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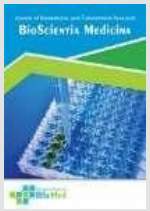

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The Role of Oxidative Stress in Atopic Dermatitis

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A B S T R A C T

Atopic dermatitis (AD) is a chronic skin inflammation found in children with a varied course caused by external and internal factors. The incidence of AD in industrialized countries is 10-20% in children and 1-3% in adults. The main etiopathogenesis of AD is genetic and skin barrier disorders, immunologic disorders, and environment. Oxidative stress (SO) is the accumulation of reactive oxygen species (ROS) that exceeds the defense capacity of the body's antioxidant system. Uncontrolled ROS production plays a major role in various skin diseases. Oxidative stress can damage the deoxyribonucleic acid (DNA) of keratinocytes through lipid oxidation, as well as disrupt skin barrier function, increase the production of proinflammatory cytokines and worsen AD lesions. The main objectives of this literature review are to determine the role of oxidative stress in AD and antioxidants as adjunctive therapy.

1. Introduction

Atopic dermatitis (AD) is a chronic and recurrent skin disease, especially starting in childhood with a varied course. Synonyms for AD include eczema, porrigo larvalis, and Hebra's prurigo.[1,2] Atopic dermatitis (AD) is classified into intrinsic and extrinsic.[3] The term atopic refers to a tendency to increase the production of immunoglobulin E (IgE) in response to certain allergens.[4] This disease is one of the most common chronic recurrent eczema disorders with severe itching and other skin symptoms.[1] Wise and Sulzberger coined the term atopic dermatitis in 1933 to describe AD found in patients with a family history of atopic disease.[2]

Atopic dermatitis is one of the most common and increasing skin diseases in the world.[1] In industrialized countries, the prevalence of AD tends to increase in the range of 10-20% for children and 1-3% for adults. The prevalence of AD in Japan in 2014 ranged from 12-13%.[5] Southeast Asia prevalence varies by region, 17.9% aged 12 years in Singapore and 1.1% aged 13-14 years in Indonesia.[6] Based on patient data, the number of visits by AD patients to the Dermatology and Venereology Outpatient Clinic at the Dr. Mohammad Hoesin General Hospital Palembang from January 2016 - December 2020 found 284 cases.

Oxidative stress (SO) is the accumulation of reactive oxygen species (ROS) that exceeds the defense capacity of the body's antioxidant system.[7] This condition has a role in the occurrence of AD in cutaneous and non-cutaneous disorders.[7] Oxidative

stress relationship to DA can damage the deoxyribonucleic acid (DNA) of keratinocytes through lipid oxidation and interfere with the skin barrier function and skin defects, leading to chronic inflammation in AD.[7] Chronic skin inflammation is associated with overproduction of reactive oxygen species (ROS), such as superoxide (O_2-) and hydrogen peroxide (H_2O_2).[7] Exogenous factors such as solar radiation or pollution and psychological processes can also increase ROS concentrations.[7] The purpose of this literature review is to determine the role of oxidative stress in atopic dermatitis. Understanding the pathogenesis of AD related to oxidative stress and antioxidants as additional therapy in AD.

Atopic dermatitis clinical manifestations

Atopic dermatitis is grouped into two types, namely intrinsic and extrinsic AD. Extrinsic AD patients typically have high IgE levels, filaggrin mutations (FLG) with skin barrier breakdown, exhibit early onset, and have a Th2 dominant response.[3] On the other hand, intrinsic AD patients exhibit different features.[3] Intrinsic AD patients usually do not show elevated IgE levels, do not have FLG mutations, exhibit adult-onset, and are associated with more Th17 and Th22 immune activation than extrinsic AD patients.[3]

The clinical diagnosis of atopic dermatitis is made based on the history, physical examination, and associated clinical symptoms.[4] The phases of clinical findings of atopic dermatitis were described as acute, chronic, and mixed. Atopic dermatitis patients may experience only one phase of eczematous lesions but most often experience a mixture of acute and chronic lesions in several parts of the body.[2] Acute eczematous lesions are characterized by erythematous papulovesicular, often with pinpoint crusts.[2] Subacute to chronic lesions often show scaling, excoriation, and lichenification.[2]

Etiopathogenesis of atopic dermatitis

Some new studies have explained the understanding of AD, but the exact etiopathogenesis of AD is still unclear.[3] Complex interactions between genetics, environmental factors, microbiota, skin barrier deficiency, immunological disorders, and possibly autoimmunity contribute to the development of AD.[3] Current understanding of the pathogenesis of AD focuses on the main etiopathogenesis of genetic and skin barrier disorders, immunologic disorders, and environment.[3,2,8]

Genetics and skin barrier disorders

The filaggrin gene found on chromosome 1q21 contains a variety of genes, including involucrin, loricrin, and calcium-binding protein S100, which are expressed during terminal differentiation of the epidermis.[2] Mutations in this gene cause loss of filaggrin function at the epidermal barrier.[2] Filaggrin (FLG) is essential for controlling transepidermal water loss (TEWL), maintaining hydration of the stratum corneum (SC), cornification, and regulation of the epidermis. Filaggrin is known to be decreased in the epidermis of AD patients, and a null mutation in FLG is the strongest risk factor for the development of AD. FLG deficiency causes an increase in skin pH, increases allergen penetration, and increases the function of the serine proteases kallikrein (KLK)5, KLK7, and KLK14 which are responsible for corneocyte release. This activated kallikrein can increase the production of interleukin (IL)-1α and IL-1β from corneocytes. In addition, binding to the protease-activated receptor type 2 (PAR2) on keratinocytes and KLK can induce the production of thymic stromal lymphopoietin (TSLP), which further triggers inflammation.[3]

Intercellular lipids are a fundamental part of SC and serve as mortar in the epidermal bricks and mortar model. These lipids are composed of ceramides, free fatty acids, and cholesterol in a ratio of 1:1:1. Lipid precursors are formed and stored in SG lamellar bodies and released into the extracellular space when keratinocytes differentiate into SCs. Abnormalities in enzymes responsible for lipid processing and lamellar body transport across cells give rise to various skin barrier breakdown diseases.[3]

Immunological disorders

Acute skin barrier disruption causes T helper-2 (Th2) imbalance.[3] Keratinocyte-derived cytokines such as TSLP affect the DA phenotype, IL-25, IL-33, and granulocyte-macrophage colony-stimulating factor (GM-CSF) affect Innate Lymphoid Cell (ILC) and increase the production of the Th2 chemokine CCL17 (thymus and activation) (regulated chemokine (TARC)), CCL22, and eosinophil chemoattractant namely CCL5 (regulated upon activation, normal T cell expressed and secreted (RANTES)).[3] In addition to Th2 cell recruitment, CCL17 has been reported to increase keratinocyte proliferation and is implicated in the development of AD.[3]

Itching or pruritus is one of the most disturbing symptoms of AD and affects an individual's quality of life. Pruritus in AD is the result of a complex interaction of many factors.[3] The exact pathogenesis is still unknown, but recent studies have shown that hyperinnervation of the epidermis, the elevation of several pruritic mediators, and central sensitization of pruritus are evident in AD.[3]

Environment

The skin microbiome is a complex and highly diverse community consisting of pathogenic and commensal bacteria, fungi, and viruses that play an important role in epidermal homeostasis. More than 90% of AD patients have skin colonization with *Staphylococcus aureus*.[8] Superantigens can enhance Th2 immune responses and exotoxins produced by colonizing S. aureus in AD patients. In addition, S. aureus toxin stimulates mast cell degranulation and Th2 inflammation. Filaggrin deficiency also increases the susceptibility of keratinocytes to cytotoxicity induced by *S. aureus* toxin.[8]

Oxidative stress in atopic dermatitis

The free radical species in human physiology are reactive oxygen species (ROS) and reactive nitrogen species (RNS).[9] There are several lists of ROS produced by keratinocytes and the most commonly encountered RNS.[9,10] Apart from ROS, RNS also plays an important role as a radical species in biology.[9] The simplest molecule of this group is nitric oxide (NO•) which plays a role in physiology and biochemistry, one of which is vasodilation and neurotransmission.[9]

Oxidative stress is defined as the formation of oxidants in human body cells acutely or chronically exceeding the antioxidant defense capacity.[11] Oxidants include free radicals or any independent species containing one or more unpaired electrons.[11] Reactive oxygen species (ROS) and reactive nitrogen species (RNS), and reactive metabolites are produced during normal metabolic activity.[11]

Types of oxidative stress

Source of endogenous free radicals

Oxygen free radicals are associated with the process of oxidative phosphorylation through the mitochondrial electron transport chain as the main source of cellular energy in the form of adenosine triphosphate (ATP).[9] Free radicals are also produced during the metabolism of xenobiotic compounds where the by-product of the degradation reaction is ROS.[9] Cellular enzymatic processes also produce ROS or RNS, either by mutation or as part of the inflammatory response.[9]

Source of exogenous free radicals

Particulate matter (PM) is a mixture of solid particles and liquids in the atmosphere that are contaminants.[9] This material acts as an oxygen free radical consisting of aerosols, ash, dirt, dust, smoke, pollen, and soot. Particulate matter can be generated directly from various sources, such as factory and vehicle exhaust, construction sites (dust), and fire.[9] Most of the PM is produced by burning fossil fuels (energy plants, cars, airplanes, etc.) which results in the production of nitrogen and sulfur oxides.[9] In the end, this gaseous pollutant undergoes a reaction that produces these free radicals. Evidence suggests that particulate matter (oxygen free radicals) plays a role in the development of inflammatory skin diseases, such as atopic dermatitis.[9]

Oxidative stress in atopic dermatitis is caused by increased lipid peroxidation and decreased

antioxidant levels.[12] Oxidative stress damages keratinocyte deoxyribonucleic acid (DNA) through lipid oxidation and disrupts barrier function, increases proinflammatory cytokine production and activates nave T cells and cellular dermal infiltration and triggers AD lesions.[13] Free radical damage occurs when protective mechanisms are threatened and depleted during an oxidative imbalance.[14]Although there is an antioxidant system (AOx) in the skin, it can be defeated by excess ROS.[14] Uncontrolled ROS production plays a major role in various skin diseases.[14]

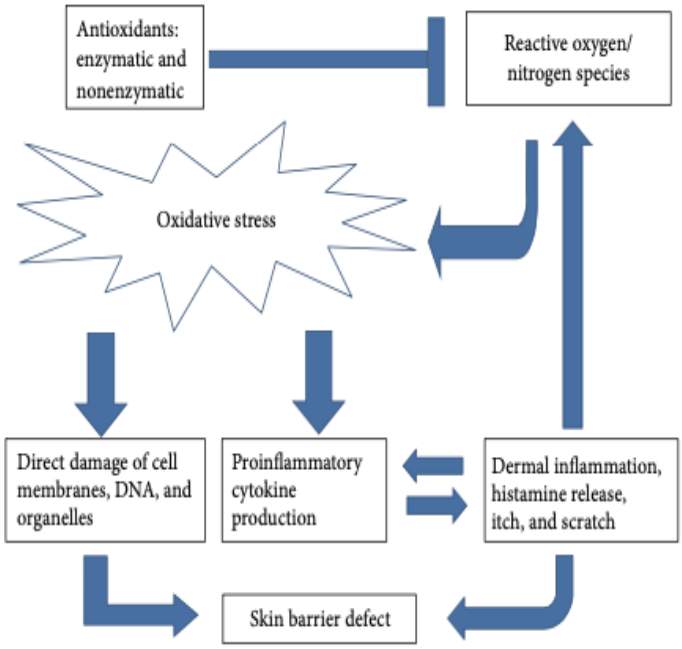

Figure 2. Interaction between oxidative stress, skin barrier defects, and inflammation in atopic dermatitis.[11]

Skin is a major target of oxidative stress due to reactive species that are continuously generated in keratinocytes in response to environmental and endogenous pro-oxidant agents.[11] Physical activity and psychological stress can also create oxidative stress on the skin.[11] Free radicals generated during normal metabolism are an integral part of normal skin function and are usually harmless because intracellular mechanisms can reduce their damaging effects.[11] Increased or prolonged free radicals can overpower the skin's antioxidant defense mechanisms and contribute to the development of skin disorders.[11]

Toxins from the environment and factors such as chemicals, irritants, allergens, and infections directly or indirectly lead to the production of reactive oxygen species (ROS) by neutrophil activation, lipid peroxidation in cell membranes, and secretion of proinflammatory cytokines.[15] Under normal physiological conditions, ROS are continuously detoxified by antioxidants.[15] In chronic inflammation or during conditions of environmental stress, overproduction of oxidants and inadequate antioxidant defense mechanisms result in disturbance of the oxidant-antioxidant balance against oxidants and contribute to oxidative stress (SO).[15,16] Oxidative stress stimulates the inflammatory response in AD.[15]

Oxidative stress levels in AD can be measured, supported by existing research. Research Novita et al., 2011 proved the clinical severity of AD is associated with levels of 8-hydroxydeoxyguanosine (8-OHdG) in the urine.[17] There were changes in the levels of nitric oxide (NO) in serum, malondialdehyde (MDA), and (8-OHdG) in AD patients.[18]

Antioxidants in the management of atopic dermatitis

Antioxidants are substances that combine to neutralize ROS preventing oxidative damage to cells

and tissues.[19] Skin antioxidant defense systems include enzyme-based (superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and peroxiredoxin), and non-enzyme-based (vitamins A, C, and E, glutathione, polyphenols, and coenzyme Q10).[11,19] Atopic dermatitis patients often have lower systemic antioxidant levels and have low intakes of antioxidant nutrients.[20] The association between systemic antioxidant status and AD risk requires further evaluation in a large prospective study.[20]

Administration of antioxidants in small doses and in combination is the safest alternative use.[19] Vitamin E works synergistically with vitamin C to regenerate tocopheryl radicals, the oxidation product of alpha-tocopherol.[19] The relationship of vitamins A, C, E, selenium, pomegranate extract, quercetin, green tea, coenzyme q10, and carotenoids such as lutein, lycopene, and zeaxanthin gave improved results in erythematous lesions and absorbed free radical levels after 4 weeks of use.[19]

2. Conclusion

Atopic dermatitis is a common chronic skin condition caused by genetic and barrier disorders, immunologic dysregulation, and the environment. Oxygen free radicals from endogenous and exogenous sources can damage the skin and contribute to the pathogenesis of AD. Antioxidants can be used as additional therapy in AD.

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