

Review Article

COPD and Serum Trace Elements: A Review

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Abstract

Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a progressive disease with persistent airflow limitation, associated with an enhanced chronic inflammatory response in the airways and the lung to the noxious particles or gases. It is well established that oxidative stress plays an important role in the pathogenesis of this disease. Increased oxidative stress comes from the increased burden of inhaled oxidants, often from cigarette smoke, air pollution or increased amounts of reactive oxygen species released from inflammatory cells. Tests that showed alterations in serum concentrations of trace elements in COPD patients suggest that they have a role in the pathophysiology of this disease by participating in the antioxidative defense. As components of the important enzymes trace elements participate in many biochemical processes. Some studies have focused on clarifying the clinical significance of serum trace element status in COPD patients. Some of the main issues in the studies are whether the deficit of serum trace elements in COPD is associated with exacerbation frequency, severity of exacerbation or lung function. Studies also focus on whether therapy with trace elements in addition to basic therapy improves the outcome of treatment or reduces the duration of illness and can they promote bronchodilatation and improve lung function. Better understanding of the role of trace elements in the pathogenesis of COPD, their association with markers of oxidative stress and lung function could lead to new diagnostic and therapeutic directions. Studies have resulted in different findings which show that the role of trace elements in the diagnosis and treatment of COPD is noteworthy, and requires further research. In this review we summarize some of these studies and current findings.

INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a project initiated by the National Heart, Lung, and Blood Institute and the World Health Organization, defines COPD as “a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases” [1]. This amplified response may result in “mucous hypersecretion (chronic bronchitis), tissue destruction (emphysema), and disruption of normal repair and defense mechanisms causing small airway inflammation and fibrosis.” According to Barnes, besides inflammation, two other processes are involved in the pathogenesis of COPD: “an imbalance between proteases and antiproteases and an imbalance between oxidants and antioxidants (oxidative stress) in the lungs [2]” Raftery et al., projected that for 2020 COPD will be the third leading cause of death worldwide (from sixth in 1990) and fifth leading cause of years lost through early mortality or handicap (disability-adjusted life years) [3].

Oxidative stress as a component of COPD pathogenesis

The presence of increased oxidative stress is not only a critical

feature in the pathogenesis of COPD [4], but it also has important consequences for its severity and treatment [5]. It results in inactivation of antiproteases, airspace epithelial injury, mucus hypersecretion, increased sequestration of neutrophils in the pulmonary microvasculature, and gene expression of pro-inflammatory mediators [4] but to have such an impact it must overcome a variety of Antioxidant defense [5]. The main oxidants are H₂O₂, O₂⁻ and OH [6]. Lungs have a well-developed antioxidant system [7] and in diseases like COPD many trace elements have activator or inhibitor roles in it [8].

Trace elements as a component of Oxidative Stress and their potential role as predictors, markers and active participants in exacerbation or therapy in COPD

The focus of many studies is the role of trace elements as predictors, markers and active participants in exacerbation or therapy in COPD. Trace elements, or trace minerals, are usually defined as “minerals that are required in amounts between 1 to 100 mg/day by adults or make up less than 0.01 percent of total body weight” [9]. Copper is essential to all living organisms as a trace dietary mineral because it is a key constituent of the respiratory enzyme complex cytochrome c oxidase. Also, a

number of important enzymes contain copper including : zinc-copper superoxide dismutase (antioxidant defense), dopamine mono-oxygenase, lysyl oxidase, ceruloplasmin, factor V, tyrosinase [9,10]. The main antioxidant elements are zinc and selenium, according to Razi et al. [11]. Selenium is involved in the metabolism of hydrogen peroxide and lipid hydroperoxides and also has important role in antioxidant defense [9,12]. Zinc, an essential dietary metal, plays essential roles in protein structure, it is the intrinsic metal component or activating cofactor for more than 70 important enzyme systems, including carbonic anhydrase, the alkaline phosphatases, dehydrogenases, and carboxypeptidases [13], participates in cellular and humoral immunity, and has anti-inflammatory and anti-oxidant function [14]. According to Zalewski "when zinc deficiency occurs in conjunction with acute lung injury or asthma, inflammation is more intense, it results in enhanced oxidative damage in the airways." [14]. Magnesium use has the potential to promote bronchodilatation, and to improve lung function in obstructive diseases [15]. Hypomagnesemia is associated with airway hyper-reactivity, impaired pulmonary function [16], and decreased muscle strength [17]. According to El-Attar et al., "trace element (Se, Mn, and Zn) status is altered in critically ill patients with COPD." [18]. In a retrospective study Aziz et al., found that stable subjects had significantly higher concentrations of serum Mg+2 than patients in exacerbations, and that a lower serum magnesium levels are seen in patients with acute exacerbations compared to patients in stabile phase [16]. Isik et al., aimed to show the levels of trace elements with action in oxidative stress. Their study on 25 patients with COPD in stabile phase, and 20 healthy non-smokers showed that the serum copper and malondialdehyde concentrations in COPD patients were higher than the control group. They suggest that "trace elements such as copper, oxidants and antioxidants such as malondialdehyde have roles in oxidative stress, and in COPD [8]. Kuys et al., investigated the antioxidant enzymes activity (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX)) and magnesium plasma level in a group of patients with COPD and in the control group, that was made up of 20 patients who were admitted for control examinations. They detected significantly decreased activity of CAT in COPD, insignificantly decreased activity of GPX and insignificantly increased activity of SOD. Patients with COPD had lowered plasma magnesium level. Their conclusion is that "COPD is accompanied by a lowered magnesium level and an alteration in antioxidant status due to possible oxidative stress in this disease." [19] Tanrikulu et. al in their study investigated the levels of lipid peroxidation, Coenzyme Q10 (CoQ10), Zn, and Cu in the COPD exacerbations. They observed that oxidative stress in the exacerbation period of COPD patients was increased and concluded that "decrease in CoQ10 level and Cu/Zn ratio and elevation in Cu and Zn levels observed in the patients probably result from the defense response of organism and are mediated by inflammatory-like substances." [20] With a similar concept, another study focused on the potential role of trace elements in diagnostic interpretation. Karul et al., searched for serum concentrations of trace elements and correlated them to malondialdehyde, which is an indirect marker of oxidative stress,

in order to clarify if routine evaluation is necessary in COPD. "Oxidative stress was not increased in clinically stable, regularly treated COPD patients. Although there was no deficiency in trace elements (Cu, Fe, Mg, and Zn), serum zinc was close to the lower limit of the reference value." They concluded that "there is no need for routine evaluation of trace elements in clinically stable, regularly treated COPD outpatients." [21] Except as a markers of oxidative stress, the levels of certain trace elements could serve as predictors of COPD exacerbations. As to Bhatt et al., "magnesium is an independent predictor of frequent readmissions for acute exacerbations of COPD" and they recommend that "serum magnesium should be determined in all patients admitted for acute exacerbation of COPD." Aziz et al., suggest [22] Aziz et al., that "a threshold level of serum Mg+2 of approximately 0.85 mmol/L may be a useful therapeutic target for magnesium supplementation, as well as a level below which clinicians may give increased vigilance for signs of exacerbation in their COPD patients. These data suggest that at the lower range of the reference interval, serum Mg+2 levels are associated with an increased risk of exacerbation of symptoms in COPD patients." [16]. Farah et al., investigated prognostic effects of hypophosphatemia in COPD patients and evaluate the correlation between phosphorus levels and severity, recurrences of attacks, ventilation duration and successful of weaning process. According to their findings "low blood phosphorus levels contribute to an increase in COPD flare-up, need for ventilation, duration of hospitalization, days in intensive care units and finally increased rate of molarity." [23] Gumus et al., emphasize the important finding of their study. It is "a positive correlation between serum magnesium level during acute exacerbation and annual number of acute exacerbation of COPD: number of attacks increased in association with serum magnesium levels." [24] Also, some studies have investigated the potential role of trace elements in the treatment of COPD patients. The subject of interest is the possibility of replacement therapy with trace elements, in addition to basic therapy. Studies have shown different results interesting for further processing. It is known that use of isotonic magnesium as an adjuvant to nebulised salbutamol promote bronchodilator response in treatment of severe asthma [25]. Edwards et al., in randomized double-blind placebo-controlled trial found no evidence of efficacy of single or repeated nebulised magnesium as an adjunct to nebulised salbutamol in acute exacerbation of COPD. They suggest that "the priority for further investigation of magnesium should be with the intravenous route of administration [26]. Mukerji et al., also investigated the effects on lung function of intravenous magnesium given with standard bronchodilator therapy in acute exacerbations of COPD. In a pilot study they concluded that it may improve lung function in the short term [27]. Skorodin et al., in randomized double blind study suggest that "magnesium sulfate, 1.2 g over 20 minutes after beta-agonist administration, is safe and modestly efficacious in the treatment of acute exacerbations of chronic obstructive pulmonary disease, and its bronchodilator effect is greater than that of a beta-agonist given alone and lasts beyond the period of magnesium sulfate administration." [28] In another randomized double-blind study, Abreu et al., showed that intravenous

administration of magnesium sulfate has no bronchodilating effect in patients with COPD exacerbations, but it does, however, "enhance the bronchodilating effect of inhaled beta-agonists." [29] Janner et al., also wanted to establish whether the addition of intravenous magnesium to standard treatments improved outcome in patients with exacerbations of COPD. Using the reported search, they found altogether 465 papers, and concluded that "intravenous magnesium is worth considering in patients with an exacerbation of COPD." [30] According to Amaral et al., "acute intravenous loading with 2 g of Mg sulfate attenuates the degree of hyperinflation of stable COPD patients and improves their maximal respiratory pressures". Their randomized, double-blinded, placebo-controlled crossover study investigated the effects of acute intravenous Mg loading on respiratory parameters of stable COPD patients [15]. It has been detected that "intravenous supplement of trace elements, like sodium selenite, zinc and manganese, together with the standard pharmacological therapy can decrease the average mechanical ventilation period of COPD patients". This was a result of a randomized double blind controlled trial made by El- Attar et al. [18].

CONCLUSION

The studies mentioned in this review are different in their objectives, methods and results. They present a source of new ideas for further research of this heterogeneous group of patients and the role of trace elements as predictors of exacerbations, active participants in inflammation, oxidative stress, pathophysiology of COPD and in various treatment options.

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