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HUMAN NUTRITION

RESEARCH NOTES

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Magnesium: A Role in the Therapy for Asthma

In the USA, alone, there are about 12 million people who suffer from asthma. Asthma is a pulmonary disease which is characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness to a variety of stimuli. The prevalence of asthma has been steadily increasing over the past two decades, as the incidence of this disease increases, so has the death rate attributed to this health problem. Its incidence is now well over 50 per thousand, and the death rate over 20 per thousand in the USA. Asthma is the number one cause for hospitalization in children, and is the leading chronic condition causing school absenteeism.

The following are the major factors contributing to the airway obstruction of asthma: airway smooth muscle spasm, edema of airway mucosa, excess mucus secretion, cellular infiltration of the airway walls (seen in chronic inflammatory and allergic asthmatic responses), and injury and shedding of the airway lining.

The largest contributor to airway obstruction was once thought to be bronchospasm. However, inflammatory disease of the airways has been recognized to play a more critical role, particularly in chronic asthma. In the inflammatory response

Table 1.

Classification of Asthma by Severity Before Treatment

Category	Symptoms	Pulmonary Function
Mild intermittent	• Symptoms ≤ 2 times a week • No symptoms and normal PEF between exacerbations • Exacerbations brief (from a few hours to a few days); intensity may vary • Nighttime symptoms ≤ 2 times a month	FEV_1 or PEF ≥ 80% predicted PEF variability < 20%
Mild persistent	• Symptoms > 2 times a week but not daily • Exacerbations that sometimes limit activity • Nighttime symptoms > 2 times a month	FEV_1 or PEF ≥ 80% predicted PEF variability 20% – 30%
Moderate persistent	• Daily symptoms • Daily use of inhaled short-acting β_2-agonist • Exacerbations that limit activity • Exacerbations ≥ 2 times a week; may last days • Nighttime symptoms > 1 time a week	FEV_1 or PEF > 60% - 80% predicted PEF variability > 30%
Severe persistent	• Continual symptoms • Limited physical activity • Frequent exacerbations • Frequent nighttime symptoms	FEV_1 or PEF ≤ 60% predicted PEF variability > 30%

PEF = Peak Expiratory Flow; FEV_1 = Forced Expiratory Volume in 1 sec.
Modified from the National Asthma Education and Prevention Program, Expert Panel Report II, National Heart, Lung, and Blood Instutute, 1997.
Merck Manual, 17th edition, Merck Research Lab; Division Merck & Co., Inc, Whitehouse Station, NJ.

seen in asthma, there is infiltration of the airway walls by eosinophils, lymphocytes, neutrophils, and mast cells. Research has shown that the concentration of eosinophils in blood and airway secretions of the asthmatic correlates with the degree of bronchial hyperresponsiveness seen in all asthmatics, which exhibits itself as an exaggerated bronchoconstriction in response to a variety of stimuli. The severity of asthma is directly linked to the degree of airway hyperreactivity.

Inflammatory mediators are released or formed as a consequence of allergic reactions in the lungs. They include histamine, leukotrienes, and thromboxanes. Additionally, allergic response gives rise to T-cell activation and their secretory products (cytokines - which promote growth and differentiation of inflammatory cells). Cytokines include interleukin (IL)-4 and (IL)-5. These inflammatory mediators contribute to bronchoconstriction, mucus secretion, and microvascular leakage seen in chronic asthma.

Additionally, acute asthmatic responses to inhaled irritants come through cholinergic reflex bronchoconstriction, but more importantly from the release of certain neuropeptides which cause vascular permeability, mucus secretion, bronchocontriction and bronchial vasodilation.

Monitoring Asthmatics

As listed in Table 1, asthma can be classified by severity before the institution of treatment. Its severity is evaluated based on the known symptoms of asthma, as well as the performance of the patient in various pulmonary function studies. In addition, eosinophil count, sputum examination, chest x-ray, and allergen or irritant exposure are all used to evaluate the category of asthma. Improvement of these symptoms and the pulmonary function study results are used to evaluate the degree of success of treatment in the asthmatic. A decrease in the symptoms of asthma, lesser need for reliance on drugs, and improvement in pulmonary function are signs of asthmatic improvement.

Although bronchospasm was once thought to be the leading contributor to airway obstruction, inflammatory response due to a variety of causes is now recognized as the leading culprit in airway obstruction. These inflammatory sequalae are the reason for the enhanced bronchial hyperresponsiveness seen in all asthmatics, and they directly relate to the severity of asthma. It is this concept that has lead researchers and clinicians to believe that the control or regulation of these inflammatory mediators is a key to managing the problems of asthma. In fact, many of the pharmacological agents that are used in the therapeutics of asthma succeed through their ability to inhibit or block the performance of these inflammatory mediators, such as leukotrienes, thromboxanes, histamines, and cytokines. These inflammatory mediators are all part of different and complex cascades of biochemical pathways, involving prostaglandins, white cells, mast cells, and histamines. These pathways are known to require a variety of chemical mediators or catalysts, each of which can require a mineral or trace mineral as a cofactor or some related determining element. As science has begun to recognize the importance of minerals to such cascades, research into the role of minerals and trace minerals in the regulation of the biochemical pathophysiology of asthma (and other diseases) has become more prevalent. In the following abstracts, the recent findings for the impact of certain minerals, especially magnesium, in the pathophysiology of asthma are reviewed.

Asthma Research – Emphasis on Magnesium

The biochemistry and pathophysiology of asthma involves several areas, including white cells (eosinophils), mast cells, cytokines, and leukotrienes (pro-inflammatory prostaglandins), as with all chronic diseases, nutrition can play an important role in the improvement or the worsening of such conditions. There are a variety of nutritional components that have been researched in connection with asthmatics. One of the minerals that has gotten attention in this regard, is magnesium.

Reduced intracellular magnesium concentrations in asthmatic patients. Emelyanov A; Fedoseev G; Barnes PJ. Eur Respir J 1999 Jan;13(1):38-40.

Low dietary intake of magnesium has been associated with airway hyperresponsiveness in

epidemiological research, and bronchomotor tone relies on magnesium as one of its regulators. This study looks at the serum, erythrocyte and urinary levels of magnesium in patients with asthma and in normal subjects. The asthmatics had lower levels of magnesium in erythrocytes and urine than the normal group, whereas the serum concentrations did not vary. It was observed that the erythrocyte concentration of magnesium did not relate to the degree of airway obstruction, but to the amount of airway hyperresponsiveness. Additionally, a magnesium tolerance test demonstrated an increased magnesium retention (58.9% of administered dose) in asthmatics as compared to only 8.9% seen in the normals. The researchers concluded that low cellular concentration of magnesium is associated with airway hyperresponsiveness in asthmatic patients.

Hypomagnesemia in chronic, stable asthmatics: prevalence, correlation with severity and hospitalization.
Alamoudi OS.
Eur Respir J 2000 Sept;16(3):427-431.

The incidence and effect of hypomagnesemia in asthmatics is not clear. Some of the signs of asthma, like airway hyperreactivity, wheeze, and impaired lung function have been associated with magnesium deficiency. This prospective study included 93 chronic stable asthmatics on regular follow-up at an asthma clinic. The study evaluates the prevalence of low serum magnesium and looks to correlate whether hypomagnesemia (serum Mg <0.74 mmol X L(-1)) is associated with the severity of asthma and the frequency of hospitalizations in chronic, stable asthmatics. Each subject was interviewed and clinically evaluated, measuring serum Mg and determining the severity level of asthma. Notation was made as to medications used and the total number of hospitalizations due to asthma problems for the 3 months prior to the date on which they determined the serum Mg. It was determined that 25 (27%) of the asthmatics had low serum Mg, while 68 (73%) had normal serum Mg. It is noteworthy that 40% of the asthmatics with low serum Mg had hospitalizations, while only 12% of those with normal serum Mg did so. Chronic asthmatics with low serum Mg tend to have more hospitalization than chronic asthmatics with normal serum Mg levels. In addition they concluded that hypomagnesemia was also associated with more severe asthma.

Assessment of magnesium status in patients with bronchial asthma.
Hashimoto Y, et al.
J Asthma 2000 Sept;37(6):489-496.

This study was done to elucidate the contribution of magnesium to bronchial hyperreactivity in patients with stable bronchial asthma. At the onset of the study, the magnesium levels in serum, erythrocytes, and lymphocytes were measured in 25 bronchial asthmatics and in 9 age matched healthy subjects, as a control. It was seen that the bronchial asthmatics had significantly lower levels of erythrocyte magnesium than the healthy controls, while the serum and lymphocyte magnesium levels of both groups were not much different. A parenteral magnesium loading test was performed to determine total magnesium body stores. This test revealed that 40% of the asthmatics and only 11% of the controls had total body store magnesium deficiency. In addition, it was observed that the lower the erythrocyte magnesium level, the higher the ratio of magnesium retention to urinary magnesium excretion seen in the parenteral magnesium loading test. In another part of this study, the subjects were administered via inhalation the methacholine provocative test. It was seen in this test that the lower the level of erythrocyte magnesium, the higher the level of bronchial reactivity to the administered methacholine. The researchers concluded that low erythrocyte magnesium levels reflected a decreased magnesium store in the bronchial asthmatics, and that 40% of these asthmatics were magnesium deficient.

In addition to these research findings, another study (Zerva E, et al., Chest 2003;123(1):113-118) determined that acute asthma is associated with lower erythrocyte magnesium levels, while plasma Mg levels were normal. This low level of erythrocyte (intracellular) magnesium occurred in all acute cases (regardless of severity), and their values normalized after the acute situation was brought under control A study on electrolyte disturbances in asthma (Alamoudi OS, Chest 2001 Aug;120(2):431-436) concluded that hypomagnesemia and hypophosphatemia were seen to be the two most common electrolyte disturbances in patients with chronic, stable asthma. The drugs used in

the treatment of asthma were seen to have no effect on the electrolyte levels. The actual cause for the depleted levels of magnesium and phosphate is not yet known.

At this point, the findings on magnesium and asthma could be summed up as follows. In general asthmatics have a tendency to be deficient in total body magnesium. Serum magnesium and white cell magnesium for asthmatics is about the same as that seen in healthy normals. However, erythrocyte (red blood cell) magnesium levels are lower than normal in asthmatics. Low red cell magnesium levels are associated with an increase in airway hyperresponsiveness in asthmatics, and the degree of hypomagnesemia is directly associated with the severity of asthma.

Key Research Finding

Oral magnesium reduces asthma morbidity in children and adolescents.
Amaral CG, et al.
European Respiratory Symposium Annual Congress (13th) Sept 2003.

The aim of this work was to investigate the effect of oral magnesium on asthma morbidity for children and adolescents. This was a randomized placebo controlled study that included 37 patients (ages 7-19) suffering from moderate persistent asthma. One group received magnesium (as Magnesium Chelazome®, Albion) at a dose of 300 mg per day for two months. The second received a placebo. All patients received fluticazone (250 mcg twice a day), and salbutamol as needed – drugs were taken via inhalation. The two groups had similar distribution for age, sex and onset of disease. The protocol called for a schedule of clinical evaluations, pulmonary function testing, and assessing of bronchial responsiveness to methacholine at the beginning and end of the study. Pulmonary function tests for the Magnesium Chelazome® group had significantly higher values after the oral magnesium supplementation for FVC, FEV1, and FEF25-75, while the placebo group did not (lone exception being a slight increase in FEV1). In addition, the number of days with asthma attacks and the need to use salbutamol were significantly lower for the Magnesium Chelazome® supplemented group.

From the above study, it can be seen that the use of Magnesium Chelazome® in these asthmatics, based on the parameters used to judge successful treatment of asthma, is positive in all of the aspects: improvement of signs and symptoms, less reliance on drugs, and objective improvement in pulmonary function studies. More studies need to be done to determine what the exact mechanism is by which this form of magnesium yields these benefits. It is of interest to note that an earlier study on the use of magnesium (as a supposed chelate) and vitamin C in asthma (Fogarty, et al., Clin Exp Allergy 2003 Oct;33(10):1355-1359 found that supplementation with vitamin C or magnesium added no clinical benefits to the current standard therapy of asthma. In speaking with the lead researcher, Dr. Fogarty, it was found that the magnesium chelate (at 450mg of magnesium per day) was actually a blend of magnesium with mixed amino acids and soy. Apparently, the actual form or source of magnesium may be essential to the benefits seen with magnesium in asthma.

Albion Advanced Nutrition will be looking for more involvement in this area of clinical need. Albion's Magnesium Chelazome® has been shown to have advantages over other forms of magnesium in repeated clinical studies: greater effectiveness, bioavailability, less interaction, and higher tolerance.

Albion's list of magnesium ingredients include:

- Magnesium Chelazome®
- Magnesium Glycyl Glutamine
- Magnesium Buffered Amino Acid Chelate
- Magnesium Amino Acid Chelate Taste-Free
- Creatine MagnaPower® (magnesium creatine chelate)
- Magnesium Aspartate (two forms)
- DiMagnesium Malate

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