

Indian Journal of Allergy, Asthma & Immunology

REVIEW ARTICLE

Year : 2016 | Volume : 30 | Issue : 1 | Page : 4--11

Clinical correlation of oxidant-antioxidant balance and Vitamin D in asthmatic patients

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Abstract

Asthma is a chronic inflammatory lung disease that results in airflow limitation, hyperreactivity, and airway remodeling. There is strong evidence that an imbalance between the reducing and oxidizing systems lead more oxidative state in asthma. Endogenous and exogenous reactive oxygen species and reactive nitrogen species play a major role in the airway inflammation and cause of severe pathogenesis. Atmospheric pollution, dietary changes, changes in allergen load, improvements in health and hygiene, and lifestyle changes have all been proposed for asthma. It has been observed, poor antioxidant rich nutrition and lack of Vitamin D are also a common cause for pathogenesis of asthma. Vitamin D as lung immunomodulator and Vitamins A, C, E as antioxidants improves the complications of inflamed airflow in asthma. In this review study, we will summarize the current knowledge and discuss the current pharmacological strategies regarding the role of antioxidant activity and Vitamin D in favor to regulate and prognose to inflammatory asthma.

How to cite this article:

Singh S, Mishra BP, Arora V K, Batra J, Lingidi JL. Clinical correlation of oxidant-antioxidant balance and Vitamin D in asthmatic patients. Indian J Allergy Asthma Immunol 2016;30:4-11

How to cite this URL:

Singh S, Mishra BP, Arora V K, Batra J, Lingidi JL. Clinical correlation of oxidant-antioxidant balance and Vitamin D in asthmatic patients. Indian J Allergy Asthma Immunol [serial online] 2016 [cited 2016 Sep 27];30:4-11

Available from: <http://www.ijaai.in/text.asp?2016/30/1/4/187551>

Full Text

INTRODUCTION

Asthma is the most common chronic inflammatory disorder with an unknown etiology associated with increased reactive oxygen species (ROS) and characterized by cough, wheezing, and dyspnea. [1],[2],[3] Airway reactivity and airflow limitations are the result of complex involvement between numerous cell types and mediators in asthma [4],[5],[6],[7],[8] [Figure 1]. According to a recently proposed hierarchical oxidative stress, [9],[10] a low level of oxidative stress, such as exposure to diesel exhaust products for 6 h at a concentration of 10-50 mg/mL, [11] leads to the activation of the transcription factor, nuclear erythroid 2 p45-related factor 2 (Nrf2), which encodes more than 200 genes. These gene

products are responsible for a wide range of antioxidant, anti-inflammatory, cytoprotective, and detoxification functions and include catalase, superoxide dismutase (SOD)-3, heme oxygenase-1, glutathione-S-transferases, nicotinamide adenine dinucleotide phosphate (NAD (P) H) quinone oxidoreductase 1, glutathione peroxidase, and glucuronosyltransferase-1a6 (UGT-1a6). [12] Antioxidants can restore cellular redox homeostasis at low level of oxidative stress. Enhancement in the level of oxidative stress could be triggering a cytotoxic response initiating in the mitochondria and may lead to cellular apoptosis or necrosis. ROS is one of the most important components of oxidative stress produced in asthmatic inflammatory process. Activated eosinophils, neutrophils, monocytes, and macrophages generate superoxides (O_2^-) via a membrane-associated NADPH-dependent complex. The subsequent dismutation of O_2^- can result in the formation of hydrogen peroxide (H_2O_2). O_2^- and H_2O_2 are moderate oxidants, and both are critical in the formation of potent cytotoxic-free radicals in biological systems through their interactions with other molecules. [13] This process is involved in asthmatic inflammation; moreover, the concentration of nitric oxide (NO) is increased in airways of asthmatic subjects. [14] Excess production of ROS is harmful because these induced oxidation of DNA, lipids, and proteins which may result to direct damage and evoke cellular responses through the production of secondary reactive species. [15] The influence of nutrition on chronic bronchial asthma has an important place in the management of this disease. Evidence suggests that specific inflammatory abnormalities exist in the airways of subjects suffering from mild-to-moderate persistent asthma, in whom an inflammatory state is often associated with increased generation of ROS and the damaging effects of free radicals. For this reason, oxidant stress may be an important pathogenic factor in the progress of the disease. The role of nutrition in bronchial asthma is related to Vitamin D and antioxidant Vitamins A, C, E, etc. {Figure 1}

The aim of this review study is to conclude the correlation of oxidant-antioxidant balance (oxidative stress) with regard to the role of Vitamin D in asthmatic patients.

PATHOPHYSIOLOGY OF ASTHMA

The etiology of allergy

When the tolerance power against the allergens fail, then the development of allergy occurs. [16] Although this process may occur at any age, it typically occurs in early infancy. The process of tolerance is facilitated largely in the neonatal and infant gut and is referred to as oral tolerance. Three factors are instrumental in the success of oral tolerance: Normal microbial gut flora colonization, antigen encounter, and a host of nonspecific immunomodulatory factors. It appears that all of these factors operating together promote oral and systemic allergen tolerance. It is supposed the development of allergy is result of delay processing of antigen tolerance; this process operates on a genetically predetermined basis. The possible etiological factors for asthma listed in [Table 1].{Table 1}

Possible factors for the rising prevalence of asthma

Atmospheric pollution, dietary changes, changes in allergen load, improvements in health and hygiene (the hygiene hypothesis), and lifestyle changes have all been proposed for this phenomenon. [17] It is studied that no one factor is responsible for asthma etiology and that the condition is probably multifactorial in etiology as well as clinical expression. There is potential role of overlapping genetic predispositions for the development of asthma. These include predisposition to abnormal lung growth, resulting in lower lung function; delayed immune maturation; predisposition to lower respiratory viral infections; early allergic sensitization; and predisposition to bronchial hyperresponsiveness. Networks of genes and environmental modification of gene expression via epigenetic mechanisms are also likely to be important. Antenatal exposures that increase the risk of asthma include tobacco smoke and ambient and indoor air pollution. Early-life environmental exposures may also increase the risk of asthma via impacts on lung growth and immune maturation. Synergistic interactions between viral lower respiratory infections and allergic sensitization in early life appear to be especially important in increasing the risk of subsequent asthma.

Oxidative stress in asthma

Free radicals are short-lived and independent chemicals that have at least one unpaired electron in their outer most orbit. Free radicals try to make more stable structures by reacting with other molecules. [18] Few factors and metabolic pathways are the path for the generation of free radicals. [19] Molecular oxygen is main source for the formation of free radicals within an organism. In certain pathological conditions, the quantity of free radicals may increase due to the formation of a large number of free oxygen radicals or inability of an organism's defense system to cope. These radicals interact with various cellular components and macromolecules and cause metabolic, structural, and functional damage that may lead to cell death. It is thought that cell damage caused by free oxygen radicals contributes to the pathogenesis of several chronic

diseases including asthma.

Inflammatory and immune cells, including macrophages, neutrophils, and eosinophils, produce more ROS in asthma patients than in healthy individuals. [19],[20] Many characteristic traits of asthma occur due to the production of hyper-ROS. Oxygen radicals are known to cause β -receptor dysfunction, [19] bronchial smooth muscle contraction, [19] bronchial hypersensitivity, [19],[21],[22] increased mucin secretion, [19],[22] and a rise in vascular permeability. [19],[22] Numerous studies suggest that in asthma oxidative stress caused by overproduction of various free radicals or by an insufficient antioxidant defense system contributes to the tissue damage induced by inflammatory cells. [19],[20],[21],[23],[24],[25],[26],[27],[28]

From basic and clinical oxidative stress in asthma

It has been studied with strong evidence that the exogenous and endogenous ROS and reactive nitrogen species (RNS) play a major role in the determination of asthma severity and airway inflammation [4],[5],[6],[7],[8] [Figure 1]. According to a recently proposed hierarchical oxidative stress, [9],[10] a low level of oxidative stress, such as exposure to diesel exhaust products for 6 h at a concentration of 10-50 mg/mL, [11] leads to the activation of the transcription factor, Nrf2, which encodes more than 200 genes. These gene products are responsible for a wide range of anti-inflammatory, cytoprotective, antioxidant, and detoxification functions and include catalase, heme oxygenase-1, and UGT-1a6. [12] At low level of oxidative stress, antioxidants can restore cellular redox homeostasis. When high levels of oxidative stimuli are present, additional sets of intracellular signaling cascades are triggered that are potentially pro-inflammatory. These include mitogen-activated protein kinase and nuclear factor-kB, which lead to the expression of inflammatory cytokines, chemokines, and adhesion molecules. A further increase in the level of oxidative stress could ultimately trigger a cytotoxic response originating in the mitochondria and lead to cellular apoptosis or necrosis [Figure 2].{Figure 2}

Exposure to endogenous reactive oxygen species and asthma

ROS may be generated by inflammatory cells (such as activated eosinophils, neutrophils, monocytes, and macrophages) and resident cells (such as epithelial and smooth muscle cells). [29],[30],[31] Mitochondrial respiratory chain, the cytosolic xanthine oxidase system, NADPH oxidase-dependent complex are the sources for the production of $O_2^{\cdot -}$. Superoxides ($O_2^{\cdot -}$) and H_2O_2 react with each other in the presence of iron and other metal ions and form $OH^{\cdot}$ in biological systems. [20],[26],[32] Eosinophils, neutrophils, and monocytes contain peroxidases that catalyze the interaction between H_2O_2 and halides leading to the formation of hypohalides such as $HOCl$. In addition, superoxide anion may also react with NO to form peroxynitrite ($ONOO^-$), a potent ROS. [20],[26],[30],[31],[32]

ROS react with proteins to form carbonyls product, whereas it reacts with nitrogen species and tyrosine to form nitrotyrosine. In murine and human studies, tyrosine nitration was shown to increase after allergen exposure in sensitized mice or atopic asthmatic humans. [33] ROS also reacts with lipids to liberate isoprostane and ethane. [34],[35],[36] As a result, 8-isoprostane, a biomarker of lipid peroxidation, is elevated in the exhaled breath condensate in adults and children with asthma. Similar to the airways and systemic circulation, urinary levels of bromotyrosine and F2-isoprostanes are elevated in patients with asthma [37] and are associated with an increased risk of having asthma.

NO is the principal nitrogen species produced in lung. Autoxidation of NO with oxygen results in the formation of nitrite, a substrate for eosinophil peroxidase (EPO) and myeloperoxidase (MPO). [38] Nitric oxide reacts with superoxide to form $ONOO^-$, which can nitrate tyrosine residues and thus damage enzymes, and structural and functional proteins. [20],[30],[31],[38] It has been observed that the higher NO levels are associated with higher risk of asthma, prompt asthma severity, and greater response to bronchodilator agents. [37],[39]

A link also exists between the increase in ROS and asthma severity. ROS production by neutrophils correlates with the severity of the reactivity of airways. [40] Increased levels of EPO and MPO correlate with the numbers and activation of eosinophils and neutrophils, respectively. [41],[42],[43] The level of 3-bromotyrosine, a unique product of EPO and eosinophils, was found to be 3 times higher in the bronchoalveolar lavage (BAL) fluid of individuals with asthma compared with that in the control subjects. [44] In the Intensive Care Unit, the level of 3-bromotyrosine in airways of severe asthma patients was 100-fold higher than that in individuals hospitalized for nonasthma causes. [45] The 2- to 3-fold elevations in chlorotyrosine are detected from allergen-challenged subsegments in asthmatic subjects [Figure 3]. [44]{Figure 3}

Exposure to exogenous reactive oxygen species and asthma

Large surface area of respiratory system that is in contact with the environment. Airborne pollutants such as sulfur dioxide, nitrogen dioxide, ozone, or cigarette smoke particulate matter in the air can trigger symptoms of asthma. [46] Recently, a clear relationship between traffic density and asthma exacerbations was demonstrated. [47] Ultrafine particles with a

diameter of 0.1 mm may directly induce mitochondrial damage and make it difficult for the lungs to cope with oxidative stress. [48] Cigarette smoke is related to asthma exacerbations, especially in young children, rate and severity of asthma are directly related to the extent of exposure to cigarette smoke and rates of asthma. [49] Cigarette smoke is a mixture of about 4000 chemical compounds distributed in aqueous, gas, and the tar phase of the smoke. The O_2^- and nitric oxide of cigarette smoke react to form highly reactive peroxynitrite. [50] The tar phase of the cigarette smoke contains organic radicals that react with molecular oxygen to form O_2^- , OH^- , and H_2O_2 . The tar phase is an effective metal chelator that chelates iron and generates H_2O_2 continuously. Aqueous phase of the cigarette smoke may undergo redox recycling for a period in the epithelial lining of the lungs. [51]

Imbalanced oxidant-antioxidant systems in asthma

Homeostasis of cellular functions during oxidative stress depends on the appropriate induction of protective antioxidant mechanisms. Antioxidants are major in vivo and in situ defense mechanisms of the cells against oxidative stress. [10],[20],[26],[30],[32] Naturally occurring antioxidants work to protect cells and tissues against the continuous production of ROS and RNS during normal metabolism. [52] Imbalance of oxidants-antioxidants system of the airway could be a determinant of asthma initiation and severity. [4],[7],[8] Antioxidant system mainly categorized into two groups. Ascorbic acid, glutathione, albumin, alpha-tocopherol, lycopene, and beta-carotene are nonenzymatic oxidants. [21],[29],[53],[54] The major enzymatic antioxidants of the lungs are SODs, catalase, and glutathione peroxidases as well as heme oxygenase-1, thioredoxins, peroxiredoxins, and glutaredoxins. [49] Asthma is characterized by the loss of antioxidant activities. Levels of the enzymes glutathione peroxidase and SOD and of the nonenzymatic components of the antioxidant system including reduced glutathione, ascorbic acid, alpha-tocopherol, lycopene, and beta-carotene were significantly lower in children with asthma compared with the healthy controls. Superoxide is the main source of ROS produced from so many sources, its dismutation by SOD is done about each and every cell. [55]

Catalase is a metalloprotein enzyme and the main scavenger of H_2O_2 . It is effective in high concentrations of H_2O_2 . Under prolonged oxidative stress, NADPH binds to the enzyme and stabilizes the structure and protects catalase from inactivation. This leads to the decrease in catalase activity. [56] Both animal and human studies have shown that catalase activity in BAL fluid is lower in patients with asthma as compared with that in healthy controls. [57] Extracellular glutathione peroxidase is higher than normal in the lungs of patients with asthma.

Enhanced oxidant-antioxidant imbalance in the airway

An increase in air pollution, an increased use of oxidant medication, and a decreased intake of antioxidants account for increased airway oxidative stress, which can cause immunity and airway inflammation.

Another explanation for the recent increase in the development of asthma may be associated with individual variations in the cellular machineries that handle intracellular antioxidants. A partial deficiency in the intracellular antioxidant defense system may critically affect oxidants when the level of increased oxidative stress goes beyond the capability of the system. [58],[59],[60],[61] Increased oxidative stress in the environment may contribute to allergic airway inflammation by inducing a break in immune tolerance in genetically predisposed individuals whose antioxidant systems are unable to handle the oxidative stress burden imposed on immune cells. The association between oxidative stress and the development of airway inflammation is depicted in [Figure 4]. It is assumed that a higher severity of asthma is also closely related to a lower ability to control oxidative stress in genetically predisposed patients. [61][Figure 4]

Therefore, intrinsic defects in certain intracellular molecules involved in the processes of intracellular oxidative stress signaling may be a plausible molecular mechanism explaining the crucial and direct role of oxidative stress in the pathogenesis of bronchial asthma, especially the chronic, severe asthma phenotype. Even genetic polymorphism leads to pathophysiological changes that result in the inflammation of the airways.

Role of vitamins and nutrients in asthma

The results of the studies evaluating the effects of vitamins and nutrients on asthma have been controversial. [62],[63],[64],[65],[66],[67],[68] In a murine study, it was shown that the administration of Vitamins C and E caused decreases in ragweed extract-induced ROS levels and is associated with lower airway allergic inflammation. [62] In an ovalbumin-sensitized rat model, 4 days of oral treatment with gamma-tocopherol diminished eosinophil infiltration in the nose, sinuses, and nasolacrimal duct but not in the lung after allergen challenge. [63]

Even though epidemiological studies have suggested that children with low dietary intake of Vitamins C and E, and other antioxidants have in general more symptoms, [65],[69] the results of the clinical studies have been largely disappointing. [66],[67],[68] Interestingly, a recent study has even suggested that vitamin supplements may increase the oxidant stress.

This emphasizes that exogenous antioxidants need to block the oxidant pathways without suppressing the endogenous antioxidant mechanisms.

Vitamin D: Role in lung immunomodulation

Vitamin D is produced by the conversion of proVitamin D to preVitamin D in the skin during exposure to sunlight. Some Vitamin D comes from food sources. PreVitamin D is converted in the liver to 25-hydroxyl Vitamin D. The active form of Vitamin D is 1,25-dihydroxy Vitamin D ($1,25(\text{OH})_2 \text{D}_3$) which is generated primarily in the kidneys. [70] $1,25(\text{OH})_2 \text{D}_3$ binds to cell membrane Vitamin D receptors and forms a complex that is then internalized. Vitamin D receptors form part of the steroid hormone nuclear receptor complex. This complex binds to the Vitamin D promoter region of the Vitamin D responsive genes that influence the rate of RNA polymerase II-mediated transcription.

The serum 25-hydroxyvitamin D level is the best indicator of overall Vitamin D status. Skin-derived Vitamin D is variable and depends on pigmentation, latitude, season, clothing, age, sunscreen use, and local weather patterns. The enzyme, 1α -hydroxylase, is present and expressed in airway epithelium (in significant quantities) and a host of lung constitutive and inflammatory cells including alveolar macrophages, dendritic cells, and lymphocytes. [71] Vitamin D₃ has various specific effects on different immune cells. $1,25(\text{OH})_2 \text{D}_3$ promotes apoptosis and inhibits maturation of bone-marrow-derived mast cell precursors. There was also a dose-dependent inhibition of mast cell differentiation by $1,25(\text{OH})_2 \text{D}_3$ at various stages of mast cell development. [72]

Vitamin D plays a role in B-cell functioning by the inhibition of plasma cell differentiation and immunoglobulin secretion (IgG and IgM), memory B-cell generation, and apoptosis of activated B cells. These mechanisms may contribute to the pathogenesis of B-lymphocyte-related diseases such as asthma. [73] Vitamin D inhibits proliferation of Th-lymphocytes. The effect of cholecalciferol on Th-mediated cytokines is variable, enhancing and suppressing secretion under different circumstances. The main effect of Vitamin D on cell-mediated immunity occurs indirectly through alteration of antigen-presenting cells, especially dendritic cells. Vitamin D is an important regulator of lymphocyte trafficking and homing, to sites of inflammation. [74],[75]

The Vitamin D receptor was found to be present in bronchial smooth muscle cells which are associated with active protein synthesis. $1,25(\text{OH})_2 \text{D}_3$ arrests the progression of airway smooth muscle cells in the S phase of the cell cycle. It is believed that matrix metalloproteinases 9 and 33 also has a role in airway remodeling, along with the aspect of airway remodeling in angiogenesis. [76] All these effects operating at a cellular level could be advantageous to protection against infection and the development of allergic lung diseases such as asthma. [77],[78]

Vitamin D has effects on the innate and adaptive immune system. In asthmatic children, low Vitamin D levels are associated with poor asthma control, reduced lung function, increased medication intake, and exacerbations. Vitamin D insufficiency is increasingly recognized in the general population and has been largely attributed to dietary, lifestyle, and behavioral changes. [79],[80] Vitamin D might be relevant in the primary prevention of asthma, in the protection against or reduction of asthma morbidity, and in the modulation of the severity of asthma exacerbations. [81],[82],[83]

DISCUSSION

Bronchial asthma is an inflammatory disease characterized by activation and accumulation of inflammatory cells in the airway. This inflammation may cause tissue damage, resulting in the pathological manifestations of disease including airflow obstruction, airway hyperresponsiveness, and permanent structural changes that include airway remodeling. Asthma is associated with strong oxidative stress that is result of both increased oxidant forces and decreased antioxidant capacity. Various bioactive mediators, factors, and cytokines are involved in the pathogenesis of asthma. ROS and RNS also have negative effects in pulmonary system that result in the tissue damage associated with asthma. It is well known that oxidative stress (imbalance in oxidant-antioxidant) is an important component in airway inflammation.

As in other inflammatory conditions, oxidative burst in asthma is nonspecific event in which numerous inflammatory processes are simultaneously activated. Asthma mediators, such as lipid mediators, chemokines, adhesion molecules, and eosinophil granulocytes, are potential stimulators of oxidant production and increase ROS and RNS production. The lung possesses an advanced antioxidant system that functions to protect from exposure to harmful oxidants; however, the oxidant-antioxidant imbalance occurs in asthma. Researchers are more interested to use antioxidants agents such as Vitamins A, C, D, and E to improve clinical and pulmonary function in asthmatic patients. These agents can decrease or prevent oxidant toxicity or respiratory systems.

CONCLUSION

The oxidative stress can be critical contributor to asthma development and can initiate various intracellular signaling pathways that lead to break in immune tolerance and exaggerated allergic inflammation. Authors speculate that combination of antioxidant agents and Vitamin D (lung immunomodulator) supplementation may in the future, prove to be beneficial in the treatment of asthma, as adjuncts to current pharmacological strategies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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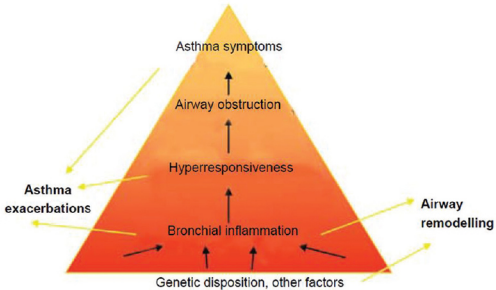
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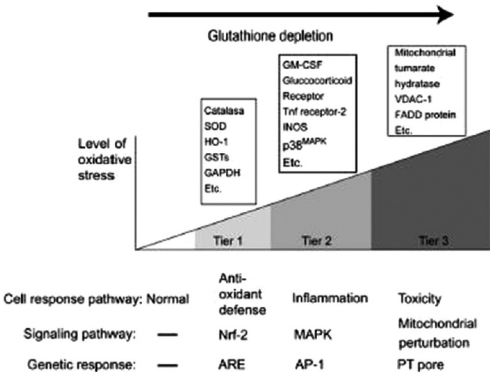
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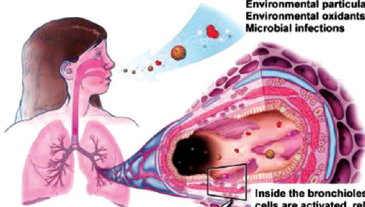
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Allergic triggers
Environmental particulates
Environmental oxidants
Microbial infections



Inside the bronchioles of the lungs cells are activated, releasing chemicals that cause inflammation or amplify inflammation, including reactive oxygen and nitrogen species.

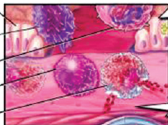
Airway epithelium

Macrophage

Eosinophil

Neutrophil

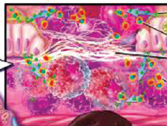
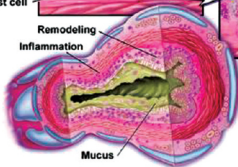
Mast cell



Remodeling

Inflammation

Mucus



Inflammatory mediators

Nitric Oxide

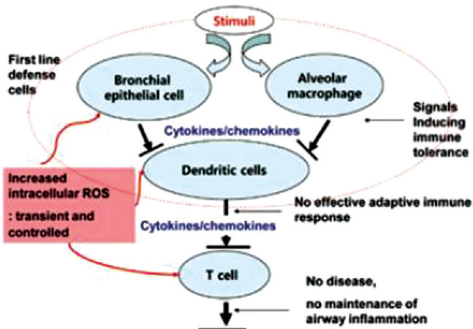
Tissue damage

Reactive Oxygen Species

As the attack escalates, wheezing and coughing occurs, leading to patient illness.



Controlled intracellular oxidative stress



Losing control of intracellular oxidant

