40%. Approximately 20% of patients are facing an uncontrolled pathology despite adequate medical treatment and modern sinus surgery[7].

The causes that determine the persistence of chronic inflammation in the sinonasal mucosa with nasal polyp formation have not been fully elucidated despite the numerous researches in this field[1,2,8-12]. The existing modern treatment of CRSwNP remains unsatisfactory, the pathological process being expressed by a high recurrence rate. There is various evidence regarding the

Corresponding author: Ala Istratenco
Address: 165 Stefan cel Mare si Sfant Bd., MD-2004, Chisinau, Republic of Moldova
e-mail: alla.istratenco@gmail.com
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prevalence of the recurrent CRSwNP, varying from 15-25%[13] to 40-50%[14]. A large, multi-center, prospective cohort study demonstrated nasal polyp recurrence in 40% of patients despite endoscopic sinus surgery plus continued medical therapy, while other cohort studies reported 50–60% recurrence rate of NP[14].

CRSwNP has a multifactorial etiology, inflammation playing one of the most important roles[8-10,15-19]. The involvement of oxidative stress (OS) in the pathogenesis of CRSwNP is being mentioned more frequently in recent studies[9,10,15-21]. Oxidative stress is a term used to describe the diseases caused by reactive oxygen species (ROS), which have a destructive and pathogenic character. The tissues of otorhinolaryngological organs, including sinonasal mucosa, are inevitably subjected to OS exposure, causing local injuries.

A challenging area in the field of CRSwNP is represented by the treatment. CRSwNP should primarily be approached as a pathology with the possibility of medical therapy. Surgical treatment, that ameliorates the condition and facilitates nasal medication, is indicated in patients in whom medical management fails or who have complications. The only method of medical therapy with demonstrated efficacy is represented by glucocorticosteroids (GCS)[22], although it induces a series of side effects and does not always prevent the recurrence. Patients with recurrent CRSwNP have a limited response to the existing treatment; therefore, they remain in a severe state and therapeutically uncontrolled, being subjected to multiple surgeries, that furthermore decline their quality of life. The presence of NP and comorbidities, such as asthma, aspirin-exacerbated respiratory pathology, are frequently associated with the "difficulty to treat"[23]. The understanding of the pathogenic mechanisms of CRSwNP can help in finding alternative treatment methods. Presumably these findings may contribute to the evaluation of the perspective related to using antioxidant therapy for patients with CRSwNP refractory to existing treatment, for patients with recurrent CRSwNP and associated with comorbidities.

Far from being exhaustive, this paper aims to review the most important data, summarizing the role of OS in the pathogenesis of CRSwNP through the new research in order to nuance pathogenic therapy.

The literature review was undertaken using a search of MEDLINE electronic databases. Relevant articles that highlight the problem of OS in association with CRSwNP were selected, using the combination of keywords such as "*chronic rhinosinusitis with nasal polyps*" and "*oxidative stress*".

CRSwNP: A MULTIFACTORIAL PATHOLOGY

CRSwNP is considered the most severe manifestation of rhinosinusitis, representing a final chronic inflammation stage of the nasal cavity, which is clinically manifested by nasal obstruction, anterior/posterior rhinorrhea, hyposmia/anosmia, headache, recurrent respiratory infections, sleep disturbances[1,2,8,9,17].

The causes that determine the persistence of chronic inflammation with irreversible histological changes, manifested by the formation of nasal polyps, have not yet been fully established[1,2,8-12]. There are theories that consider nasal polyps as a consequence of conditions that cause chronic sinonasal inflammation, characterized by stromal edema and the presence of various cellular infiltrates. There is a considerable amount of literature on the role of several factors involved in the pathogenesis of CRSwNP. Among them, there are: the impact of allergy, mucosal allergy, eosinophilic mediators, Bernouilli phenomenon, nitric oxide, infection, fungal infection, genetic predisposition, aspirin intolerance/sensitivity, vasomotor imbalance, epithelial rupture, superantigens, genetic polymorphism of inflammatory genes, environmental factors[1,2,12,21,24-27]. Numerous cytokines, chemokines, adhesion cells and receptors with various target activities favour the inflammatory response in the nasal polyps[15,24].

In recent years, there has been a great deal of attention toward the field of the implication of OS in the pathogenesis of CRSwNP. It is ironic that oxygen, an element indispensable for life, under certain situations, has deleterious effects on the human body. OS and oxidants are involved in the pathogenesis of over one hundred diseases of the human species by aggression on all types of biomolecules, causing various pathological conditions such as inflammation, tumors, atherosclerosis, degenerative pathologies[12].

OXIDATIVE STRESS: SOURCES OF PROVENANCE AND INJURY MECHANISMS

Oxidative stress (OS) is the term used to describe the conditions produced by reactive oxygen species (ROS) that are highly reactive molecules, produced by the human body, having harmful and pathogenic effects. Human body, at the same time, is equipped with antioxidant systems, which eliminate the harmful effects of ROS, preventing or reducing the damage caused by oxidation. In essence, in OS there is a disturbance of oxidants/antioxidants balance in favour of oxidants. The imbalance between oxidants and antioxidants leads to cell injury, cell death, underlying tissue damage and chronic inflammation development[12]. OS and ROS are inherent in human metabolism. ROS are essential in the maintenance of normal cellular function. At low concentrations they can act as cellular and intracellular signalling molecules that facilitate normal biological processes. The excess of ROS due to the acceleration in their production or a

deficiency in the antioxidant defence system attacks important macromolecules, leading to cell damage and homeostatic disruption. Targets of ROS include all kinds of molecules in the body: carbohydrates, lipids, nucleic acids and proteins[12,28-30].

Oxidants and sources of their provenance in the human body

From a chemical point of view, oxidants or ROS are compounds derived from molecular oxygen and have a tendency either to donate an electron to or accept an electron from other molecules. Therefore, they can behave as oxidants or reductants and be capable of initiating aggressive oxidative reactions on the cell membrane or intracellularly if they cannot be counteracted by antioxidants[12,29,30]. There are two types of ROS: *free radicals* (superoxide, hydroxyl, peroxyl, alkoxyl, hydroxyperoxyl) and *non-radicals* (hydrogen peroxide, hypochlorous acid, ozone, singlet oxygen, peroxynitrite). Free radicals (FR) are highly reactive species with one or more unpaired electrons in their outer electron shell. Non-radicals are created when 2 free radicals share their unpaired electrons. 3 major ROS have physiological significance: superoxide anion radical, hydroxyl radical and hydrogen peroxide[12,29,20].

The major sources of provenance of ROS in the human body can be conventionally divided into *endogenous* and *exogenous* sources. ROS are generated in the human body by various endogenous systems in normal essential metabolic processes, by exposure to different physiochemical conditions and pathological states. FR are derived from the enzyme activity of the mitochondria, xanthine oxidase, peroxisomes, inflammation, phagocytosis, arachidonate pathways, ischemia/reperfusion injury[30]. FR can be formed as a result of reperfusion after ischemia and cellular necrosis, associated with the release of purines, which are responsible for producing two superoxide radicals. Furthermore, FR can occur in association with tissue haemorrhage, which is responsible for the generation of free hydroxyl radicals from hydrogen peroxide. FR can be derived from the metabolism of purines (from the DNA of damaged cells), catecholamines, prostaglandins and uric acid biosynthesis[12]. ROS can be generated from exogenous sources, penetrating the human body from the external environment following the exposure to ionizing radiation, ozone, hyperoxia, cigarette smoking, heavy metal ions, harmful air pollutants, industrial chemicals, certain drugs, pesticides, foods, etc.[12,29,30]. If the impact of exogenous FR on the human body can be limited by endeavour, this is not possible with endogenous FR.

ROS manifest not only a negative impact on cells function, but also a positive one, being expressed by their intervention in antibacterial immunity (by destruction of phagocytic organisms), by active participation in the biological signalling processes, by stimulation of stress-inducible genes that participate in cellular repair (in cases of adequate growth)[12].

Antioxidant defence systems and sources of their provenance in the human body

The human body is equipped with integrated antioxidant defence systems that protect against ROS and their unfavourable effects. Antioxidants (AO) are substances that, at relatively small concentrations, are effective in blocking harmful effect of ROS. AO can be produced by the human body; they can be absorbed from dietary intake or direct consumption of drugs with antioxidant effect. Therefore, AO can be divided into several groups, this depending on their cellular localization, chemical nature and sources of provenance. Hence, there are intracellular AO (reduced glutathione, thioredoxin reductase), extracellular AO (uric acid, albumin, bilirubin, vitamin C, β-carotene, vitamin E, folic acid), enzymatic AO (superoxide-dismutase, glutathione peroxidase, glutathione reductase, catalase), inorganic AO (selenium, zinc, magnesium) and drugs with antioxidant effect (local anaesthetics, calcium channel blockers)[12].

An excessive production of ROS and/or a deficiency in the antioxidant defence system conduct to an imbalance, which induces injuries to biomolecules, triggering a number of diseases. The tissues of the human body, including ENT organs, are inevitably exposed to OS, causing local injuries. According to the literature, many otorhinolaryngological nosological entities are associated with OS: rhinitis, allergic rhinitis, CRS, CRSwNP, otitis media (with effusion and chronic), cholesteatoma, tympanosclerosis, Meniere's disease, neurosensory deafness, tonsillitis, laryngeal pathologies, tumors[12,31].

INVOLVEMENT OF OXIDATIVE STRESS IN THE PATHOGENESIS OF CRSwNP

CRSwNP is a multifactorial disease, inflammation playing an important role. Depending on the duration and the activity of the inflammatory process, oxidative reactions initiated by ROS emerge from a physiological adaptation mechanism to a pathological one, forming an important pathogenic link. Many studies have been reported that histological changes in CRSwNP are correlated with the infiltration of inflammatory cells. As a result of the inflammation, activated neutrophils migrate to the inflammatory site where they exert bactericidal function by producing ROS that, at the same time, trigger a set of cellular and intracellular disturbances at the sinonasal mucosa level.

The examination of bacterial biofilms' prevalence in different areas of the sinonasal mucosa in patients with chronic rhinosinusitis (CRS) has related that it prevails more in patients with CRSwNP compared to patients

with chronic rhinosinusitis without polyps (CRSsNP), being more distributed in the area of the ethmoid bulla and the uncinate process compared to the middle turbinate[32]. This supports the involvement of bacterial biofilm in the pathogenesis of CRSwNP[32]. Thus, in the nasal and paranasal tissues, the most common sources of FR are neutrophils, which release ROS as a part of the innate inflammatory response. ROS are capable of destroying bacteria and fungi. ROS formation is favoured by proinflammatory cytokines, like Interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α).

NP is considered a tissue response to the inflammatory condition associated with OS and an increase in the inflammatory cells amount, especially the eosinophils. The major basic protein (MBP), a proinflammatory mediator released by eosinophils, is able to increase the influx of Na^+ into the apical epithelium of the nasal polyps, resulting in the development of edema – the major histopathological characterization of nasal polyps[25].

Nasal epithelium plays a crucial role in NP formation. A pathogenic mechanism of CRSwNP, described by Norlander et al., assumes that a defect of the nasal epithelium or a deep mucosa trauma induced by any microorganism can be essential in NP formation[16,33]. Wladislavosky-Waserman et al. have reported about the involvement of epithelial damage in NP[16,34]. Dagli et al. have described that NP tissue damage is caused by FR, claiming that ROS lead to mucosal edema in early stages and epithelial damage in advanced stages. Edema of the nasal mucosa occurs as a result of affecting the transport of ions through the nasal epithelium as a consequence of transport pump dysfunction. Oxidants affect the cell membrane of the ion pump, favouring the increase in intracellular Na^+, movement of Ca^{2+} into the cell and the decrease in intracellular K^+ [16].

Myofibroblasts from the sinonasal tissue are involved in nasal polyps' formation by inducing extracellular matrix accumulation. ROS are released during differentiation of fibroblasts to myofibroblasts. Stimulation with transforming growth factor β1 (TGF-β1) increases the production of ROS by nasal fibroblasts. The differentiation of myofibroblasts and the production of collagen in nasal polyps can be prevented by inhibiting ROS by some antioxidant medication, such as diphenyliodonium, N-acetylcysteine and ebselen[12].

A study was performed based on the hypothesis that FR of oxygen plays an important role in the pathogenesis of CRSwNP. The main aim of the study was to identify the genetic polymorphisms of the antioxidant enzymes, such as superoxide dismutase (SOD2), catalase (CAT), inducible nitric oxide synthase (iNOS), in patients with eosinophilic and non-eosinophilic CRSwNP and their effect on CRSwNP pathogenesis. As a result of the study, significant differences between eosinophilic CRSwNP and control groups were obtained for polymorphism in the gene segments encoding iNOS enzymes (the GG genotype distribution for the (-277) A/G polymorphism in iNOS gene) and CAT enzymes (the TT genotype distribution for A/T polymorphism in CAT gene at position -21). Therefore, FR increased level may occur due to genetic polymorphism of the enzymes in the antioxidant system and might contribute to the pathophysiology of NP[26].

Nitric oxide radical (NO), a highly reactive and diffusible FR, is implicated in the regulation of various physiological and pathological events. NO has an important role in the pathogenesis of CRSwNP. The sinonasal epithelial cells appear to be the primary source of NO in the respiratory system. NO has multiple effects on tissues. At sinonasal level, NO plays a dual role – it increases ciliary beat frequency through intracellular signalling pathways and diffuses into the mucus, where it fights against bacteria and viruses as part of the innate immune response[12,35,36]. In addition to the physiological effect, NO is an important cofactor regarding the migration and proliferation of keratocytes, angiogenesis and collagen deposition. NO is involved in recruitment of inflammatory cells, inhibiting apoptosis of eosinophils, disturbance of the cytoarchitecture leading to modifications of the extracellular matrix, and extravascular leakage with consequent edema[12,36]. It has been previously demonstrated that upper respiratory epithelial cells receptors detect some quorum-sensing molecules, secreted by Gram-negative bacteria, which subsequently trigger the production of NO with a bactericidal effect. According to several research data, quorum-sensing molecules secreted by Staphylococcus aureus (Gram-positive bacteria) and by Staphylococcus epidermidis (Gram-positive, coagulase-negative bacteria) trigger a naturally NO-mediated innate response in sinonasal epithelial cells, expressed by secretion of NO. Patients' reaction to NO secretion as a response to pathogen molecules secreted by bacteria is heterogeneous. This may contribute to a complex interplay between genes and environment, predisposing some CRS patients to Gram-positive infections. Genetic differences in NO production triggered by bacteria may play a role in the pathogenesis of CRS[35,37].

Nasal epithelium is the first respiratory epithelial surface exposed to environmental pollution. Epidemiologically, there is an association between air pollution and the increased prevalence of chronic sinonasal pathology. A component of the innate defence of the sinonasal mucosa against inhaled pathogens includes the continuous release of low levels of hydrogen peroxide (H_2O_2) into the nasal secretions. For a better understanding of the effects of pollutants on the nasal mucosa, the release of H_2O_2 and the level of Interleukin-8 (IL-8) were studied after exposure of the sinonasal mucosa to pollutant substances (particulate matter). As a result of the study, an increased amount of H_2O_2 se-

creted by epithelial cells was obtained, thus demonstrating the contribution of pollutants to the installation of the OS, as part of a normal defence mechanism against pollutants. However, prolonged exposure to pollutants results in increased levels of H_2O_2, IL-8 and mucin production. Therefore, the effort to reduce air pollutants (particulate matter) may lead to the decrease in H_2O_2, proinflammatory cytokine IL-8 and the production of mucin, preventing the installation of the OS in the sinonasal epithelium[38].

Hypochlorous acid (HOCl), a non-radical derived from oxygen, is formed as a result of the action of myeloperoxidase in the sinonasal tissues. HOCl has the ability to damage the underlying tissues. However, in low concentrations, HOCl has been demonstrated to express both antibacterial and antiviral activity (against the influenza virus, rhinovirus) as part of a normal defence mechanism[12].

Ozone, a non-radical derived from oxygen, directly increases the level of FR and DNA synthesis. Ozone exposure affects mucociliary transport of the sinonasal epithelium, increases cell permeability and facilitates the migration of inflammatory cells with proliferative and secretory responses. Cytokines released by effector cells of innate immunity due to exposure to ozone as well as cyclooxygenase and lipoxygenase activity facilitate the elevation of FR, diminishing the mucociliary clearance and contribute to the pathophysiology of CRS[12].

MEDICAL TREATMENT OF CRSwNP AND ITS IMPACT ON OXIDATIVE STRESS

Currently, there is a wide variety of medical treatments of CRSwNP. Recent research opts for the use of anti-IL-5, anti-IgE, anti-IL-4 antibodies, calcium channel blockers, assuming promising results. However, further studies are needed to implement the immunomodulatory therapy[39]. The only method of medical treatment with demonstrated efficacy is represented by GCS, which continue to be the cornerstone of medical therapy of the CRSwNP. Nevertheless, GCS, especially those that are systemically administered, might induce side effects and do not always prevent the recurrence.

According to a survey on CRS, performed by Passali et al., CRSwNP is encountered in 20-40 % of all patients with CRS. The medical treatment options for CRSwNP were found to be nasal GCS (90%), systemic GCS (50%), nasal washes (46%) and systemic antibiotic therapy (34%)[40]. The topical (intranasal) GCS are widely used in the treatment of CRSwNP, considering that inflammation is the major component, despite little information regarding the quality of life after GCS use (very low-quality evidence), improvement in all symptoms of CRSwNP (low-quality evidence). There seems to be a moderate-sized benefit for nasal blockage and a small benefit for rhinorrhea (moderate-quality evidence), whereas the risk of epistaxis is increased (high-quality evidence)[41].

GCS can regulate the expression of GRX-1 (glutaredoxin, glutathione-dependent oxidoreductase). The expression of GRX-1 represents the primary line of defence against OS from chronic sinonasal inflammation. GRX-1 expression from the mucosa of patients with CRSwNP is significantly higher than in the normal nasal mucosa. IL-1β increases the production of intracellular ROS. This increase can be inhibited by N-acetylcysteine. GCS can regulate the expression of GRX-1 and, respectively, IL-1β-induced ROS formation[12].

Antibiotics are widely and heavily used in the treatment of CRS. Antibiotics with a bactericidal effect favour ROS formation and support inflammation in sinonasal human cells. Kohanski et al. performed an experimental study, which investigated the influence of bactericidal antibiotics (amoxicillin and levofloxacin) and of bacteriostatic antibiotic (clarithromycin) on the sinonasal epithelial cells collected during endoscopic surgery. As a result, it has been established that bactericidal antibiotics significantly increase the level of ROS with an associated increase in antioxidant gene expression as well as the expression and production of proinflammatory cytokine TNF-α and IL-1β. Therefore, this may suggest that prolonged or inappropriate use of bactericidal antibiotics in the treatment of rhinosinusitis may result in OS injury to the sinonasal epithelial cells as a result of ROS action[42].

Hypochlorous acid (HOCl), even if it can harm sinonasal tissues, exhibits both antibacterial and antiviral activity (anti-rhinovirus and anti-influenza virus activity)[12,43]. The treatment with HOCl can significantly inhibit the secretion of interleukins IL-6 and IL-8, the synthesis of which is induced by a human rhinovirus, thus reducing the titer of the virus in sinonasal tissues[12]. The irrigation of the sinonasal mucosa of patients with CRSwNP refractory to medical treatment for 8 weeks with low concentrations of HOCl has demonstrated an improvement in the symptomatology of CRS by decreasing in SNOT-20 score (20-Item Sino-Nasal Outcome Test), Rhinosinusitis Disability Index (RSDI) and bacterial growth rate. Therefore, a low dose of HOCl can be used in patients with CRS refractory to traditional medical therapy as an adjuvant treatment[43].

RELATIONSHIP BETWEEN OXIDATIVE STRESS AND CRSwNP

Inflammatory conditions established in the nose and paranasal sinuses are perfectly suitable with the formation of NP. The investigations of OS parameters in NP have revealed that there is a strong relationship be-

tween OS and CRSwNP pathogenesis. The amount of FR in polyp tissue corresponds to the severity of the pathology[9,11,12]. In the nasal polyp tissue, the level of oxidants is increased, while the level of antioxidants is decreased. Malondialdehyde (MDA) is a major end product of lipid peroxidation that can be used as an indicator of FR levels. High levels of MDA in nasal polyps reflect the involvement of OS and signal injury by FR[9,12,16,20]. The levels of Advanced Oxidation Protein Products (AOPP) can be used as markers of OS in the etiology of CRSwNP. The results of one research report that patients with NP have significantly higher AOPP values than patients without NP[12,44].

In normal state, ROS are controlled by the antioxidant system, including superoxide dismutase (SOD), catalase (CAT), xanthine oxidase (XO), glutathione peroxidase (GPx) and glutathione (GSH). In NP, a decrease in GPx activity is noted, while the activity of CAT and XO is increased[9,12,15,20]. SOD and NO play important roles in OS. The values of SOD and NO are significantly lower in CRSwNP patients compared to the control group[8]. The severity of OS in NP is expressed in Total Antioxidant Status and NO that are significantly correlated with the severity of nasal obstruction and congestion[11,12]. Colantonio et al. found that NO level was correlated directly with the extent of polyposis and that successful treatment, with reduction in polyp volume, was associated with a rise in NO level[12,15]. Pasto et al. evaluated the relationship between NO concentration and the production of superoxide in NP, finding an important contribution of the phagocytic-derived superoxide to the reduction of sinus NO concentration[15].

CONCLUSIONS

CRSwNP is a multifactorial pathology with not fully elucidated pathogenesis despite remarkable studies in this field. Therefore, it remains a difficult-to-treat entity with unsatisfactory outcomes of current management options and consequently a research challenge for the otorhinolaryngologists to enhance knowledge in this domain. The findings of recent studies have demonstrated that OS is increased in patients with NP, suggesting that it is one of the involved factors in the pathogenesis of CRSwNP. Based on the studied articles, there is strong evidence related to OS in the pathogenesis of CRSwNP. There are abnormalities in lipid peroxidation, protein oxidation as well as in the antioxidant defence mechanism in patients with NP. The amount of FR in the nasal polyp tissue corresponds to the severity of the pathology. The level of oxidants in nasal polyp tissues is increased, whereas the level of antioxidants is decreased.

The inflammation, a common feature of chronic sinonasal diseases, can be caused by ROS. The inflammation, markers of inflammation and conventionally nasal polyp formation can be prevented by blocking ROS, eliminating them, or by promoting their decomposition. It is hypothesized that antioxidants may have a preventive role in CRSwNP. Therefore, ROS formation in sinonasal tissues derived under the influence of genetic polymorphism of enzymes in the antioxidant system, under the action of sinonasal bacterial biofilm or the bactericidal effect of antibiotics, under the environmental pollution can be prevented or can be reduced by using the antioxidant medication (diphenyliodonium, N-acetylcysteine, ebselen) as well as the GCS (GCS regulates the expression of GRX-1 and respectively IL-1β-induced ROS formation).

Nevertheless, additional research is required to further evaluate the effectiveness of antioxidant therapy. The investigation of OS-related pathophysiology of CRSwNP will suggest novel insights for clinical application and therapeutic target. The current studies definitely provide significant information to further expand the research in this domain.

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REFERENCES

1. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl [Internet]. 2012;23:3 p preceding table of contents, 1-298. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22764607.
2. Newton JR, Ah-See KW. A review of nasal polyposis. Ther Clin Risk Manag. 2008;4(2):507–12.
3. Bengtsson C, Lindberg E, Jonsson L, Holmstrom M, Sundbom F, Hedner J, et al. Chronic rhinosinusitis impairs sleep quality: results of the GA2LEN study. Sleep. 2017;40(1). DOI: 10.1093/sleep/zsw021.
4. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngol Head Neck Surg. 2015;152(2 Suppl):S1–39. DOI: 10.1177/0194599815572097.
5. Bhattacharyya N, Orlandi RR, Grebner J, Martinson M. Cost burden of chronic rhinosinusitis: a claims-based study. Otolaryngol Head Neck Surg. 2011;144(3):440–5. DOI: 10.1177/0194599810391852. Epub 2011 Feb 3.
6. Mahdavinia M, Schleimer RP, Keshavarzian A. Sleep disruption in chronic rhinosinusitis. Expert Rev Anti Infect Ther. 2017;15(5):457-65. DOI: 10.1080/14787210.1294063. Epub 2017 Feb 17.
7. Wagenmann M, Scheckenbach K, Chaker AM. Endotypes in chronic rhinosinusitis: biomarkers based on a mechanistic insight for targeted treatment? ORL J Otorhinolaryngol Relat Spec. 2017;79(1–2):78–84. DOI: 10.1159/000455721. Epub 2017 Feb 24.
8. Cekin E, Ipcioglu OM, Erkul BE, Kapucu B, Ozcan O, Cincik H, et al. The association of oxidative stress and nasal polyposis. J Int Med Res. 2009;37(2):325–30.
9. Cheng YK, Tsai MH, Lin CD, Hwang GY, Hang LW, Tseng GC, et al. Oxidative

stress in nonallergic nasal polyps associated with bronchial hyperresponsiveness. Allergy. 2006;61(11):1290–8.
10. Bozkus F, San I, Ulas T, Iynen I, Yesilova Y, Guler Y, et al. Evaluation of total oxidative stress parameters in patients with nasal polyps. Acta Otorhinolaryngol Ital. 2013;33(4):248–53.
11. Topal O, Kulaksizoglu S, Erbek SS. Oxidative stress and nasal polyposis: does it affect the severity of the disease? Am J Rhinol Allergy. 2014;28(1):e1-4. DOI: 10.2500/ajra.2014.28.3963.
12. Holecek V, Rokyta R, Slipka J. Free radicals in nasal and paranasal diseases. In: Miller J, Le Prell CG, Rybak L, editors. Free radicals in ENT pathology. Humana Press; 2015, p.479–92.
13. Esmatinia F, Bakhshaei M. Recurrent sinonasal polyposis after the endoscopic sinus surgery. Rev Clin Med. 2014;1(2):86-92. DOI: 10.17463/RCM.2014.02.010.
14. Burgess A, Shah K, Hough O, Hynynen K. Focused ultrasound-mediated drug delivery through the blood-brain barrier. Expert Rev Neurother. 2015;15(5):477–91. DOI: 10.1586/14737175.2015.1028369.
15. Cheng YK, Hwang GY, Lin CD, Tsai MH, Tsai SW, Chang WC. Altered expression profile of superoxide dismutase isoforms in nasal polyps from nonallergic patients. Laryngoscope. 2006;116(3):417–22.
16. Dagli M, Eryilmaz A, Besler T, Akmansu H, Acar A, Korkmaz H. Role of free radicals and antioxidants in nasal polyps. Laryngoscope. 2004;114(7):1200–3.
17. Sagit M, Erdamar H, Saka C, Yalcin S, Akin I. Effect of antioxidants on the clinical outcome of patients with nasal polyposis. J Laryngol Otol. 2011;125(08):811–5. DOI: 10.1017/S0022215111001149. Epub 2011 Jun 14.
18. Bozkus F, Ulas T, San I, Yesilova Y, Iynen I, Guldur ME, et al. Evaluation of ceruloplasmin levels in patients undergoing surgical interventions with nasal polyps. Auris Nasus Larynx. 2013;40(3):282–5. DOI: 10.1016/j.anl.2012.07.018. Epub 2012 Oct 30.
19. Yu Z, Wang Y, Zhang J, Li L, Wu X, Ma R, et al. Expression of heme oxygenase-1 in eosinophilic and non-eosinophilic chronic rhinosinusitis with nasal polyps: modulation by cytokines. Int Forum Allergy Rhinol. 2015;5(8):734-40. DOI: 10.1002/alr.21530. Epub 2015 Apr 23.
20. Taysi S, Uslu C, Yilmaz A, Aktan B, Altas E. Lipid peroxidation and some antioxidant enzymes in nasal polyp tissue. Cell Biochem Funct. 2006;24(5):461–5.
21. Kirtsreesakul V. Update on nasal polyps: etiopathogenesis. J Med Assoc Thail. 2005;88(12):1966–72.
22. Assanasen P. Medical and surgical management of nasal polyps. Curr Opin Otolaryngol Head Neck Surg. 2016;9(1):27–36.
23. Lopez-Chacon M, Mullol J, Pujols L. Clinical and biological markers of difficult-to-treat severe chronic rhinosinusitis. Curr Allergy Asthma Rep. 2015;15(5):19. DOI: 10.1007/s11882-015-0520-6.
24. Duda R. The role of inflammatory mediators in the pathogenesis of nasal polyposis: Literature review. Rom J Rhinol. 2015;5(18):81–5. DOI: 10.1515/rjr-2015-0009.
25. Önerci MT, Ferguson BJ. Nasal polyposis: Pathogenesis, medical and surgical treatment. Springer Science & Business Media; 2010.
26. Akyigit A, Keles E, Etem EO, Ozercan I, Akyol H, Sakallioglu O, et al. Genetic polymorphism of antioxidant enzymes in eosinophilic and non-eosinophilic nasal polyposis. Eur Arch Otorhinolaryngol. 2017;274(1):267–73. DOI: 10.1007/s00405-016-4259-z. Epub 2016 Aug 11.
27. Lee JM, McKnight CL, Aves T, Yip J, Grewal AS, Gupta S. Nasal nitric oxide as a marker of sinus mucosal health in patients with nasal polyposis. Int Forum Allergy Rhinol. 2015;5(10):894–9. DOI: 10.1002/alr.21598. Epub 2015 Jul 17.
28. Egea J, Fabregat I, Frapart YM, Ghezzi P, Görlach A, Kietzmann T, et al. Corrigendum to "European contribution to the study of ROS: A summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS)" [Redox Biol. 13 (2017) 94–162]. Redox Biol. 2018;14:694–6. DOI: 10.1016/j.redox.2017.10.001. Epub 2017 Oct 26.
29. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012;5(1):9–19. DOI: 10.1097/WOX.0b013e3182439613. Epub 2012 Jan 13.
30. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev. 2010 Jul;4(8):118–26.
31. Asher BF, Guilford FT. Oxidative stress and low glutathione in common ear, nose, and throat conditions: A systematic review. Altern Ther Health Med. 2016;22(5):44–50.
32. Arild Danielsen K, Eskeland Ø, Fridrich-Aas K, Cecilie Orszagh V, Bachmann-Harildstad G, Burum-Auensen E. Bacterial biofilms in chronic rhinosinusitis; distribution and prevalence. Acta Otolaryngol. 2016;136(1):109–12. DOI: 10.3109/00016489.2015.1092169. Epub 2015 Sep 25.
33. Norlander T, Fukami M, Westrin KM, Stierna P, Carlsöö B. Formation of mucosal polyps in the nasal and maxillary sinus cavities by infection. Otolaryngol Head Neck Surg. 1993;109(3 Pt 1):522-9.
34. Wladislavosky-Waserman P, Kern EB, Holley KE, Eisenbrey AB, Gleich GJ. Epithelial damage in nasal polyps. Clin Allergy. 1984;14(3):241–7.
35. Carey RM, Workman AD, Chen B, Adappa ND, Palmer JN, Kennedy DW, et al. Staphylococcus aureus triggers nitric oxide production in human upper airway epithelium. Int Forum Allergy Rhinol. 2015;5(9):808–13. DOI: 10.1002/alr.21568. Epub 2015 Jun 22.
36. Tamashiro E, Banks CA, Cohen NA. New Areas for Investigation: Nitric Oxide. In: Önerci TM, Ferguson BJ, editors. Nasal Polyposis: Pathogenesis, Medical and Surgical Treatment. Springer-Verlag Berlin Heidelberg; 2010, p.175-83.
37. Carey RM, Chen B, Adappa ND, Palmer JN, Kennedy DW, Lee RJ, et al. Human upper airway epithelium produces nitric oxide in response to Staphylococcus epidermidis. Int Forum Allergy Rhinol. 2016;6(12):1238–44. DOI: 10.1002/alr.21837. Epub 2016 Aug 10.
38. Cho DY, Le W, Bravo DT, Hwang PH, Illek B, Fischer H, et al. Air pollutants cause release of hydrogen peroxide and interleukin-8 in a human primary nasal tissue culture model. Int Forum Allergy Rhinol. 2014;4(12):966–71. DOI: 10.1002/alr.21413. Epub 2014 Nov 14.
39. Smith KA, Rudmik L. Medical therapy, refractory chronic rhinosinusitis, and productivity costs. Curr Opin Allergy Clin Immunol. 2017;17(1):5–11. DOI: 10.1097/ACI.0000000000000329.
40. Passali D, Cingi C, Cambi J, Passali F, Muluk NB, Bellussi ML. A survey on chronic rhinosinusitis: opinions from experts of 50 countries. Eur Arch Otorhinolaryngol. 2016;273(8):2097–109. DOI: 10.1007/s00405-015-3880-6. Epub 2016 Jan 7.
41. Chong LY, Head K, Hopkins C, Philpott C, Schilder AGM, Burton MJ. Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016;4:CD011996. DOI: 10.1002/14650858.CD011996.pub.2.
42. Kohanski MA, Tharakan A, Lane AP, Ramanathan M Jr. Bactericidal antibiotics promote reactive oxygen species formation and inflammation in human sinonasal epithelial cells. Int Forum Allergy Rhinol. 2016;6(2):191–200. DOI: 10.1002/alr.21646. Epub 2015 Dec 1.
43. Yu MS, Kim BH, Kang SH, Lim DJ. Low-concentration hypochlorous acid nasal irrigation for chronic sinonasal symptoms: a prospective randomized placebo-controlled study. Eur Arch Otorhinolaryngol. 2017;274(3):1527–33. DOI: 10.1007/s00405-016-4387-5. Epub 2016 Nov 17.
44. Veyseller B, Aksoy E, Ertas B, Keskin M, Ozturan O, Yildirim YS, et al. A new oxidative stress marker in patients with nasal polyposis: advanced oxidation protein products (AOPP). B-ENT. 2010;6(2):105–9.