Magnesium Supplementation Decreases Airway Responsiveness among Hyperreactive Subjects

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Zusammenfassung

Magnesium ist beteiligt an physiologischen Reaktionen die Muskelkontraktilität betreffend und eine kürzlich durchgeführte epidemiologische Studie hat eine Relation gezeigt zwischen der Ansprechbarkeit der Atemwege und verminderten Magnesiums in der Nahrung. In der vorliegenden Pilotstudie wurden Patienten mit erhöhter Ansprechbarkeit der Atemwege, gemessen durch den Methacholine-Test, ausgewählt und der Hälfte der Gruppe wurde sechs Wochen lang Magnesium verabreicht. In der behandelten Gruppe wurde eine fortschreitende Abnahme der Atemwegsansprechbarkeit festgestellt. Die Ergebnisse lassen vermuten, daß eine Magnesiumsupplementation nützlich sein kann, um Symptome der Atemwegsentzündung zu lindern.

Summary

Magnesium participates in a number of physiological reactions related to muscular contractility and a previous population study has shown a relation between airway responsiveness and lack of magnesium in the food. In this pilot study, subjects with an increased airway responsiveness, as evaluated with the methacholine test, were selected and half of the group was given magnesium tablets for a period of 6 weeks. In the treated group, there was a progressive decrease in airway responsiveness. The results suggest that magnesium supplementation may be useful to relieve symptoms of airways inflammation.

Résumé

Le Mg participie à plusieurs réactions physiologiques reliées à la contractilité musculaire. Une étude antérieure sur une population a montré une relation entre la réponsivité de la voie respiratoire et une carence en magnésium dans l'alimentation. Dans cette étude pilote des participants avec une réponse de la voie respiratoire augmentée – comme évalué avec le test métacholine – étaient sélectionnés. On administrait des comprimés de magnésium à la moitié du groupe pendant une période de 6 semaines. Ce groupe traité montrait une diminution progressive de la réponsivité de la voie respiratoire. Les résultats suggèrent que la supplémentation de magnésium peut être utile pour réduire les symptômes de l'inflammation de la voie respiratoire.

Introduction

Airways inflammation is a widespread disease among persons exposed to environmental agents such as organic dusts and tobacco smoke [1]. It is also common among asthmatics. The disease is characterized by cough, nose and throat irritation and an increased sensitivity to various air pollutants which in themselves may cause an exacerbation of the inflammation.

There is increasing evidence that dietary factors play an important role for the risk for pulmonary disease [2]. Abundant information is available on the protective effect of vegetable consumption against lung cancer [3, 4] and an impact on other respiratory disease has also been found [5]. Airways inflammation and the clinical sequelae in terms of increased airway responsiveness, are mediated by cell reactivity and contraction of airway smooth muscle, and it is thus logical to investigate dietary agents of importance for these functions.

A previous review has demonstrated evidence that magnesium is such an agent [6]. Magnesium is an important element in many enzymes which regulate energy expenditure and muscular contraction. Magnesium effects a multitude of cellular functions, such as ATP-control or the passage of ions through the cell membrane. Cardiac arrhythmia, muscular fibrillations, fatigue, excitability and poor muscular function are some of the clinical consequences [7]. Also, magnesium and calcium form complexes with phospholipids that are integral parts of the cell membrane. A lack of magnesium could thus cause muscular cell function disturbances and cell membrane penetration of inflammatory mediators. This hypothesis is supported by the results from a recent study where a negative association was found between magnesium intake in food and airway responsiveness in 2633 randomly sampled adults in England [8].

In view of the above, a pilot study was undertaken to further investigate the possible role for magnesium on airways inflammation. A group of persons with an increased airway responsiveness was selected and half of the groups was given magnesium tablets. The airway responsiveness was measured at 10 day intervals.

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Material and Methods

Subjects

The subjects were recruited into the study by advertising at the local university and a number of never smoking (< 100 cigarettes during lifetime) students of both sexes applied. They underwent an airway responsiveness test (see below) and 18 persons with a fall of 10% or more in forced expiratory volume in one second (FEV_1) after the methacholine challenge were chosen as sub-

jects. Persons on continuous medication with anti-asthma or anti-inflammatory drugs were not included in the study.

Airway Responsiveness

Airway responsiveness was assessed using the methacholine challenge test according to *Yan* et al. [9] with some modifications as previously described by *Carvalheiro* et al. [10]. The subjects inhaled three puffs (3 μl) of saline from an automated Pari Boy inhalation device and spirometry was performed according to standard ATS criteria. This FEV_1-value was used as a reference for values obtained after the methacholine inhalations and expressed as percent of the predicted value for persons of the same age, sex and height [11]. Thereafter, they inhaled 3 μl of methacholine in increasing doses at three minute intervals up till a total dose of 1.2 mg. Spirometry was performed after each dose. The results were expressed as the average decrease in FEV_1 as compared to the post saline value. If a subject decreased more than 20% after any dose of methacholine, the test was discontinued.

Measurements of airway responsiveness were made before the magnesium supplementation started, three times at about 10 day intervals, and at the end of the study. During the experiment, it was found that some subjects in the supplementation and control groups could not be given the highest methacholine dose according to the safety criteria given above, and the next highest dose was therefore used as the comparison value for the groups at the different occasions.

Magnesium Supply and Determination

The subjects were randomly divided into two groups and one group (n = 9) received magnesium tablets (Mg 75 mg). They were instructed to take 4 tablets daily throughout the study. The reference group (n = 9) did not receive any treatment.

Before the magnesium treatment started and at the end of the study, a sample of venous blood was drawn and the amount of magnesium in the serum was determined at the clinical laboratory, Sahlgren's hospital, Gothenburg, using atomic absorption spectrophotometry.

Tab. 1: Decrease in FEV_1 (% of preexposure saline value) after 0.8 mg methacholine in subjects with and without magnesium supplementation. Mean and standard deviation. About 10 days between different test occasions.

Test occasions	Magnesium		Reference	
	n		n	
Before	9	−8.2 ± 5.8	9	−13.0 ± 9.2
1	8	−5.8 ± 3.4	8	−9.4 ± 5.2
2	8	−7.0 ± 10.1	8	−15.6 ± 10.2
3	6	−4.5 ± 4.5	7	−11.8 ± 9.5
After	8	−3.6 ± 4.3	7	−11.6 ± 12.5

Results

Regarding spirometry, the baseline FEV_1 values ranged between 99.6% and 107.4% of predicted values with no significant differences between groups or at different times. The results from the measurements of airway responsiveness are shown in Table 1. The slight variation in number of persons tested on the different occasions is because some subjects were out of town or because they on a particular occasion reacted with more than 20% decrease FEV_1. The distribution of this dropout was similar in the two groups. The average value before supplementation was slightly lower in the group receiving magnesium, but the difference to the reference group was not statistically significant. It is seen that the average decrease in FEV_1 after methacholine became lower during the course of the experiment in the group given magnesium. At the end of the experiment, the difference was statistically significant ($p = 0.01$, Wilcoxon's paired test).

Table 2 shows the serum magnesium values in the two groups.

It is seen that no differences in magnesium value were present between or within the groups before and after magnesium supplementation. There was no change in the average serum magnesium levels before and after medication in either group. Individual differences were, however, present – in some persons the serum magnesium value increased and in others it decreased.

The relation between the change in serum magnesium values in individual subjects before and after the study (ΔMg) and the decrease in FEV_1 after the methacholine exposure was calculated. One person with an extreme decrease (38% as compared to the average in the group – 7.3, SD 9.6), and judged to be caused by a technical error, was deleted from the material.

Tab. 2: Serum magnesium levels in test persons with and without magnesium supplementation before and after supplementation. Mean and standard deviation.

	Magnesium	Reference
n	9	9
Before	0.88 ± 0.08	0.89 ± 0.04
After	0.87 ± 0.05	0.87 ± 0.04

It was found that the difference in serum magnesium value before and after the experiment was negatively related to the decrease in FEV_1 after methacholine. In persons where magnesium values increased over the time course of the experiment, there was a smaller decrease in FEV_1 after methacholine ($r_{xy} = 0.592$; $p = 0.012$).

Discussion

The present study is of a pilot nature and for technical reasons, no placebo could be administered. It is highly unlikely, however, that the decrease in airway responsiveness among the subjects taking magnesium could be induced by the awareness of the magnesium supplement.

The method to evaluate airway responsiveness used is different from the traditional clinical testing. Instead of titrating the dose required for a certain decrease in FEV_1 e.g. PD_{20}, the average reaction to the highest cumulative dose given in a relatively short time was calculated. The same procedure has been used in other studies [10, 12, 13]. As the definition of airway responsiveness is operational rather than absolute, there are no theoretical objections towards

evaluating airway responsiveness this way.

The results from the present study are in line with the results from the large dietary study in England [8], showing an inverse relation between magnesium intake and airway responsiveness. The mechanism behind the effects of magnesium supplementation might be related to an increased inhibition of Ca^{2+} influx through airway smooth muscle cells, leading to a bronchodilatation [14]. Previous studies have shown a relation between magnesium level in drinking water and cardiovascular mortality [15–17]. It is possible that the underlying mechanism on the muscle cells contractility is the same for cardiovascular effects and airway responsiveness.

Mean serum magnesium levels were not influenced by the intake of magnesium tablets. This is in accordance with previous experience which shows that serum magnesium is a poor descriptor of the body burden of magnesium. A relation was, however, found between the degree of airway responsiveness and the difference between magnesium levels before and after the intervention. The importance of this finding and the underlying pathogenic mechanism is open for speculation.

New studies with control of all sources of magnesium intake and performed over a longer time period are required before final conclusions can be drawn. If the results can be confirmed, an added intake of magnesium could be a useful medical remedy to decrease airway responsiveness and thus respiratory discomfort for persons with airways inflammation, either due to specific sensitization or as a result from exposure to irritants. The result also suggest that the magnesium status could be a confounder when relations between environmental exposures and airways inflammation are studied.

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