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OXIDATIVE STRESS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND EFFECT OF LYCOPENE (A DIETARY SUPPLEMENT) ON MARKERS OF OXIDATIVE STRESS, INFLAMMATION & PULMONARY FUNCTION

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HOW TO CITE THIS ARTICLE:

Amit Kumar Verma, Akshar Aggarwal, Kuldeep Kumar. "Oxidative stress in chronic obstructive pulmonary disease and effect of lycopene (A dietary supplement) on markers of oxidative stress, inflammation & pulmonary function". Journal of Evolution of Medical and Dental Sciences 2013; Vol2, Issue 38, September 23; Page: 7317-7323.

ABSTRACT: COPD is one of few diseases, where morbidity and mortality is on rise. Oxidative stress, inflammation, protease-antiprotease imbalance and apoptosis are the pathological principles responsible for COPD. In a particular patient each of the above component interact and leads to different forms of disease. Standard treatment for COPD includes cessation of smoking, bronchodilators, antinflammatory drugs, theophyllins & vaccinations. Management of oxidative stress in COPD is not recommended. This may be due to non availability of standard formulations for management of oxidative stress and more importantly lack of reliable data to support benefit of such compounds.

There are many substances e.g lycopene, Vit-C & Vit-E which are available naturally and can be added as food supplement in the management of oxidative stress in many diseases including COPD. With the currently available data it is clear that lycopene supplementation significantly reduces serum levels of oxidative stress like Malondialdehyde (MDA), Superoxide dismutase(SOD), Interleukine-6(IL-6), Tumor necrotic factor- (TNF- α). It also shows improvement in lung function indices.

INTRODUCTION: Worldwide, COPD is a health problem with severe economic and social impact. At the personal level, COPD is a major cause of patient disability and of low quality of life for patients and their family members.^(1,2) According to the World Health Organization, 80 million people suffer from moderate or severe COPD.⁽³⁾ COPD is currently fifth leading cause among all cause deaths and number one cause of deaths due to respiratory diseases.

Fig 1:COPD will be leading cause of death due to respiratory diseases

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In the last century increase in the mortality rate for COPD is in contrasts with the marked reduction in the mortality rate for diseases such as cancer, coronary disease, cerebrovascular accident and AIDS. This reduction is largely attributed to a greater efficacy in the diagnosis and treatment of these diseases, which in turn results, at least in part, from a better understanding of the etiopathogenic mechanisms of these diseases.

By definition COPD is a chronic and progressive reduction in airflow, secondary to an abnormal inflammatory response of the lungs to the inhalation of noxious particles or toxic gases. This inflammation produces alterations of varying severity in the bronchi (chronic bronchitis), bronchioles (obstructive bronchiolitis), lung parenchyma (emphysema), or any combination of the three.^(4,5) In addition to affecting the lungs, systemic manifestations are also present in COPD, that have a serious impact on the health of patients.⁽⁶⁾

Fig 2: Systemic manifestations in chronic obstructive pulmonary diseases⁽⁶⁾

The terms inflammation and airflow reduction are central to the definition of COPD. The inflammation in COPD does not, significantly respond to steroids. The reduction in airflow in COPD has a significant irreversible component, secondary to structural changes in the airways, ^(7,8) such as peribronchiolar fibrosis and increased collapsibility, resulting from the destruction of the lung tissue. These changes are triggered by a complex mechanism that initiates well before the first clinical and functional manifestations.⁽⁹⁾ Therefore, a better understanding of the mechanisms involved in the apparently complex etiopathogenesis of COPD will allow not only an earlier diagnosis but also the development of therapeutic agents that can favorably alter the course of the disease before the development of permanent structural changes.

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The factors responsible for the alterations observed in COPD:

- 1-oxidative stress;
- 2-inflammation;
- 3-protease-antiprotease imbalance;
- 4-apoptosis.⁽⁹⁾

The relative contribution of each of these mechanisms varies and possibly explains the different forms of presentation of the disease. Oxidative stress has been attributed a central role in the pathogenesis of COPD because, in addition to causing direct injury to the respiratory tract, oxidative stress triggers and exacerbates the other mechanisms.⁽¹⁰⁻¹³⁾

Oxidative stress and free radicals: Free radicals are atoms, groups of atoms or molecules that have unpaired electrons on the outer orbit. They are instable and highly reactive molecules.⁽¹⁴⁾ However, the term free radical is not ideal to describe the group of reactive pathogenic species, because some of them do not have unpaired electrons on the outer orbital, although they participate in redox reactions. Therefore, the terms reactive oxygen species (ROS) and reactive nitrogen species (RNS) are considered to be more appropriate because they better describe these chemical agents.

The ROS are found in all biological systems and originate from the metabolism of molecular oxygen (O₂). Under physiological conditions, O₂ undergoes reduction by accepting four electrons, which results in the formation of water.⁽¹⁵⁾ During this process, reactive intermediates such as the superoxide (O₂⁻) radical, the hydrogen peroxide (H₂O₂) radical and the hydroxyl (OH⁻) radical are formed. Most of the RNS are formed from the synthesis of nitric oxide (NO) through the conversion of L-arginine into L-citrulline by nitric oxide synthases.⁽¹⁶⁾

The production of reactive species is an integral part of metabolism and is present under normal conditions, notably in the physiological processes involved in the production of energy, regulation of cell growth, phagocytosis, intracellular signaling and synthesis of important substances, such as hormones and enzymes.⁽¹⁷⁾ In order to offset this production and its potential negative effects, the body has an antioxidant system. In situations in which there is an imbalance between the pro-oxidant system and the antioxidant system, oxidative stress occurs.⁽¹⁷⁾ Oxidative stress plays an important role in the pathogenesis of COPD through direct injurious effects in lungs but also activates molecular mechanisms that initiate lung inflammation.⁽¹⁸⁾ Several studies show relationships between oxidative stress markers and the degree of airflow limitation in COPD.

Oxidative stress and lipid peroxidation: Lipid peroxidation basically consists of the incorporation of molecular oxygen into a poly-unsaturated fatty acid, resulting in oxidative degradation of the later. Cell membrane phospholipids are particularly susceptible to peroxidation. This leads to alterations in the structure and permeability of the membrane, resulting in loss of ion-exchange selectivity, release of the contents of organelles such as the hydrolytic enzymes of the lysosomes and formation of cytotoxic products e.g., Malondialdehyde (MDA).⁽²¹⁾

In biological systems, cell membrane phospholipids can be hydrolyzed by the phospholipase enzyme, producing non-esterified arachidonic acid, which can undergo peroxidation through two pathways: the enzymatic pathway, involving cyclo-oxygenases and lipoxygenases, and the non-enzymatic pathway, through the participation of ROS, RNS, transition metals and other free radicals (Figure 3).⁽²²⁾

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The end products of the lipid peroxidation mediated by reactive species include 4-hydroxynonenal (4-HNE), MDA and isoprostanes. Among isoprostanes, 8-iso-prostaglandinF2 α (8-isoprostane) has been extensively studied as a marker of pulmonary and systemic oxidative stress. (23)

Fig3: The metabolism of phospholipids

Oxidative stress and inflammation: Chronic inflammation in COPD is associated with an increase in the production of various mediators and pro-inflammatory proteins, including cytokines, chemokines, inflammatory enzymes, receptors and adhesion molecules which are regulated by gene transcription factors.^(24,25) Among the mediators, those that are chemotactic for inflammatory cells, in particular leukotriene B4 and IL-8, as well as pro-inflammatory cytokines, such as TNF- α , IL-1 β and IL-6, are note worthy. Growth factors, including TGF- β , which induces fibrosis in the small airways, are also considered important. ⁽²⁵⁾

Measurement of oxidative stress in COPD: Oxidative stress in lungs can be measured in several different ways, either by direct measurements of the oxidative burden, as the responses to oxidative stress, or by the effects of oxidative stress on target molecules

Direct measurements of oxidative burden	-Hydrogen peroxide in breath condensate or BAL fluid -BAL/peripheral blood leukocyte reactive oxygen species production -Nitric oxide in exhaled breath
Responses to oxidative stress	- Carbon monoxide in breath (reflecting hemoxygenase activity) - Antioxidants, antioxidant enzymes(superoxide dismutase(SOD), catalase, glutathione peroxidase(GPx)), non-enzymatic antioxidants(reduced glutathione(GSH), ubiquinone, uric acid) ^(19,20) in blood, sputum, BAL, and lung tissue
Effects of oxidative	- Oxidized proteins (e.g., carbonyl residues, oxidase, and nitrated

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stress on target molecules	proteins)Lipid peroxidation products (e.g., F2-isoprostains, 4-hydroxy-2-nonenal,hydrocarbons) in breath condensate, sputum, BAL, blood, urine, lung tissue
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BAL –Bronchoalveolar lavage

Lycopene as antioxidant ⁽²⁶⁾: Lycopene is an antioxidant carotenoid present in fruits and vegetables such as tomato, watermelon, guava and pink grapefruit. As a natural antioxidant, lycopene is associated with the prevention of some chronic diseases including cardiovascular diseases and various cancers in the human. Since tobacco smoke contains more than 10^{15} oxidant molecules/ puff, it is conceivable that dietary carotenoid intake may influence the progression of COPD.

During the last century, a many studies have shown importance of diet, especially of the antioxidants and micronutrients such as of vitamin C and E in the prevention and management of many diseases including COPD and asthma. Analyzing the data from the Third National Health and Nutritional Examination Survey (NHANES III) on the US population in 1988-1994 (n=18162 subjects of age 17 year or above), the authors reported a better lung function with higher levels of antioxidant nutrients. Findings of these epidemiological observations demonstrating benefits with dietary supplements have therefore raised the hope of managing COPD with an additional approach to currently available therapy.

In a study done by Gamze K et.al ⁽²⁶⁾ the effect of lycopene supplementation on chronic obstructive lung disease was studied. They give lycopene 20 mg daily to a group of 15 patients along with standard treatment for COPD, in another group of similar demographic profile only standard treatment for COPD was given. The duration of intervention was four months.

At the end they concluded that serum levels of MDA, IL-6, IL-1 β & TNF were significantly lower and serum levels of SOD, catalase were significantly higher (for all, $p < 0.05$) in group receiving lycopene in addition to standard COPD treatment. Although there was no significant improvement of (forced expiratory volume in one second) FEV1 values but FEV1/ (forced vital capacity) FVC was significantly improved. There was no relation between oxidative markers and disease stage of COPD. On evaluation of the levels of oxidant-antioxidant, inflammatory and pulmonary function parameters in placebo treated group, they saw no difference between pre and post treatment levels.

The authors concluded that, that lycopene supplementation may have favorable effects on oxidant-antioxidant balance in patients with COPD. However, the lack of a significant effect on FEV1 (% predicted) could be due to its short term use in this clinical setting.

So what we can say that in currently available literature it is clear that lycopene supplementation significantly reduces markers of oxidative stress and inflammation in many diseases including COPD. It had been shown to improve lung function indices. Hence we may recommend lycopene supplementation in patients of COPD as a dietary measure. So that patient is not devoid of beneficial effects of lycopene.

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Date of Submission: 17/08/2013.
Date of Peer Review: 18/08/2013.
Date of Acceptance: 16/09/2013.
Date of Publishing: 20/09/2013