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The antioxidant barrier, oxidative/nitrosative stress, and protein glycation in allergy: from basic research to clinical practice

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Recent studies indicate that oxidative/nitrosative stress is involved in the pathogenesis of asthma, allergic rhinitis, atopic dermatitis, and urticaria. The article aimed to review the latest literature on disruptions in redox homeostasis and protein glycation in allergy patients. It has been shown that enzymatic and non-enzymatic antioxidant systems are impaired in allergic conditions, which increases cell susceptibility to oxidative damage. Reactive oxygen/nitrogen species exacerbate the severity of asthma symptoms by activating inflammatory mediators that cause airway smooth muscle contraction, promote mucus hypersecretion, increase the permeability of lung capillaries, and damage cell membranes. Redox biomarkers could have considerable diagnostic potential in allergy patients. There is no compelling evidence to indicate that antioxidants reduce allergy symptoms' severity or slow disease progression.

KEYWORDS

allergy, oxidative stress, nitrosative stress, protein glycation, antioxidants

Introduction

The pathogenesis of allergies has been studied extensively by researchers and clinicians for more than 100 years. The term "allergy" was first used in 1906 by Clemens von Pirquet to describe patients who were hyperresponsive or hypersensitive to exogenous substances (1). In the 1960s, Gell and Coombs defined allergy as an exaggerated or inappropriate immune response, and they divided allergic responses into four pathophysiological types: anaphylaxis (type I), antibody-mediated cytotoxic reactions (type II), immune complex-mediated reactions (type III), and cell-mediated delayed hypersensitivity (type IV) (2). Most atopic diseases (the Greek word *atopos* means "out of place") are caused by type I hypersensitivity reactions. Anaphylaxis is induced antigen cross-linking of antigen-specific IgE antibodies that

bind to high-affinity IgE receptors on the surface of basophils and mast cells. The main clinical manifestations of atopy are allergic rhinitis (AR), atopic dermatitis (AD), allergic (atopic) asthma and some allergies (3).

Allergies are increasingly prevalent in highly developed countries. According to estimates, atopic diseases affect 25-30% of the global population. Similarly to hypertension, coronary artery disease, and cancer, allergies have been classified as lifestyle diseases (4). Environmental pollution, low levels of physical activity, poor nutrition, and prolonged stress increase the risk of lifestyle diseases and contribute to the overproduction of reactive oxygen species (ROS). ROS are the by-products of normal metabolic processes in aerobic organisms. When present in physiological concentrations, they participate in the regulation of immune processes, including T cell activation and leukocyte adhesion to endothelial cells. However, environmental factors can increase ROS production (5). When more ROS are produced than scavenged, the resulting pro-oxidant/antioxidant imbalance leads to oxidative stress (6). A pro-oxidant/antioxidant imbalance can occur inside individual cells or in subcellular compartments without modifying the redox status of the cell or the entire organism (7). It should also be noted that lungs and skin are particularly sensitive to oxidative damage. These organs are directly exposed to high oxygen concentrations as well as oxidative stress caused by normal aerobic metabolism or exposure to irritant compounds and other xenobiotics in air (such as cigarette smoke and air pollutants) (8). To counteract the overproduction of ROS, the body has developed specialized antioxidant systems, whose first line of defense are antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), but also other redox proteins such as thioredoxins (TRX), peroxiredoxins (PRX) and glutaredoxins. Non-enzymatic low-molecular-weight antioxidants (LMWA) include hydrophilic uric acid (UA), vitamin C and reduced glutathione (GSH; L-γ-glutamyl-L-cysteinyl-L-glycine) as well as lipophilic compounds like vitamins A, D and E (9, 10).

Numerous epidemiological and clinical studies have shown that oxidative stress directly or indirectly contributes to the risk of lifestyle diseases (11–14). Due to the decreased cellular proliferation, loss of adaptive immune function, and immunosenescence, ROS overproduction is an important hallmark of age-related diseases (15). Oxidative stress can exacerbate pre-existing health conditions, and it is one of the main causes of chronic inflammation. ROS are mainly produced in host defense response cells such as neutrophils and polymorphonuclear neutrophils (PMNs) (16). Allergens, chemicals and infections increase the ROS production, which activates nuclear factor kappa B (NF-KB) (17). Pro-inflammatory enzymes such as myeloperoxidase (MPO), NADPH oxidase (NOX), and inducible nitric oxide synthase (iNOS) are activated through cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism (5). These enzymes, in combination with NF-KB induction, not only increase the synthesis and secretion of cytokines, chemokines, and growth factors. They also lead to the overproduction of ROS and reactive nitrogen species (RNS) (18). Under these conditions, superoxide anion radical is produced in very large quantities. Superoxide can rapidly combine with nitric oxide (NO) to form peroxynitrite ($ONOO^-$), the strongest oxidizing agent *in vivo* (19). This reaction is three to four times faster than superoxide dismutation by SOD (18). RNS, in turn, induce nitrosative stress, adding to the pro-inflammatory burden of ROS (20). It was shown that oxidative stress is not only responsible for impaired intracellular signaling, but also abnormal immune responses and oxidative DNA damage (21). The damaging effects of inflammation-related oxidative stress are particularly exacerbated under hypoxic conditions. Low oxygen levels trigger a number of responses that are associated with numerous physiological and pathophysiological scenarios (22). Hypoxia results in inefficient respiratory electron transfer, leading to overproduction of mitochondrial ROS and irreversible intracellular damage (23, 24).

According to recent research, oxidative and nitrosative stress plays a key role in the pathogenesis of respiratory (including asthma) and skin allergies (AD, urticaria) (25–27). Moreover, food allergies were found to be associated with carbonyl stress resulting from the accumulation of advanced glycation end products (AGEs) and other carbonyl compounds in body tissues (26, 28, 29). The prevalence of atopic diseases has reached epidemic proportions in the 21st century, which is why the role of oxidative, nitrosative and carbonyl stress in selected atopic diseases should be carefully scrutinized. In view of the general scarcity of studies summarizing the latest knowledge in this area, the aim of this article was to review the literature on disruptions in redox homeostasis in allergy patients.

Abbreviations: 8-iso-PGF2alpha, 8-iso-prostaglandin F2alpha; 8-OHdG, 8-hydroxy-2'-doxyguanosine; ACTH, adrenocorticotropic hormone; AD, atopic dermatitis; AGEs, advanced glycation end products; ALEs, advanced lipoxidation end products; AR, allergic rhinitis; AOPPs, advanced oxidation protein products; APC, antigen presenting cell; ATP, adenosine triphosphate; BAL-bronchoalveolar lavage; cGMP, cyclic guanosine monophosphate; CO, carbon monoxide; CSU- chronic spontaneous urticaria; DC, dendritic cells; DEPs, Diesel exhaust particles; EAR, early asthmatic reaction; ECF-A- eosinophil chemotactic factor of anaphylaxis; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EPO, eosinophil peroxidase; F2-IsoPs, F2-isoprostanes; GALT, gut-associated lymphoid tissue; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSH, glutathione; ICAM 1, intercellular adhesion molecule 1; IgE, immunoglobulin E; IL, interleukin; IFN- γ, interferon γ; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LAR, late asthmatic response; LPO, lipoxygenase; LTB4, leukotriene B4; LTC4, leukotriene C4; MALT, mucosa-associated lymphoid tissue; MAPK, mitogen-activated protein kinase; MBP, major basic protein; MHC, major histocompatibility complex; MDA, malondialdehyde; MgSO4, magnesium sulfate; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; NCF, neutrophil chemotactic factor; NF-KB, nuclear factor kappa B; NO, nitric oxide; O2•-superoxide anion; PAF, platelet-activating factor; PGD2, prostaglandin D2; PUFAs, polyunsaturated fatty acids; RANTES, regulated on activation, normal T-cell expressed and secreted; RBC, red blood cells; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; SPO, salivary peroxidase; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late antigen-4.

Respiratory allergies

Allergic asthma and oxidative stress

Bronchial asthma is an inflammatory disorder of the lower respiratory tract which usually occurs in childhood and persists throughout life. According to epidemiological research, bronchial asthma is caused mainly by hypersensitivity to inhalant allergens (3). Allergy-induced asthma is observed in around 70-90% of asthma patients. In all types of asthma, the immune response involves mainly T cells, but according to some reports, regulatory T cells are also implicated in the progression of asthma and other allergic diseases (30). Activated Th2 cells produce IL-4, IL-3, IL-5, IL-13, and the granulocyte-macrophage colony-stimulating factor (GM-CSF) which affect the target cells of allergic reactions such as B cells, mast cells, eosinophils, and macrophages (Figure 1). These cells secrete various mediators that are directly responsible for the progression of allergy and bronchial obturation in asthma (31). Interleukin 4 is produced not only by Th2 cells, and it plays a key role in the initiation of an allergic response. This cytokine causes isotype switching to IgE in B cells, increases the expression of the vascular cell adhesion molecule 1 (VCAM-1), controls Fc-e IgE expression, cytokine and chemokine receptors, and the number of leukocytes that participate in the allergic inflammatory cascade. It should also be noted that IL-4 promotes the differentiation of Th0 cells into Th2 cells, exacerbates the inflammatory response, and leads to IgE production in the absence of an allergen. Interleukin 6 potentiates IgE production by enhancing the effects of IL-4, and increased IL-6 synthesis in asthma patients has been well documented (32, 33). There are two types of asthmatic responses: early and late. The early-phase response occurs 10-20 minutes after allergen inhalation, and it causes bronchoconstriction. Inflammatory mediators such as histamine, proteolytic enzymes, glycolytic enzymes, and heparin, as well as *de novo* synthesized prostaglandin D2 (PGD2), leukotriene C4 (LTC4), adenosine, and ROS are released from mast cell granules (34), and they directly induce

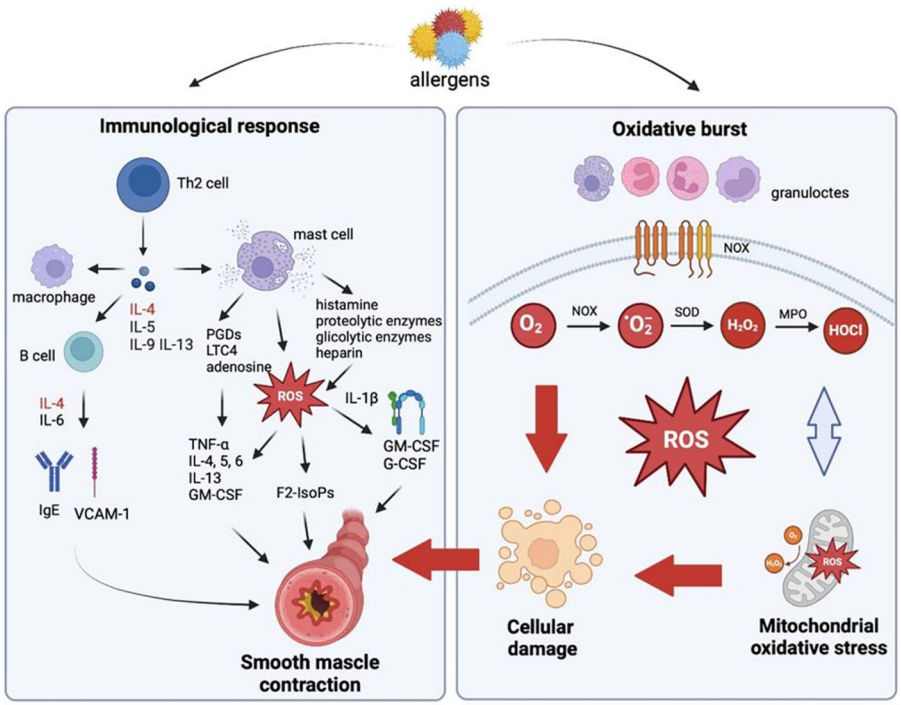

FIGURE 1
Oxidative stress-mediated inflammation in allergic diseases (Created in Biorender.com). Activated Th2 cells produce interleukin (IL)-4 (IL-4), -5 (IL-5), -9 (IL-9), -13 (IL-13), and the granulocyte-macrophage colony-stimulating factor (GM-CSF) which affect the target cells of allergic reactions such as B cells, mast cells, eosinophils, and macrophages. Histamine, proteolytic enzymes, glycolytic enzymes, and heparin, as well as *de novo* synthesized prostaglandin D2 (PGD2), leukotriene C4 (LTC4), adenosine, and reactive oxygen species (ROS) are released from mast cell granules, and they directly induce oxidative stress. These mediators cause airway smooth muscle contraction, sensitize nerve terminals, promote mucus hypersecretion, vasodilation, and plasma extravasation from microvessels. In allergy, spontaneous or stimulated overproduction of ROS in mast cells, eosinophils, neutrophils, macrophages and monocytes is also observed. The endothelial enzyme NADPH oxidase (NOX) activated by airborne allergens are a rich source of superoxide anions ($O_2^{\bullet -}$). $O_2^{\bullet -}$ radicals are not highly reactive or toxic, but they are rapidly converted to hydrogen peroxide (H_2O_2). H_2O_2 is used mainly by myeloperoxidase (MPO) which catalyzes oxidation reactions with the involvement of chlorine ions to produce hypochlorous acid (HOCl), hydroxyl radicals ($OH^{\bullet}$), singlet oxygen (O_2^1), and ozone (O_3) with strong bactericidal properties. ROS increase the severity of allergic diseases by activating numerous inflammatory mediators which cause bronchial hyperreactivity by contracting the airway smooth muscle, promoting mucus hypersecretion, increasing the permeability of pulmonary capillaries, and damaging cell membranes. B cell, lymphocyte type B; F2-IsoPs- F2-isoprostanes; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; H_2O_2, hydrogen peroxide; HOCl, hypochlorous acid; IgE, immunoglobulin E; IL, interleukin; LTC4- leukotriene C4; MPO, myeloperoxidase; NOX, NADPH oxidase; O_2, oxygen; O2•, superoxide anion; PGDs, prostaglandins; ROS, reactive oxygen species; SOD, superoxide dismutase; Th cell, T helper cell; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule 1.

oxidative stress (Figure 1). These mediators cause airway smooth muscle contraction, sensitize nerve terminals, promote mucus hypersecretion, vasodilation, and plasma extravasation from microvessels. F2-isoprostanes (F2-IsoPs) are potent vasoconstrictors (35)These compounds are similar to prostaglandins, and they are produced during non-enzymatic ROS peroxidation of polyunsaturated fatty acids (PUFAs), mainly arachidonic acid. F2-IsoPs are directly responsible for airway smooth muscle contraction and plasma extravasation from the vascular bed (36). Under exposure to IL-1β, F2-IsoPs release GM-CSF and the granulocyte colony stimulating factor (G-CSF) (37). F2-IsoPs also activate the PGF2α receptor, which inhibits air flow due to bronchial obturation and leads to respiratory distress (36). At the same time, mast cells secrete cytokines that directly trigger the late-phase asthmatic response (TNF-a, IL-4, -5, -6) and recruit other inflammatory cells (IL-13 and GM-CSF). Bronchial contractions that occur 6-12 hours later are known as the late-phase asthmatic response. According to research, the late phase has a much greater impact on the pathogenesis of asthma than the early phase (36). The mediators secreted by mast cells trigger the expression of adhesion molecules in the endothelium of vessels responsible for leukocyte migration to the inflammation site (31). ROS intensify T cell activation and induce leukocyte adhesion to the endothelium, thus recruiting circulating leukocytes to the inflammation site (11). The following adhesion molecules play a key role in cell transmigration and activation in asthma: intercellular adhesion molecule 1 (ICAM-1), VCAM-1, and its ligand VLA-4. Adhesion molecules bind to their ligands present on leukocytes, which enables them to closely adhere to the microvascular endothelium. In a process known as diapedesis, cells respond to chemokines and cross the endothelial barrier to reach the inflammation site (38). The number of eosinophils, neutrophils, and CD4 and CD8 T cells increases in the late-phase asthmatic response. Mast cells also migrate to the epithelium. Recent research has shown that epithelial cells play a role in inflammation (39). Cytokines produced by Th2 cells secrete chemokines that induce and sustain inflammation in tissues (40). There is also evidence to suggest that epithelial cells promote the differentiation of Th2 cells (41, 42). Prolonged inflammation leads to bronchial hyperreactivity to non-specific stimuli. Migrating inflammatory cells are activated by the released or locally produced factors, and they become hypersensitive to various stimuli. The activation of inflammatory cells leads to the release of other mediators that cause smooth muscle contraction, hyperemia, edema and damage to respiratory mucosa, and stimulation of nerve terminals (43).

There is considerable evidence that oxidative stress increases the severity of bronchial asthma (43–45). Spontaneous or stimulated overproduction of ROS in mast cells, eosinophils (46), neutrophils (47), macrophages (48) and monocytes (38) is observed in asthma. Activated phagocytes utilize ROS to eliminate allergens. This process is known as respiratory burst, and it increases oxygen consumption in cells several dozen-fold. The endothelial enzyme NOX plays a key role in respiratory burst (49). NOX is activated by airborne allergens that are a rich source of this enzyme (36). Overexpression of NOX generates superoxide anion radicals ($O_2^{\bullet-}$). $O_2^{\bullet-}$ radicals are produced when electrons from NADPH produced in the pentose phosphate pathway are converted to molecular oxygen (O_2) in extracellular fluid or inside phagosomes. $O_2^{\bullet-}$ radicals are not highly reactive or toxic, but they are rapidly converted to hydrogen peroxide (H_2O_2). This compound is more stable than $O_2^{\bullet-}$, and it can penetrate cell membranes (50). Hydrogen peroxide produced by neutrophils is used mainly by MPO which catalyzes oxidation reactions with the involvement of chlorine ions to produce hypochlorous acid (HOCl), hydroxyl radicals ($OH^{\bullet}$), singlet oxygen (O_2^1), and ozone (O_3) with strong bactericidal properties (49). ROS are also produced in the Haber-Weiss reaction ($O_2^{\bullet-} + H_2O_2 \rightarrow OH^{\bullet-} + OH^- + O_2$) and the Fenton reaction ($H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^{\bullet-} + OH^-$) with the participation of pro-oxidant ions of transition metals (mostly Fe^{2+}/Cu^{2+}) (51). Inflammatory cells produce much larger quantities of ROS/RNS under allergic conditions than in healthy subjects (52). Acidophilic granulocytes are immune cells with the greatest potential for ROS generation (46).

In bronchial asthma, ROS act as mediators of asthmatic inflammation and deliver direct pro-asthmatic effects (53, 54). ROS increase the severity of bronchial asthma by activating numerous inflammatory mediators, including leukotrienes B4 (55) and D4, regulated on activation, normal T-cell expressed and secreted (RANTES) chemokines, eotaxins, IL-5 (55), IL-1, -4, -6, GM-CSF, interferon (INF), platelet-activating factor (PAF), tumor necrosis factor α (TNFa), adhesion molecules (VCAM-1) (56) and major basic protein (MBP) (57). Inflammatory mediators cause bronchial hyperreactivity by contracting the airway smooth muscle, promoting mucus hypersecretion, increasing the permeability of pulmonary capillaries, and damaging cell membranes (58). Pro-inflammatory mediators are overexpressed via the mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-KB), and activator protein 1 (AP-1) signaling pathways which not only regulate the inflammatory response, but also intensify ROS production and oxidative stress (59–61). These processes further disrupt redox homeostasis (62). Oxidative stress causes cell membrane oxidation in the lipid peroxidation process, which alters the physical properties of cell membranes, induces changes in membrane fluidity and cell integrity. The activity of membrane enzymes and transport proteins is also inhibited (7). Protein oxidation leads to the cleavage of the polypeptide chain, changes in amino acid residues, and the formation of dimers and/or protein aggregates, which disrupts the functions of structural and transport proteins. Oxidative stress also causes breaks in the DNA strand, which leads to changes in gene expression and genetic mutations (8, 63). Indeed, ragweed pollen extract depleted cellular GSH and induced lipid peroxidation, which directly induced tyrosine phosphorylation of p38 MAPK and subsequent production of interleukin IL-8. The resulting oxidative stress induced mucous cell metaplasia and the accumulation of inflammatory cells in bronchoalveolar lavage (BAL) fluids and peribronchial areas (64). Pollen glucans can also stimulate Toll-like receptors (TLRs) in phagocytes and dendritic cells (DCs), and they can contribute to mitochondrial dysfunctions that also lead to the overproduction of ROS (65). Ragweed pollen extract caused oxidative damage to ubiquinol-cytochrome c reductase core protein II (UQCRC2) and intensified the release of hydrogen peroxide from mitochondrial complex III (66). Mitochondria are an important source of ROS in

most cells. Therefore, increased production of mitochondrial ROS can modify allergic airway inflammation and bronchial hyperreactivity (65, 66). It was shown that mitochondrial oxidative stress occurs mainly during hypoxic conditions. Hypoxia-inducible factor 1α (HIF-1α) is a crucial transcription factor modulating the high energy requirements of immune cells to perform their effector functions in low-oxygen states (67–70). Hypoxia increases mitochondrial ROS formation and leads to enhanced infiltration of activated inflammatory cells (71). A better understanding of the role of hypoxia in immunological reactions may result in developing new therapeutic strategies for allergic diseases (67).

The toxic effects of ROS are mitigated by antioxidant enzymes, including catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), as well as non-enzymatic antioxidants such as glutathione (GSH), vitamins C and E, and uric acid. In asthma, oxidative stress can be caused by the weakening of enzymatic and non-enzymatic antioxidant mechanisms that accompany chronic inflammations (72) (Table 1). In asthma patients, lower levels of SOD, CAT (73) and GPx (74) activity were observed in BAL fluids and respiratory epithelial cells. A significant decrease was also noted in the plasma concentrations of non-enzymatic antioxidants: hydrophilic ascorbic acid and hydrophobic α-tocopherol. The activity of salivary antioxidant enzymes (salivary peroxidase, SPO; SOD) was also significantly lower in asthma patients (75). A marked decrease was also reported in the serum levels of antioxidant vitamins (C and E) (76–78). A weakened antioxidant barrier contributes to oxidative changes in cellular biomolecules. Orally administered antioxidants (vitamins C and E) decreased bronchial hyperreactivity in asthma patients (79) and reduced the consumption of inhalation corticosteroids (80). In an experimental study, antioxidants decreased the accumulation of acidophilic granulocytes in the respiratory tract of animals with inhalant allergies (81). For this reason, antioxidant supplements are recommended in the treatment of asthma. The efficacy of antioxidant enzymes in asthma treatment has been also investigated, and a study of liposome-encapsulated SOD and CAT generated promising results (82). Liposome-encapsulated enzymes decreased bronchial hyperreactivity in the experimental animals. Attempts have also been made to synthesize SOD mimetics, and initial results suggest that these enzymes have therapeutic potential in asthma (83).

Oxidative stress plays a key role in the pathogenesis of asthma, which is why redox biomarkers could have considerable diagnostic potential in asthma (Table 1). ROS production rate was also correlated with disease severity (84). Inhaled corticosteroids were found to decrease ROS concentrations in the respiratory tract. Peripheral eosinophil counts were significantly higher in asthma patients than in the control group, and were correlated with disease severity. F2-IsoPs deserve special attention because serum F2-IsoPs levels were higher in asthma patients than in healthy subjects, and were also correlated with disease progression (85). Other researchers also reported an increase in F2-IsoPs concentrations in the blood serum (78) and exhaled breath condensate of asthma patients (86). F2-IsoPs are stable products of arachidonic acid oxidation, and their levels can increase even six-fold during an acute asthma episode, and decrease in response to corticosteroid therapy (85). F2-IsoPs are effective vasoconstrictors that induce mitogenesis in vascular smooth muscle cells. They also modulate platelet functions (85). In asthma patients, oxidative stress is also manifested by a rise in the levels of malondialdehyde (MDA), a product of lipid peroxidation with cytotoxic and mutagenic properties (87, 88). Elevated MDA levels were reported in the serum, plasma, hemolysate, and exhaled breath condensate of asthma patients relative to healthy controls. Interestingly, MDA concentration increases significantly in acute asthma, which suggests that peroxidation processes are intensified during disease progression (89). Lipid peroxidation in cell membranes stimulates phospholipase enzymes (including phospholipase A2), which triggers the arachidonic acid cascade catalyzed by cyclooxygenases and lipoxygenases (38). ROS damage membrane enzyme complexes and increase the flow of calcium to cells, which contributes to the secondary activation of cellular proteases and phospholipases. These processes damage cell membranes and membrane receptors in the respiratory tract. Despite extensive research, there is considerable debate on whether heightened oxidative stress in the respiratory tract of asthma patients is the cause or consequence of inflammation, oxidative stress preceded asthma symptoms (allergic inflammation and respiratory sensitization) (90). In atopic patients, oxidative stress can initiate intercellular signaling pathways, leading to a break in immune tolerance (61).

Allergic asthma and nitrosative stress

Nitrosative stress is closely associated with oxidative stress in the progression of asthma. Nitrosative stress leads to the overproduction of RNS, including nitric oxide (NO) which triggers an immune response, and its derivatives: nitrous acid (HNO_2), nitrogen dioxide (NO_2), and nitric acid (HNO_3) (91). NO is biosynthesized with the involvement of NOS enzymes that catalyze the oxidation of the guanidinium group in L-arginine to NO and L-citrulline. There are three isoforms of NOS, where inducible NOS (iNOS, type II NOS) plays the key role in the pathogenesis of asthma (92). This enzyme is expressed on bronchial epithelial cells, endothelial cells, fibroblasts, type II pneumocytes, and infiltrating inflammatory cells (93). In asthma patients, iNOS expression in respiratory epithelial cells and NO concentration in exhaled breath condensate were markedly higher due to ongoing inflammatory processes (94). The expression of iNOS is induced by exposure to allergens, pro-inflammatory cytokines (IL-1β, IFN-γ, TNF-α), bacterial lipopolysaccharide, and pro-oxidants (92). The concentration of NO produced under such conditions can be even 1000 times higher than the concentration of NO produced by constitutive NOS (neuronal NOS, nNOS, or endothelial NOS, eNOS). It should also be noted that significant quantities of $O_2^{\bullet-}$ are produced in the reactions catalyzed by iNOS, and $O_2^{\bullet-}$ reacts with NO to generate peroxynitrite ($ONOO^-$) with strong oxidizing and nitriding properties (95). The adverse effects of NO on the respiratory tract can be attributed mostly to the production of $ONOO^-$ and other RNS (NO_2) (93).

TABLE 1 Redox biomarkers in patients with allergic diseases.

Study group	Control group	Marker	Material	Changes vs control group	Reference	Comments
Asthma						
15 asthmatic patients (M/F-8/7) <18 years – 9 ≥18 years - 6	15 healthy subjects (M/F-8/7) <18 years – 9 ≥18 years - 6	8-iso-PGF2alpha (EIA)	Plasma	Increase (p 0.0044)	(2000) Wood LG (85).	8-iso-PGF2α levels were found to be associated with clinical asthma severity (P = 0.044) (R=0.367)
12 asthmatic children undergoing steroid treatment (M/F-5/7) (5-17 years)	11 healthy children (M/F-8/7) (2-18 years)	8-iso-PGF2alpha (CL)	Exhaled breath condensate	Increase (p < 0.01)	(2005) Shahid SK (86).	Inhaled corticosteroids were administered at ≤ 600 μg/day to 6 children and at >600 μg/day to 6 children
12 asthmatic children undergoing non-steroid treatment (M/F-4/8) (5-17 years)	11 healthy children (M/F-8/7) (2-18 years)	8-iso-PGF2alpha (CL)	Exhaled breath condensate	Increase (p < 0.01)	(2005) Shahid SK (86).	10 patients with mild intermittent asthma and 2 patients with moderate persistent asthma
30 asthmatic children (M/F-19/11) (4-15 years)	21 healthy children (M/F-14/15) (5-13 years)	carbon monoxide (chemical analyzer)	Exhaled breath condensate	increase (p<0.01)	(2002) Zanconato S (112).	Nineteen (63%) of the children had persistent asthma and were undergoing a long-term treatment with low doses of inhaled steroids for at least 1 month; 7 children (23%) were also administered long-acting β2 agonists. The remaining 11 children had intermittent asthma and did not receive long-term treatment
29 asthmatic children (M/F-18/11) (4-15 years)	23 healthy children (M/F-11/12) (5-13 years)	nitric oxide (CL)	Exhaled breath condensate	increase (p<0.0001)	(2002) Zanconato S (112).	Children were treated with oral prednisone for 5 days (1 mg/kg/day)
50 patients with asthma (M/F -25/25) (15- 65 year)	healthy subjects (M/F -25/25) (15- 65 year)	MDA (spectrophotometry)	Plasma	increase (p ≤ 0.05)	(2014) Abeer M.A (271)	
12 children during an asthma episode (6-18 years)	14 healthy children (6-16 years)	SPO, TSA, SOD (NBS)	Saliva	decrease (p<0.05)	(2006) Bentur L (75).	No correlation was found between saliva antioxidant levels
15 asthmatic patients	16 healthy subjects	total carotenoids, lycopene, lutein, β-cryptoxanthin, β-carotene, and α-carotene (HPLC)	Sputum, whole blood	decrease (p<0.001)	(2005) Wood LG (76).	
81 asthmatic patients (M/F -27/54) (44–58 years)	43 healthy subjects (M/F -19/23) (36-56 years)	Vitamin C, α-tocopherol, retinol, β-carotene, α-carotene, lycopene (HPLC)	Plasma	decrease (p<0.001)	(2005) Misso LA (77).	53 patients with mild to moderate asthma and 28 patients with severe asthma
8 patients with mild asthma	6 healthy subjects	NF-κB (ELISA)	BAL	decrease (p<0.05)	(1999) Thomassen MJ. (98)	
24 patients with mild asthma (M/F -18/6) (21–33 years)	24 healthy subjects (M/F -13/11) (22–32 years)	NO (WB)	Exhaled breath condensate	increase (p<0.001)	(2003) Hansel TT (106).	All study and control group patients received 200 mg of SC-51 before the study
38 asthmatic patients (M/F -21/17) (22–63 years)	32 subjects (M/F -18/14) (20–63 years)	leukocyte GPx, vitamin C (spectrophotometry)	Serum	decrease (p<0.01)	(2005) Vural H (78).	All patients had mild asthma without acute episodes in the past 3 months. They regularly took inhaled corticosteroids at

(Continued)

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TABLE 1 Continued

Study group	Control group	Marker	Material	Changes vs control group	Reference	Comments
Asthma						
						low doses and short-acting β2 agonist when needed.
81 asthmatic patients (M/F -27/54) (44–58 years)	43 healthy subjects (M/F -19/23) (36-56 years)	Vitamin C, α-tocopherol, retinol, β-carotene, α-carotene, lycopene (HPLC)	Plasma	decrease ($p<0.001$)	(2005) Misso LA (77).	53 patients with mild to moderate asthma and 28 patients with severe asthma
Allergic rhinitis						
40 patients (M/F -18/22) (10–53 years)	40 patients (M/F -16/24) (13–48 years)	AOPPs	Serum	increase ($p=0.0015$)	(2009) Aksoy F (133).	Patients with allergic rhinitis received subcutaneous immunotherapy (SCIT)
100 children with asthma and allergic rhinitis (M/F -37/63) (8-13 years)	74 healthy children (M/F -42/32) (8-12 years)	MDA (HPLC)	Exhaled breath condensate (nasal and oral)	increase ($p < 0.01$)	(2012) Celik M (136).	Nasal and oral MDA ($r = 0.684$, $p < 0.001$) were positively correlated with GSH concentrations ($r = 0.684$, $p < 0.001$). Negative correlations were found between GSH and MDA levels in both nasal ($r = 0.573$, $p < 0.001$) and oral samples ($r = 0.387$, $p < 0.001$)
17 children with allergic rhinitis (M/F -9/8) (10-14 years)	74 healthy children (M/F -42/32) (8-12 years)	MDA (HPLC)	Exhaled breath condensate (nasal and oral)	increase ($p < 0.01$)	(2012) Celik M (136).	
100 children with asthma and allergic rhinitis (M/F -37/63) (8-13years)	74 healthy children (M/F -42/32) (8-12 years)	GSH (HPLC)	Exhaled breath condensate (nasal and oral)	decrease ($p < 0.01$)	(2012) Celik M (136).	
17 children with allergic rhinitis (M/F -9/8) (10-14 years)	74 healthy children (M/F -42/32) (8-12 years)	GSH (HPLC)	Exhaled breath condensate (nasal and oral)	decrease ($p < 0.01$)	(2012) Celik M (136).	
70 patients with allergic rhinitis (mild and moderate)	24 healthy subjects	MDA (spectrophotometry)	Exhaled breath condensate	increase ($p < 0.01$)	(2021) Gadzhimirzaev GA (139).	
11 patients with allergic rhinitis (M/F -8/3) (15-56 years)	18 patients with non-allergic rhinitis (M/F -17/1) (15-56 years)	Nitrotyrosine (immunohisto-chemistry)	nasal mucosa	increase ($p<0.05$)	(2000) Kang BH (135).	Allergic rhinitis patients who required turbinectomy
93 patients with severe allergic rhinitis (20-22 years)	40 non-allergic subjects (24-48 years)	Nitrotyrosine (HPLC)	nasal mucosa	increase ($p<0.05$)	(1998) Sato M (134).	
6 patients with allergic rhinitis (M/F -1/5) (26-54 years)	13 non-allergic subjects	Carbon monoxide (infrared analyzer)	nasal airways	increase ($p<0.005$)	(2002) Andersson JA. (138)	
86 patients with allergic rhinitis (M/F -32/54) (37-41 years)	30 non-allergic subjects (M/F -34/40) (26-54 years)	carbon monoxide (EC50 analyzer)	Exhaled breath condensate	increase ($p<0.005$)	(1999) Monma M (137).	

(Continued)

TABLE 1 Continued

Study group	Control group	Marker	Material	Changes vs control group	Reference	Comments
Atopic dermatitis						
21 patients with atopic dermatitis (M/F -14/7) (21-76 years)	20 healthy subjects (M/F -16/4) (25-95 years)	Nitrate (Griess method)	urine	increase ($p<0.05$)	(2009) Nakai K (25).	MDA and 8-OHdG were also measured. Urinary nitrate levels, but not 8-OHdG or malondialdehyde, were significantly higher in atopic dermatitis patients than in healthy controls. The Eczema Area and Severity Index (EASI) score was significantly correlated with urinary nitrate ($r = 0.647$, $P = 0.03$) and urinary malondialdehyde levels ($r = 0.472$, $P = 0.03$). The EASI score was not correlated with urinary 8-OHdG levels
17 patients (M/F -4/13) (16-36 years)	17 healthy subjects (M/F -4/13) (19-34 years)	8-OHdG (ELISA)	Urine	increase ($p< 0.0001$)	(1998) Tsuboi H (152).	
13 children with AD (M/F -4/9) (8.5-11.5 years)	28 healthy children (M/F -10/18) (1.5-10 years)	8-OHdG, acrolein-lysine adducts, BOM (bilirubin oxidative metabolites) (ELISA)	Urine	increase ($p<0.001$)	(2003) Tsukahara H (150).	
33 children with AD (2.5-6 years)	23 healthy children (2.5-5.5 years)	8-isoprostane, LTB4 (EIA)	Exhaled breath condensate	increase ($p<0.01$)	(2009) Peroni DG (272).	
15 patients with AD (M/F -7/8) (27-33 years)	40 healthy subjects (M/F -20/20) (29-35 years)	carbon monoxide (electrochemical analyzer)	Exhaled breath condensate	increase ($p<0.0001$)	(1999) Horvath I (151).	
75 patients with AD (M/F -37/38) (20-53 years)	15 healthy controls and 22 diseased controls, including 12 patients with contact dermatitis and 10 patients with cutaneous dermatophyte infection or cutaneous candidiasis	4-hydroxy-2-nonenal, carbonyl moieties, SOD (spectrophotometry)	skin biopsies	increase ($p<0.05$)	(2003) Niwa Y (155).	
75 patients with AD (M/F -37/38) (20-53 years)	15 healthy controls and 22 diseased controls, including 12 patients with contact dermatitis and 10 patients with cutaneous dermatophyte infection or cutaneous candidiasis	Vitamin E (MS)	skin biopsies	decrease ($p<0.05$)	(2003) Niwa Y (155).	
5 patients with AD (23-46 years)	5 healthy subjects	Vitamin C (MS)	skin biopsies	decrease ($p<0.05$)	(2003) Leveque N (154).	
Urticaria						
16 patients with urticaria (20-63 years)	11 healthy subjects	MDA, SOD, GSH (immuno-dot blot assay)	skin biopsies	increase ($p<0.05$)	(2003) Raho G (164).	
85 patients with urticaria (M/F -31/54) (16-77 years)	64 healthy subjects	AOPPs (spectrophotometry)	Serum	increase ($p<0.0001$)	(2017) Nettis E (167).	AGEs were also measured. No significant differences were found between AGE levels in patients and controls.

(Continued)

TABLE 1 Continued

Study group	Control group	Marker	Material	Changes vs control group	Reference	Comments
Urticaria						
31 children with urticaria (M/F -16/15) (7-15 years)	22 healthy children (M/F -10/12) (7-13 years)	NOx metabolites (nitrite, nitrate) (Greiss method)	Serum	increase ($p<0.0001$)	(2017) Dilek F (27).	
25 patients with urticaria (M/F -6/19) (mean age 35 years)	20 healthy subjects	Vitamin E (MS), catalase, CSH-Px (spectrophotometry)	Plasma	decrease ($p<0.0001$)	(2001) Briganti S (148).	

8-iso-PGF2alpha, 8-iso-Prostaglandin; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; AD, atopic dermatitis; AOPPs, advanced oxidation protein products; BOM, bilirubin oxidative metabolites; CL, chemiluminescence; GPx, glutathione peroxidase; EISA, Eczema Area and Severity Index; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; GSH, glutathione; HPLC, high-performance liquid chromatography; LTB4, leukotriene B4; MDA, malondialdehyde, MS, mass spectrometry; NBS, thionitrobenzoic acid assay; NOx, nitrogen oxides; SOD, superoxide dismutase; SPO, salivary peroxidase; TSA, thiol-specific antioxidant protein; WB, Western Blot.

It should also be noted that NO plays a dual role in the pathogenesis of asthma. NO can act as a vasodilator, neurotransmitter, and immune response regulator (96). However, NO can also induce inflammation by generating toxic RNS (97). According to Tomassen and Raychaudhuri (98), NO plays a protective role in asthma by interacting with NF-KB and modulating the inflammatory response. Research has demonstrated that NO donors inhibit the production of inflammatory cytokines (TNF-α, IL-1, MIP-1α) and NF-KB activation in lung macrophages. The expression of NF-KB in BAL fluids is much lower in asthma patients than in healthy subjects due to greater bioavailability of NO in the respiratory tract (99). The results of an experiment conducted on murine Th1 and Th2 cells suggest that NO can exacerbate the inflammatory response in asthma by disrupting the balance between T helper cells (100). After reacting with the allergen and degranulating mast cells in the early phase, NO downregulates the mediators of smooth muscle contraction and induces smooth muscle relaxation by interacting with cyclic guanosine monophosphate (cGMP) (96). However, NO also increases vascular permeability and promotes mucus secretion from the respiratory tract. This vasodilator increases the availability of inflammatory mediators (TNF-α, L-selectin) which, at high concentrations, can damage epithelial cells and lead to bronchial contraction (101). Research has also shown that NO exerts cytotoxic effects on respiratory epithelial cells and disrupts oxygen uptake by type II pneumocytes (93). NO can also activate matrix metalloproteinases (MMPs) which play a role in lung damage (102). There is a growing body of evidence to suggest that NO participates in airway remodeling in asthma (58, 103). An *in situ* analysis of respiratory epithelial cells from asthma patients revealed that iNOS expression is inhibited by glucocorticoids. The levels of NO in exhaled breath condensate returned to normal after treatment (98). An *in vitro* study revealed that glucocorticoids decrease iNOS expression by inhibiting gene transcription and promoting the degradation of enzyme proteins. Selective iNOS inhibitors are used to remove excess NO from the respiratory tract (104). These compounds can decrease the rate of NO production to constitutive NO production levels (105, 106). Zhang et al. (107, 108) demonstrated that rapamycin and budesonide inhibit iNOS and NO synthesis in asthma patients.

The levels of NO in exhaled breath condensate can have a significant diagnostic value in asthma patients (Table 1). Numerous studies have shown that NO is a sensitive biomarker of eosinophil-mediated inflammation and that it is positively correlated with other diagnostic markers in bioptates, BAL fluids, and induced sputum (104, 109, 110). NO is particularly useful for monitoring the effectiveness of inhaled steroids in asthma (111). Exhaled NO measurement is a simple, non-invasive, and safe test that reliably assesses inflammation severity in the lower respiratory tract. Interestingly, increased levels of exhaled NO can be associated with a higher risk of asthma (106), and can point to the coexistence of asthma in patients with chronic obstructive pulmonary disease (COPD) (112).

Allergic rhinitis and oxidative stress

Allergic rhinitis is yet another atopic disease that is caused by ROS and RNS overproduction. It is an IgE-dependent inflammation of the nasal mucosa under exposure to an allergen. This disease is highly prevalent, and it is a common comorbidity of asthma. Inflammation of the nasal mucosa is caused by complex immune responses to an allergen (113). Under exposure to an allergen, Th2 cells begin to secrete cytokines (IL-4, IL-3) which recruit IgE antibody-producing B cells and cause eosinophils to migrate to the subepithelial layer. Inflammatory mediators are released within seconds due to the overproduction of IgE which binds to mast cells and allergens. Histamine is the key inflammatory mediator, but other substances are also released by mast cells, including PAF, eicosanoids, prostaglandins, leukotrienes, substance P, and ROS. ROS play a particularly important role in inflammation (114). Overproduction of ROS leads to the translocation of NF-κB to the cell nucleus and provides cytokine, chemokine, and growth factor genes with access to promoter regions. Intracellular

concentration of Ca^{2+} increases, which triggers an inflammatory response. Similarly to asthma, mast cells, Th2 cells, basophils, and epithelial cells synthesize and release cytokines and chemokines (IL-3, IL-4, IL-5, IL-10, IL-13, GM-CSF, and RANTES), which are responsible for sustaining allergic inflammation and the associated oxidative/nitrosative stress (115). Eosinophils, which are responsible for the late-phase reaction, are mobilized in the next stage. Eosinophils damage epithelial cells, the basement membrane, and nerve terminals via toxic MBP and eosinophil cationic proteins (ECP), which leads to edema of the nasal mucosa (116–118).

Interestingly, dust and gaseous air pollutants can contribute to oxidative and nitrosative stress in AR patients. Airborne substances not only exacerbate, but can also induce inflammations of the upper airway mucosa. Their toxicity is determined by chemical composition, duration of exposure, and the accumulation of these substances in the body. Research has demonstrated that household dust stimulates eosinophils to overproduce hydrogen peroxide (119). Ozone also sensitizes airway mucosa to allergens. Ozone facilitates allergen penetration and intensifies disease symptoms (120–122). In turn, NO_2 exerts negative effects by increasing the prevalence of both AR and bronchial asthma. This relationship was reported by Italian researchers who observed that increased NO_2 concentration in combination with high temperature increases the prevalence of allergies (123). Diesel exhaust particles (DEP) also exert harmful effects and significantly contribute to risk of inhalant allergies in children and adults by exacerbating oxidative stress and the resulting inflammations (124). The adjuvant effect of DEP on IgE synthesis induces hypersensitivity to inhalant allergens (125). There is evidence to suggest that DEP increase Th2-mediated immune responses and promote allergic reactions (126). Allergic responses to cigarette smoke may be triggered by the same mechanism. Inhaled elemental carbon ultrafine particles activate the NF-KB signaling pathway, which augments allergen-induced lung inflammation and airway hyperresponsiveness (127). Cigarette smoke also contributes to mitochondrial DNA mutations, which increases ROS production and exacerbates neutrophilic airway inflammation (128). Diesel exhaust particles (DEPs) can also adsorb airborne allergens released by pollen, thus intensifying IgE-mediated immune responses (129). Porębski et al. (130) observed that the prevalence of inhalant allergies was higher in children residing in the immediate vicinity of major road networks.

Redox homeostasis in AR patients has been investigated by very few studies to date (Table 1). However, it is believed that oxidative and nitrosative stress in AR is associated with chronic upper and lower airway inflammation (131, 132). Aksoy et al. reported higher concentrations of protein oxidation products in AR patients (133), whereas Hang et al. and Sato (134, 135) observed an increase in 3-nitrotyrosine levels (a product of tyrosine nitration) in severe allergic reactions. Other studies revealed that lipid peroxidation products, mainly MDA, are effective biomarkers of inflammation in the progression of AR (136). Carbon monoxide (CO) levels in exhaled breath condensate were also higher in AR patients (137, 138). Most importantly, these findings indicate that protein and lipid oxidation products can be used as potential diagnostic markers in AR (139).

Skin allergies

Atopic dermatitis and oxidative stress

Atopic dermatitis is a chronic recurrent skin disease associated with elevated IgE levels, sensitization to common food and inhalant allergens, and skin barrier defects (3). Patients with AD are strongly predisposed to IgE-mediated sensitivity to exogenous and endogenous antigens in both type I and IV hypersensitivity reactions (140). In this disease, CD4 T cells differentiate mainly into Th2 cells, whereas Th1 proliferation is inhibited (141). In AD patients, the imbalance in T cell populations weakens the local immune response to bacterial and viral infections, increases skin colonization by pathogenic microorganisms, and decreases late-phase hypersensitivity (142). Increased Th2 activity enhances cytokine production, in particular IL-4, IL-5, and IL-13, and decreases IFN- γ synthesis (143). In addition to elevated Th2 levels in peripheral blood and skin, immune cells were also activated by an increase in the number of specific surface receptors (142). In AD, cytokines overproduce IgE and contribute to allergic inflammation (3). The production of ROS and RNS also increases, which enhances cytokine and chemokine secretion (140). IgE-mediated antigen presentation plays an important role in the pathogenesis of atopy despite the fact that serum IgE levels in AD patients are frequently uncorrelated with the severity of disease symptoms (144). IgE receptors are present in many immune cells, and their expression is higher in AD patients than in healthy subjects. These receptors increase the antigen-presenting capacity of Langerhans cells hundreds or even thousands of times. IgE-specific receptors are also found in T and B cells, monocytes, macrophages, eosinophils, and blood platelets (145). For this reason, IgE-mediated reactions are triggered by various mechanisms (140). Elevated IgE antibody levels were noted in around of 80% AD patients, and IgE specific for common inhalant and food allergens were also detected in most patients (144). Inhalant and food allergens easily penetrate mucous membranes, enter the blood stream, and cause skin lesions (146). Skin barrier dysfunction is observed in AD patients, and allergens can easily reach deeper skin layers to stimulate sensitized memory cells via antigen-presenting cells (APCs) (3, 147). Circulating IgE autoantibodies against self-proteins have been identified in most AD patients. The presence of IgE autoantibodies can partly explain the chronic and recurrent character of AD, as well as problems with identifying allergens that cause skin lesions (144). A polyclonal response to superantigen-producing bacteria and fungi that often colonize the skin has been also observed in AD patients. These superantigens do not have to be stimulated by Langerhans cells, and they can activate many lymphocytes via non-specific receptors (3).

Briganti et al. (148) reported dense lymphocytic, monocytic, and eosinophilic infiltrates in skin bioptates of AD patients. These cells generate large amounts of $O_2^{\bullet-}$ and NO• which damage skin cells. The skin acts as a physical barrier between the internal and the external environment. It protects the body against UV radiation, mechanical damage, xenobiotics, and microorganisms, and it is highly susceptible to oxidative damage (149). The concentrations of

lipid peroxidation products (acrolein-lysine adducts) are thus higher in AD patients (150). Isoprostanes are also robust indicators of oxidative stress. Increased 8-isoprostane levels in various biological materials (plasma, BAL fluids, exhaled breath condensate, urine) are indicative of intensified lipid peroxidation in AD patients (150). Exhaled CO levels were also found to be higher in AD patients than in healthy controls (151). Overproduction of ROS can also lead to DNA damage. Tsuboi et al. (152) reported an increase in daily urine levels of 8-hydroxy-2'-doxyguanosine (8-OHdG, a marker of DNA damage) in AD patients, which points to oxidative stress. Nucleic acids are least susceptible to oxidative damage because they feature highly effective repair mechanisms and are localized inside cells (153).

In skin allergies, oxidative stress can be intensified by the weakening of endogenous antioxidant defense mechanisms (Table 1). Vitamin C and E concentrations are lower in AD patients, which further promotes OH generation and lipid peroxidation (154, 155). Research has shown that N-acetyl-L-cysteine (NAC) and GSH strongly inhibit IL-4 production by Th2 cells and exert a minor inhibitory effect on IL-5 and INF synthesis, which indicates that these compounds are useful in the treatment of Th2-associated diseases, including AD (156–158).

Atopic dermatitis and nitrosative stress

The role of RNS in the pathogenesis of skin allergies has been examined less extensively than in bronchial asthma (62). Nakai et al. (25) indicate that nitrate concentrations were significantly higher in the urine of AD patients and correlated with disease progression. Indeed, the Eczema Area and Severity Index (EASI) score was significantly correlated with urinary nitrate ($r = 0.647$, $P = 0.03$). The researchers request that nitrates may be a valuable biomarker of nitrosative stress in AD patients. In another study (159), Kubo et al. investigated the contribution of NO to the growth of skin lesions in an animal model for AD. The expression of iNOS was increased, while the nNOS expression was decreased in the epidermal skin lesions. Moreover, the immunohistochemical localization of nitrotyrosine was noticed in nearly eosinophils. It is therefore suggested that RNS generation in eosinophils may be connected with AD's pathogenesis. Further research is needed to clarify the contribution of nitrosative stress to skin allergies.

Urticaria and oxidative stress

Allergic urticaria is one of the most common skin diseases that affects 15-20% of the global population (3). Urticaria is a heterogeneous group of skin disorders provoked by various exogenous and endogenous factors. The disease is caused by the release of inflammatory mediators from mast cells during an immune response involving specific IgE, as well as food, inhalant, and contact allergens (160). The main inflammatory mediator is histamine, responsible for the sudden outbreak of swollen bumps or plaques on the skin (161), and a similar role is played by PGD2. In turn, the late-phase allergic response is triggered by leukotriene B4 (LTB4), neutrophil chemotactic factor (NCF), eosinophil chemotactic factor of anaphylaxis (ECF-A), and PAF. The late-phase response involves neutrophils and eosinophils, followed by macrophages and lymphocytes. Mast cell serine proteases, tryptase, chymase, and carboxypeptidase, further contribute to mast cell degranulation (161). The Hageman factor and complement and kinin systems are activated, which leads to collagen degradation and increases the permeability of cutaneous vessels (162). These processes contribute to ROS and RNS overproduction and oxidative stress which intensifies cytokine secretion in keratinocytes (163). Keratinocytes produce numerous inflammatory cytokines, including IL-1, IL-3, IL-6, IL-8, GM-CSF, and TNF-α. Keratinocytes interact with immune cells recruited to the site of inflammation and increase the expression of adhesion molecules, which enables immune cells to adhere to the vascular endothelium (3).

According to the literature, oxidative and nitrosative stress plays a role in the progression of chronic spontaneous urticaria (CSU) (Table 1) (164, 165). In CSU patients, skin lesion biopsies revealed higher activity of macrophages and basophils which are responsible for ROS and RNS overproduction (166). Oxidative stress markers, including MDA, were significantly elevated and correlated with reduced synthesis of GSH, the most important skin antioxidant (164). Nettis et al. (167) examined advanced oxidation protein products (AOPPs) and AGEs and found that plasma AOPP levels were considerably higher in urticaria patients than in the control group. However, no significant changes in AGE concentration were observed, which suggests that proteins are intensively oxidized, but not glycated in urticaria (166). During oxidative stress, ROS directly interact with amino acid side chains (mainly lysine, arginine, proline, and threonine), or peptide bonds in the polypeptide chain are broken and carbonyl groups are formed inside the polypeptide structure (168). AOPPs are the end products of these processes. ROS also interact with unsaturated fatty acids in phospholipids, and aldehydes such as 4-hydroxynonenal, 4-hydroxyhexanal, acrolein, and MDA are the most reactive compounds (87). These compounds can interact with the amino acid residues of proteins, mainly histidine, cysteine, and lysine, to form carbonyl derivatives known as advanced lipoxidation end-products (ALEs) (169). The accumulation of glucose and its metabolites in cells, for example in diabetes patients, enables this monosaccharide to interact with amino acid residues, which leads to the production of AGEs (168). In urticaria, redox imbalance can be caused by dysfunction of the enzymatic and non-enzymatic antioxidant barrier. A decrease in the levels and activity of antioxidants, including vitamin E, GSH, CAT, and GPx, were indeed noted in urticaria patients (170). However, elevated SOD activity was observed in some patients (171), which points to an adaptive response to ROS overproduction. SOD is the main antioxidant enzyme that eliminates the first product of one-electron reduction of molecular oxygen ($O_2^{\bullet-}$). In a dismutation reaction, SOD converts $O_2^{\bullet-}$ to hydrogen peroxide which is then removed by CAT, GPx, and metallothioneins. Therefore, SOD is regarded as the first line of defense against the toxic effects of ROS (172). An increase in SOD activity points to an adaptive response in urticaria patients, but the reserves of other antioxidants that

scavenge ROS can become depleted as the diseases progresses. Further research is needed to examine these processes (164).

Urticaria and nitrosative stress

Dilek et al. (27) examined the possible role of nitrosative stress in urticaria progression. They reported higher plasma levels of NOx metabolites (nitrates and nitrites) in 22 children with chronic spontaneous urticaria. They also found a positive correlation between NOx metabolites and disease progression measured by urticaria activity score (UAS) (27). Further research is needed to clarify the effects of nitrosative stress in urticaria.

Food allergies

Pathogenesis of food allergies

A food allergy is an immune response in persons who are highly sensitized to substances that occur naturally in food products (3). These individuals produce IgE antibodies against food ingredients that are well tolerated by the general population (173). IgE-mediated food allergies have numerous symptoms, including systemic reactions (anaphylaxis), acute or chronic skin symptoms (urticaria, AD, angioedema), respiratory symptoms (asthma, rhinitis, laryngitis, ear inflammation), and gastrointestinal symptoms (abdominal pain, nausea, diarrhea, bloating, loss of appetite, vomiting) (174). Neurological symptoms such as headaches and sleep disorders can be also associated with food allergies (175). Symptoms can manifest already several minutes after allergen ingestion, or after several hours or days in late-phase reactions (164).

Gut-associated lymphoid tissue (GALT), which is a component of mucosa-associated lymphoid tissue (MALT), i.e. the mucosal immune system, plays a key role in food allergies (176). Foodborne allergens are transported by M cells from the intestinal lumen to lymphatic tissue beneath the epithelium (177). A food tolerance response or a food allergy (food intolerance) can occur at this stage (3). Allergens transported across the surface of mucous membranes are captured by APCs which engulf and process antigens and present them to T cells. Antigens are bound by class II major histocompatibility complex (MHC) proteins on the surface of APCs (178). Cytokine signaling and the interactions between adhesion molecules and receptors on APCs (ICAM-1, LFA-3) and lymphocytes (LFA-1, CD-2) play a key role in this process. Activated Th0 cells give rise to Th1 and Th2 cell subpopulations (173). Th1 cells can produce interferon- γ (IFN- γ) which inhibits the proliferation and activity of Th2 cells. Th1 cells differentiate from Th0 cells in the presence of IL-12 which is produced manly by mast cells and APCs, i.e. macrophages and DCs (IL-12 is not produced by B cells). The above leads to the overproduction of ROS and RNS, and it intensifies cytokine and chemokine secretion via a positive feedback loop (174). Th1 cells promote the delayed cell-mediated immune response, but they can also stimulate B cells to produce antibodies when their ratio is appropriate. The generation of Th2 cells is stimulated by IL-4 which is secreted by antigen-stimulated Th2 cells, but also by mast cells and basophils (176). Th2 cells produce IL-4, IL-10, and IL-13, which inhibit Th1 differentiation and sustain and enhance the humoral immune response (immediate response). Under the influence of IL-4 and IL-13 and the interactions between adhesion molecules on B cells (class II MHC molecules: CD80/CD86, CD40, and ICAM-1) and T cells (CD3, CD4, CD28, CD40L, and LFA-1 receptors), B cells switch from expressing IgM, IgG2, and IgG3 to IgG4 and IgE (179). This mechanism is responsible for the production of antigen-specific IgE (Figure 1) (180). Stimulated B and T cells can migrate to the blood (IgE and the allergen are distributed throughout the body with bodily fluids), and they are transported back to mucous membranes and the associated lymphatic structures (mainly GALT) where the allergen was first encountered. This mechanism is responsible for allergic reactions not only in the gastrointestinal tract, but also in distant organs such as the skin or lungs (173).

An allergen that binds to at least two IgE antibodies reaches a sensitized mast cell and leads to its degranulation via an antigen bridge. Other activators can also participate in mast cell degranulation. For example, strawberries contain lectins that cross-link adjacent IgE molecules and provoke urticaria symptoms in some consumers, in particular children (181). Mast cell degranulation leads to the release and *de novo* synthesis of many mediators, including ROS. These substances can be also produced by basophils, eosinophils, and macrophages under the influence of cytokines secreted by Th2 (IL-3, IL-4, IL-5, IL-13, GM-CSF) (182, 183). The resulting mediators and enzymes, such as leukotrienes, prostaglandins, histamine, tryptase, kininogenase, chymase, and toxic basic proteins (MBP; ECP; eosinophil peroxidase, EPO; eosinophil-derived neurotoxin, EDN), are responsible for allergic reactions, including anaphylaxis (180). Increased EPO activity in food allergies deserves special attention. This enzyme catalyzes the reaction between H_2O_2 and halide ions which leads to the production of periodic acid with strong pro-oxidant effects. Similarly to OH, periodic acid damages proteins in intestinal villi and induces cell lysis (184). Mutual interactions between mast cells, basophils, eosinophils, and macrophages, and the secreted mediators (cytokines, chemokines, enzymes, and ROS) can damage the epithelium of intestinal villi (185). ROS exert cytotoxic effects, mainly by promoting rapid peroxidation of membrane lipids (186). Lipids are cell components that are most susceptible to oxidative modifications. Lipid oxidation products (in particular aldehydes such as MDA) can modify the biophysical properties of cell membranes. These compounds increase cell permeability and inhibit the activity of selected membrane enzymes/transport proteins, but they can also induce COX-2 expression in macrophages (87).

The maillard reaction and food allergies

Allergens occur naturally in food products. The most common food allergens are cow's milk, egg, and wheat proteins, fish, seafood, nuts, tomatoes, celery, spices, and food additives (such as colorants, flavor enhancers, and preservatives). These compounds can be also

produced during thermal processing which not only causes structural changes in food components, but also affects interactions with other proteins, lipids, and carbohydrates (180). Numerous studies have shown that the Maillard reaction is responsible for the immunogenicity and allergenicity of food proteins (187–189). The Maillard reaction involves many chemical processes that are initiated by direct interactions between a carboxyl or hemiacetal group in a reducing sugar and an amine group in an amino acid or a peptide. The Maillard reaction leads to the formation of AGEs, and the role of oxidative and carbonyl stress in the pathogenesis of food allergies has been investigated worldwide (180).

Most food allergies are IgE-dependent (185). IgE recognizes specific structure of epitopes in the structured regions of allergenic proteins (190). Numerous studies had been undertaken to determine whether glycation of food allergens during the Maillard reaction modifies IgE reactivity and leads to the formation of new IgE epitopes (191). The results are presented in Table 2. It was found that the Maillard reaction can prevent IgE from binding to food allergens (192). Some individuals are allergic only to stored or cooked foods (such as processed fish and peanuts), but not to raw foods. Thermal processing induces changes in the structure of allergenic proteins (193). Food proteins are denatured under exposure to high temperatures, whereas protein refolding, oligomerization, and aggregation are observed at low temperatures. As a result, IgE reactivity may be enhanced in some allergens because some IgE epitopes become more exposed through heat treatment (185). Glycation could be the main factor that decreases the affinity and/or availability of allergens for specific IgE antibodies by modifying the electric charge, hydrophobicity, and/or structure of protein molecules. However, heat treatment can also alter the allergenicity of food proteins. An *in vitro* study demonstrated that glycation can mask IgE proteins and decrease their availability for specific IgE antibodies, which decreases a protein's allergenicity (193). Therefore, the Maillard reaction can be helpful in reducing the allergenic potential of some thermally processed food products (194).

Recent research suggests that Maillard reaction products affect APCs (in particular macrophages and DCs) and disrupt T cell responses under exposure to an allergen. DCs express several receptors for AGEs (RAGE) (195), including galectin-3 (28), type I and II class A macrophage scavenging receptors (SR-A), type I class B scavenger receptor (SR-B), and CD36 (196). An *in vitro* study revealed that AGEs binding to RAGE on macrophages and microglia promote oxidative stress by activating NF-KB, and MAPK, c-Jun N-terminal kinase (JNK), and p21RAS signaling pathways (197). NF-KB is sensitive to ROS, and it modulates the transcription of genes encoding endothelin-1, tissue factor, and thrombomodulin (198). The above increases the production of pro-inflammatory cytokines, chemokines, and growth factors (187, 199, 200). The involvement of AGEs in food allergies is further evidenced by the fact that AGEs induce DC maturation, thus stimulating T cell responses directed against allergens (201). However, AGEs were found to both stimulate (202) and inhibit (203) APC maturation. In a study by Ge et al., AGEs of bovine serum albumin (AGE-BSA) stimulated the maturation of human DCs and increased their ability to activate T cells (204). In turn, Price et al. reported that AGEs of the adrenocorticotropic hormone (ACTH) inhibited the maturation of human DCs (201). These apparent discrepancies could be attributed to differences in the expression of AGE receptors on the surface of various cell types. In addition, glycated food allergens can increase the immunogenicity of T cells and decrease the threshold doses of food allergens that produce an adverse reaction (202). However, further research is needed to expand our knowledge about the glycation of structures that bind to different AGE receptors and the impact of AGE on DC maturation (205).

Antioxidant therapies for allergic diseases

As previously demonstrated, enzymatic and non-enzymatic antioxidant systems are impaired in asthma, AR, AD and urticaria, which increases cell susceptibility to oxidative damage (59, 145, 171, 206). The antioxidant barrier consists of antioxidant enzymes, free radical scavengers, and preventive antioxidants (10). Antioxidants significantly decrease ROS generation, and antioxidant supplements may be effective in allergy treatment. Antioxidant vitamins (A, C, D, E) and minerals ions (iron, zinc, selenium) are also known to suppress inflammation (207, 208). Vitamin A is essential for the maturation and differentiation of lymphocytes, monocytes, neutrophils, and eosinophils. Vitamin C increases the absorption and mobilisation of non-heme iron, which is essential for the proper functioning of the immune system. Due to its reducing properties, vitamin C protects neutrophils, lymphocytes and macrophages from ROS overproduction. It also participates in the energy metabolism of the cell (209). Vitamin D has strong immunomodulatory properties. The active form of vitamin D (calcitriol) stimulates the innate response (i.e. chemotactic and phagocytotic properties), but also the production of antimicrobial peptides, i.e. cathelicidins (210). Vitamin D deficiency is associated with numerous autoimmune, infectious and cancerous diseases (211). The action of vitamin E includes scavenging of organic radicals and terminating lipid peroxidation in biological membranes. Vitamin E attenuates the synthesis of prostaglandin E2 (PGE2), thereby regulating the balance between Th1 and Th2 lymphocytes in favour of Th2 cells (209). Anti-inflammantory and antioxidant effects of vitamin A (212, 213), C (214, 215), D (216, 217) and E (213) also involve inhibition of NF-kB as well as activation of *Nrf-2* signaling pathways involved in cellular antioxidant response (218, 219). Polyunsaturated fatty acids (PUFAs) also have antioxidant and anti-inflammatory properties. PUFAs of the n-3 and n-6 series cannot be synthesised by humans and must be supplied in the diet. These include α-linolenic acid (C 18:3), which is a precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and linoleic acid (C 18:2), the precursor of arachidonic acid (AA) (220, 221). Also intake a flavonoids/polyphenols as antioxidants to decrease ROS generation [(218, 219)].

The role of vitamin D in the treatment of allergic diseases has not been fully elucidated (Table 3) (222). However, recent research suggests that vitamin D deficiency could be linked with the

TABLE 2 The influence of protein glycation on IgE reactivity.

Allergen(s)	Sugar	Treatment	Influence of glycation on IgE reactivity and/or mediator release capacity of allergen	Reference
Peanut (allergens)				
Ara h 1	Glucose	heating, 15 min, 100°C	↓IgE reactivity and mediator release capacity in response to heating	Blanc F (273). (2011)
Ara h 1	Glucose	incubation, 20 min, 145°C	↓ IgE reactivity and enhanced mediator release capacity in response to heating. Significant ↓ in IgE reactivity in response to glycation	Vissers Y (274). (2011)
Ara h 1	Glucose	heating, 60 min, 100°C	Enhanced IgE reactivities of Ara h 1 and Ara h 2 in response to incubation with selected sugars	Maleki S (275). (2000)
Ara h 2	Maltose Mannose Xylose		Enhanced IgE reactivities of Ara h 1 and Ara h 2 in response to incubation with selected sugars	
Ara h 2	Glucose Fructose Maltose Ribose	heating, 100 min, 90°C	Enhanced IgE reactivity in response to incubation with ribose	Gruber P (276). (2005)
Ara h 2/6	Glucose	heating, 15 min, 110°C	↓ IgE reactivity and mediator release capacity in response to heating	Vissers Y (277). (2011)
Ara h 2/6	Glucose	incubation, 20 min, 145°C	↓ IgE reactivity and mediator release capacity in response to heating	Vissers Y (274). (2011)
Hazelnuts (allergens)				
Cor a 11	Glucose	incubation, 20 min, 145°C	↓IgE reactivity and enhanced mediator release capacity in response to heating. Glycation promoted the reduction of IgE reactivity and counteracted enhanced mediator release capacity in response to heating	Iwan M (278). (2011)
Cherry (allergens)				
Pru av 1	Glucose Fructose Maltose Ribose	heating, 30-90 min, 100°C	↓ IgE reactivity in response to incubation with ribose for 90 min	Gruber P (279). (2005)
Apples (allergens)				
Mal d 3	Glucose	boiling, 20 min at 100°C or 120 min at 90°C	↓ IgE reactivity and mediator release capacity in response to boiling at 100° C for 2 h. Glycation counteracted the boiling effect.	Sancho A (280). (2005)
Shellfish (allergens)				
Tropomyosin	Glucose Maltotriose Maltose Ribose	Incubation: 60°C for 30 min – 48 h; 60°C for 12 h-15 days; 60°C for 5-180 min	↑ IgE reactivity in response to incubation with glucose	Nakamura A (281). (2005)
Squid (allergens)				
Tropomyosin	Ribose	incubation, 180 min, 60°C	↓IgE reactivity	Nakamura A (282). (2006)
Eggs (allergens)				
Ovomucoid	Glucose	incubation, 96h, 50°C	↓IgE reactivity	Jiménez-Saiz R (283). (2011)
Milk (allergens)				
β-Lactoglobulin	Galactose Glucose Lactose Rhamnose Ribose Arabinose	heating, 72h, 60°C	↓IgE reactivity	Taheri-Kafrani A (284). (2009)

↓ means "decresed".

induction and severity of allergic asthma (223). A negative correlation was noted between serum vitamin D levels and the prevalence of bronchial asthma (224, 225). Vitamin D is an antioxidant that decreases ROS generation (222). This compound modulates macrophage and DC functions, induces CD4+ and CD25+ T cells, and stimulates the development of Th2 cells. Vitamin D also increases the number of Treg cells that inhibit allergic skin reactions, and it exerts anti-inflammatory effects by limiting the overproduction of TNF-α (226). This compound also induces the expression of thymic stromal lymphopoietin (TSLP) which participates in the induction of an AD-like phenotype (227). However, despite low vitamin D levels in asthma patients, hypovitaminosis D has not been linked with a higher risk or increased severity of asthma (228). There is no evidence to

TABLE 3 Antioxidants and their supplementation in allergic diseases.

Study group	Control group	Methods	Endpoints	Reference
Vitamin D				
80 asthmatic patients (aged 18-50)	80 healthy subjects (aged 18-50)	25-hydroxyvitamin D3 (ELISA)	No correlations between 25-hydroxyvitamin D3 levels and asthma severity	Deveruex (2010) (224)
989 children aged 6 (M/F - 554/435) and and 1380 children aged 14 - (M/F - 714/666)	No control group	25-hydroxyvitamin D3 (ELISA)	Vitamin D deficiency increases the risk of atopy, bronchial hyperresponsiveness (BHR), and asthma.	Hollams (2011) (225)
85 asthmatic patients aged 45-48 (M/F - 26/59)	73 healthy subjects aged 40-44 (M/F - 37/36)	25-hydroxyvitamin D3 (ELISA)	Vitamin D levels were lower in asthmatic patients than in the control group	Tamašauskienė (2015) (211)
30 patients with moderate asthma (vitamin D supplementation 60,000 IU/week)	30 patients with moderate asthma (without vitamin D supplementation)	25-hydroxyvitamin D3, pulmonary function tests (spirometry)	Vitamin D supplementation failed to improve lung function in adults with moderate asthma administered inhaled corticosteroids	Sharma (2017) (229)
Vitamin A				
35 asthmatic children aged 2-12 (M/F - 24/11)	29 asthmatic children aged 2-12 (M/F - 19/10)	vitamin A (HPLC)	Vitamin A levels were significantly lower in children with asthma than in controls ($p<0.0001$).	Arora (2002) (235)
Vitamin C				
18737 children aged 6-7		Standardized respiratory questionnaires	Consumption of fruit rich in vitamin C, even at low intake levels, may reduce wheezing in children with asthma	Forastiere (2002) (234)
62 children with AD aged 1-13 (M/F - 33/29) (individual intake was calculated)		vitamin C (HPLC)	vitamin C helps improve chronic inflammation and positively influences AD	Lim (2013) (233)
280,041 children born to pregnant smokers (vitamin C - 500 mg/day)	260,429 children born to pregnant smokers (vitamin C - 60 mg/day)	Analysis of asthma prevalence between birth and the age of 18 years	Vitamin C supplementation in pregnant smokers is a safe and inexpensive intervention that may reduce the economic burden of pediatric asthma	Yieh (2018) (285)
71 patients aged 28-60 (ascorbate 7.5 g/ 50 ml/day)		observational study	Intravenous high-dose vitamin C treatment reduces allergy-related symptoms	Vollbracht (2018) (286)
30 patients with chronic asthma (vitamin C - 1000 mg/day)	30 patients with chronic asthma (placebo)	standard pulmonary function test (PFT)	In group A (vitamin C - 1000 mg/day), spirometry parameters did not change after one month of treatment, indicating that vitamin C treatment had no effect on spirometry parameters.	Nadi (2012) (269)
Selenium				
25 patients with asthma aged 28-42 (M/F - 9/17)	25 healthy subjects aged 28-48 (M/F-9-16)	Selenium (spectrophotometry)	Abnormal distribution of Se may aggravate oxidative damage and inflammation, increase CD4/CD8 lymphocyte ratios, and decrease lung function in asthma	Chih-Hung Guo (2011) (39)
54 subjects with asthma aged 15-33		nutritional questionnaire	Increased Se intake in patients with asthma	Daniel Antonio de Luis (2003) (90)
46 patients with asthma aged 28-69 (M/F - 29/17)	75 healthy donors aged 45-59 (M/F - 9/17) (	Selenium (spectrophotometry)	Serum Se levels are significantly lower in asthmatic patients	Durdi Qujeq (2003) (248)
42 asthmatic children aged 2-13 (M/F - 24/20)	30 healthy children aged 2-14 (M/F - 19/13)	Selenium (spectrophotometry)	Decreased Se levels increase asthma risk	Kocyigit (2004) (287)

(Continued)

TABLE 3 Continued

Study group	Control group	Methods	Endpoints	Reference
PUFAs				
166 children with asthma	169 healthy children	Questionnaires on dietary intake of n-3 and n-6 PUFAs	Foods rich in n-3 PUFAs and low in n-6 PUFAs deliver modulatory effects and protect children against asthma	Oddy (2004) (259)
Children of mothers with a family history of asthma receiving omega-3 supplements (500 mg/day)	Children of mothers without a family history of asthma receiving n-3 PUFA- supplements	n-3 PUFA levels	High plasma levels of n-3 PUFAs had no effect on the prevalence of diagnosed asthma or atopy	Mihrshahi (2004) (262)
393 children aged 18 months, 400 children aged 3 years, and 396 children aged 5 years (500 mg/day)		Plasma levels of n-3 and n-6 PUFAs (gas chromatography)	Plasma levels of fatty acids, dietary intake, and supplementation were not associated with any respiratory or allergic outcomes	Almqvist (2007) (261)
368 pregnant women administered 2.4 g of n-3 LCPUFA/day	368 pregnant women (placebo)	cohort study	Less persistent wheezing/asthma between the ages of 3 to 5 years	Bisgaard (2016) (265)
266 pregnant women administered 2.7 g of n-3 PUFAs/day)	136 pregnant women administered capsules with olive oil and 136 pregnant women not administered olive oil capsules	cohort study	Assuming that the administered dose of olive oil was inert, increased intake of n-3 PUFAs in late pregnancy may prevent asthma in the offspring	Olsen (2008) (266)

ELISA, enzyme-linked immunosorbent assay; HPLC, high-performance liquid chromatography; PFT, pulmonary function test; PUFAs, polyunsaturated fatty acids.

indicate that vitamin D is effective in preventing asthma or the associated complications. One study demonstrated that vitamin D deficiency plays a key role in asthma induction and that vitamin D supplements are effective in preventing or alleviating asthma symptoms (211). In another study, vitamin D supplements did not improve asthma symptoms in patients undergoing conventional therapy (229). Individual responses to vitamin D supplementation may vary, and they are determined by many factors, including baseline blood levels of vitamin D and the patient's age. Vitamin D supplementation may be particularly effective in individuals with hypovitaminosis D. The analyzed studies investigated different vitamin D doses and supplementation periods, which could have affected the results (228). However, it should be remembered that the main source of vitamin D in the body is sun exposure, and only a small amount is carried through the diet (230).

Vitamin C is a potent antioxidant. Vitamin C can donate two electrons, and it functions as a cofactor in many enzymatic reactions and participates in the regeneration of other antioxidants (231, 232). Lim et al. found that vitamin C supplementation reduced the severity of AD symptoms in children (233). Research conducted on AD and asthma patients revealed that foods rich in vitamins C and A reduce the risk of these diseases (234, 235). Interestingly, Rosenluld et al. (236) observed an inverse association between β-carotene intake and rhinitis in a study of 246 children. It was shown that vitamin C and vitamin A have immunomodulatory properties that promote a balanced immune response, reduce the production of pro-inflammatory mediators and inhibit allergic reactions (237). Importantly, vitamin A is one of the few antioxidants with the ability to remove singlet oxygen and organic lipid peroxides (238).

Selenium is an essential micronutrient very important for various aspects of human health (239). Adequate selenium levels are crucial for initiating and regulating the immune response and inhibiting chronic inflammation (240, 241). Dietary selenium, mainly through incorporation into selenoproteins (242, 243), can influence various leukocyte functions such as adhesion, migration, phagocytosis and cytokine secretion. Members of the selenoprotein family regulate or are regulated by cellular redox balance. The link between selenoproteins and Ca^{2+} flux is especially important. This compound regulates the oxidative burst that is required for optimal immune cell activation (244, 245). What is more selenium significantly influences the activation, proliferation, and differentiation of T cells during the initiation of immune response (242). In a study of mice fed diets with a low, moderate, and high content of selenium, CD4+ T cells differed in the expression of T-cell receptors (TCRs). High selenium intake enhanced T cell proliferation and promoted the differentiation of $CD4^+$ T cells into Th1 (246). Moreover, selenium is a component of the active center of GPx, one of the key enzymes that reduce hydrogen peroxide in cells (242). Allergies are mediated by oxidative stress, which is why dietary selenium can play an important role in the pathogenesis of these diseases. By inhibiting GPx activity, selenium deficiency can contribute to inflammation in asthma (247). According to some researchers, selenium intake is associated with the prevalence and progression of asthma (90, 248). Selenium supplementation considerably increased selenium levels and GPx activity in the blood and significantly improved the quality of patients' life, but it had no effect on the clinical parameters of lung function or airway hyperreactivity (246, 247). However, respiratory function was found to be impaired in asthma patients characterized by lower selenium levels than control group subjects (39). There is evidence to suggest

that selenium supplementation may be helpful in standard therapy of chronic asthma. Selenium supplements may reduce glucocorticoid consumption in asthma patients (246, 249). A study conducted on an animal model revealed that similarly to vitamin D, the benefits of selenium supplementation are largely influenced by baseline selenium concentration (250). The above could be attributed to baseline T cell differentiation status, which is partly influenced by selenium (247). These results seem to confirm previous observations that selenium intake is not linked with allergic airway inflammation (246). There is no compelling evidence to indicate that dietary selenium is helpful in reducing allergic asthma (250). However, due to its antioxidant and anti-inflammatory properties, selenium can boost resistance to infections, and it may be administered as adjunct therapy in allergies (247). Studies showed that vitamins C and E promote selenium absorption. Higher serum levels of selenium have been associated with decreased prevalence of asthma (251) and increased lung function (252).

Magnesium supplementation may also be helpful in the treatment of allergic diseases. Rosenluld et al. (236) in a study of 246 children observed that magnesium intake was inversely associated with asthma and atopic sensitisation. Magnesium has been shown to stimulate complement activation and phagocytosis reducing the formation of pro-inflammatory interleukins or ROS (253). However, the exact role of magnesium in alleviating asthma complications remains unknown and requires further research.

n-3 PUFAs also modulate cellular redox homeostasis and influence the progression of allergic reactions. They have been shown to inhibit the production of IL-1, 2 and 6 and the phosphorylation of IkB kinase (IkappaB) (254), and thus the NF-kB signalling pathway. In addition, n-3 PUFAs regulate the synthesis of leukotrienes, prostaglandins and thromboxanes. As a result, n-3 PUFAs may deliver protective effects in inflammatory diseases, including asthma (255). Studies have shown that consumption of oily fish (256, 257) and n-3 PUFA supplementation reduce the incidence of asthma in children (258). In turn, high consumption of n-6 PUFAs has been linked with increased prevalence of allergies in children (259), but this observation was not confirmed by other studies (260–262). There is no conclusive evidence to indicate that n-3 PUFAs exert positive effects and n-6 PUFAs exert negative effects or that the dietary n-6:n-3 PUFA ratio influences the prevalence of asthma in adults (258). However, the moment when patients start taking supplemental n-3 PUFAs is important. Numerous studies have demonstrated that maternal nutrition affects infant health and predisposition to allergic diseases not only in childhood, but also in adulthood (263–267).

Research findings suggest that dietary antioxidants and modulators of redox homeostasis, including vitamins C and D, selenium, and n-3 PUFAs, are modifiable risk factors in the development of allergic diseases, although further clinical trials are needed to confirm this hypothesis (Table 3) (268). These compounds can be administered as adjuvant therapy to improve clinical outcomes in allergy patients (261, 269). However, there is no compelling evidence to indicate that antioxidants reduce the severity of allergy symptoms or slow down disease progression. These discrepancies can be attributed to differences in the patients' dietary habits, comorbidities, antioxidant doses, and duration of therapy. In addition, recent studies indicate that some drugs routinely used in the treatment of allergies (H1 receptor antagonists) have additional anti-glycooxidant and anti-inflammatory effects, which may offset allergy complications caused by oxidative and carbonyl stress (270). Further research on the use of H1 blockers and antioxidants in the treatment of allergic diseases is needed.

Conclusions

There is some evidence to indicate that oxidative and nitrosative stress is involved in the pathogenesis of asthma, AR, AD and urticaria. Inflammatory cells produce much larger quantities of ROS/RNS in allergic patients than in healthy subjects. Exposure to both inhalant allergens (ultrafine carbon particles, DEPs, cigarette smoke, pollen) and food allergens leads to ROS overproduction. Although the exact molecular mechanisms are not known, ROS and RNS play an important role in respiratory and skin allergies. ROS exacerbate the severity of asthma symptoms by activating inflammatory mediators that cause airway smooth muscle contraction, promote mucus hypersecretion, increase the permeability of lung capillaries, and damage cell membranes. Enzymatic and non-enzymatic antioxidant systems are impaired in allergic conditions, which increases cell susceptibility to oxidative damage. Although even low doses of antioxidants can prevent or delay the oxidation of proteins, lipids and nucleic acids, there is no convincing evidence to suggest that antioxidants reduce the severity of allergy symptoms or slow the progression of the disease. However, antioxidants and modulators of redox homeostasis could be modifiable risk factors in the onset and progression of allergies. Therefore, further basic and clinical research is needed to elucidate the role of oxidative stress in allergic diseases.

Author contributions

GB: Conceptualization, Data curation, Resources, Writing – original draft, Writing – review & editing. BW-B: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. JD: Data curation, Formal analysis, Writing – review & editing. MM: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

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Conflict of interest

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