A review on clinical association of serum magnesium and serum fibrinogen levels with acute exacerbation of chronic obstructive pulmonary disease

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation due to infiltration of small airways with inflammatory cells, causing narrowing, and by destruction of the elastic recoil of lung parenchyma resulting in hyperinflation. Exacerbations occur after infection, irritation, and ambient temperature changes. Exacerbations are often associated with increased neutrophilic or eosinophilic infiltration depending on severity.

Acute exacerbation of COPD (AECOPD) represents a key moment in the progression of COPD. The association between AECOPD and decline in health status and lung function is well recognized. These events absorb around 50% of direct cost for COPD.

AEs that compromise quality of life accelerate a decline in respiratory functions, and increase the economic costs may occur during the course of stable COPD. COPD exacerbation was defined as an acute worsening of respiratory symptoms (increased dyspnea, increased cough or change in the amount, and purulence of sputum) that was beyond normal day-to-day variations of symptoms.

SERUM MAGNESIUM

Magnesium is involved in such important functions as bronchodilation and contraction in respiratory tract smooth muscles, mast cell stabilization, neurohumoral mediator release, and mucociliary clearance. Magnesium is thought to have a protective effect against chronic respiratory tract diseases. It has been suggested that insufficient magnesium intake through diet may lead to the development of asthma and COPD.

A growing body of evidence suggests that Mg deficiency contributes to exacerbations of asthma and, as a corollary, that Mg is useful in alleviating bronchospasm in these patients. COPD represents an overlap of chronic bronchitis and emphysema, and patients with COPD have an element of asthmatic bronchitis. Bronchospasm is a contributing factor in...
their inability to clear secretions. Thus, Mg$^{2+}$ may have a role in maintaining disease stability in COPD patients.$^{[10]}$

Magnesium is one of the major intracellular cations. For normal neuromuscular activity, humans need normal concentration of extracellular calcium and magnesium. Intracellular magnesium is an important cofactor for various enzymes, transporters, and nucleic acids that are essential for normal cellular function, replication, and energy metabolism.$^{[11]}$ Normal range: 0.7–1 mmol/L (1.5–2 mEq/L; 1.7–2.4 mg/DL)$^{[11,12]}$ Critical value: Less than 1 and more than 4.9 mg/DL.$^{[12]}$

Hypermagnesemia causes vasodilation and neuromuscular blockade vasopressors or hypotension refractory, muscular weakness, paralysis, respiratory failure, and coma, with decreased tendon reflexes. Paralytic ileus, flushing of face, dilation of pupils, paradoxical bradycardia, heart block, and prolongation of the PR, QRS, and QT intervals are other features of magnesium toxicity.

Hypomagnesemia causes muscle weakness, ataxia, nystagmus, vertigo, tetany, tremor, seizures, apathy, depression, irritability, delirium, and psychosis.$^{[11,12]}$

**SERUM FIBRINOGEN**

Fibrinogen has emerged as a promising biomarker in COPD and is currently being considered for qualification as a drug development tool by the US Food and Drug Administration and the European Medicines Agency.$^{[13]}$

Fibrinogen is a soluble protein that is produced in the liver and released into the bloodstream. When tissue or blood vessels are damaged, the coagulation cascade is initiated by platelets, and clotting factors are activated to the site as needed, one after another.

At the end of the cascade, fibrinogen is converted to fibrin. Fibrin is an insoluble protein that forms a threaded mesh over the injury site. Thrombin is the enzyme that activates this conversion.$^{[14]}$

However, even though the plasma level of fibrinogen in patients with obstructive ventilatory disorder has been investigated, these levels have not yet been clearly determined in the patients with restrictive pulmonary disease such as pulmonary fibrosis.$^{[15,16]}$ Normal fibrinogen levels in the blood are between 1.5 and 3.5 g/L.

Hypofibrinogenemia causes end-stage liver disease, severe malnutrition, disseminated intravascular coagulation, abnormal fibrinolysis: Acute, and large volume blood transfusions: Acute. Hyperfibrinogenemia causes inflammation, infection, cancer, tissue damage/trauma, acute coronary syndromes, and stroke.$^{[17]}$

**RELATIONSHIP BETWEEN COPD AND SERUM MAGNESIUM**

The study, predicted percentage of forced expiratory volume in 1 s, serum magnesium levels were identified as independent predictors of AEs of COPD and serum magnesium level was the most significant of these predictors. The most important finding of this study is the positive correlation between serum magnesium levels during AE and annual number of COPD-AE. Number of attacks increased in association with serum magnesium levels. This is a significant finding. To the best of our knowledge, this is the first time that this correlation has been identified. Although it is not proven, it is generally believed that due to its bronchodilating effect, a decreased level of magnesium increases COPD exacerbations.

**RELATIONSHIP BETWEEN COPD AND SERUM FIBRINOGEN**

Higher fibrinogen is associated with an increased rate of exacerbations in cohorts of individuals with COPD; individuals with GOLD Stage II disease in the ECLIPSE cohort had a higher risk of exacerbation if their plasma fibrinogen was $>1$ standard deviation above the mean.$^{[18]}$ An earlier 1-year study with moderate to severe disease did not find an association between fibrinogen and exacerbation frequency,$^{[19]}$ but the numbers were likely to have been too small to detect any effect. There may also be an association between fibrinogen and the risk of severe exacerbations, that is, those necessitating hospital admission.$^{[20]}$ Large-scale longitudinal studies in cohorts of the general population also found that those with the highest fibrinogen had increased admission rates with COPD exacerbations during the follow-up period.$^{[21]}$

In individuals with COPD, higher levels of fibrinogen are associated with a reduced level of physical activity. Moreover, decreased levels of physical activity are linked to an increased risk of death. Fibrinogen was higher in non-survivors, although it was not associated with the risk of death in a study of individuals with stable COPD leaving physical activity to be the strongest predictor of all-cause mortality in individuals with COPD. In summary, there is evolving evidence that fibrinogen is a useful biomarker in COPD, particularly in defining those more likely to exacerbate, linking to important clinical endpoints, and in acting as a surrogate marker of treatment success.
RELATIONSHIP BETWEEN SERUM MAGNESIUM AND SERUM FIBRINOGEN

The prevalence of hypomagnesemia in AECOPD is high. Low serum magnesium may predict AECOPD. Low serum magnesium levels may be a risk factor for AECOPD for which further large-scale studies are required. Low serum magnesium is a modifiable risk factor.

Plasma fibrinogen may be an ideal blood biomarker for the existence of systemic inflammation. The levels are easily measured and are already integrated into clinical diagnostic practice. Furthermore, blood biomarkers can be readily measured in patients without the need for invasive procedures. These practical reasons have made it a candidate biomarker in a number of diseases including COPD.

DIFFERENCE BETWEEN ASTHMA AND COPD

COPD can coexist with asthma; both are characterized by an underlying airway inflammation. The underlying chronic airway inflammation is very different in these two diseases. However, individuals with asthma who are exposed to noxious agents, particularly cigarette smoke may develop fixed airflow limitation and a mixture of “asthma-like” and “COPD-like” inflammation. Furthermore, there is epidemiologic evidence that long-standing asthma on its own can lead to fixed airflow limitation. Other patients with COPD may have features of asthma such as a mixed inflammatory pattern with increased eosinophils. Thus, while asthma can usually be distinguished from COPD, in some individuals with chronic respiratory symptoms and fixed airflow limitation it remains difficult to differentiate the two diseases. There are differences between cause, airway inflammation, and airflow limitation between asthma and COPD.

Differences

Asthma is defined as an obstruction that is reversible, where COPD is an obstruction that is irreversible. The inflammation occurring in asthma and COPD is different. Asthma is primarily caused by allergies, whereas COPD is caused by bacteria. Asthma and COPD respond differently to anti-inflammatory medications due to the differences in inflammation. The goal of treatment is different; asthma is treated to suppress chronic inflammation, whereas COPD is treated to reduce symptoms.

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REFERENCES


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