Oral magnesium supplementation in children with cystic fibrosis improves clinical and functional variables: a double-blind, randomized, placebo-controlled crossover trial

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ABSTRACT

Background: Magnesium is one of the most important minerals in the body. Although some studies reported that patients with cystic fibrosis (CF) lack magnesium, no international study has assessed the importance of oral magnesium supplementation in CF patients.

Objective: We prospectively investigated the long-term effect of oral magnesium supplementation on respiratory muscle strength by using manuvacuometry and the Shwachman-Kulczycki (SK) score among children and adolescents with CF.

Design: This double-blind, randomized, placebo-controlled crossover study included 44 CF patients (aged 7–19 y; 20 males) who were randomly assigned to receive magnesium (n = 22; 300 mg/d) or placebo (n = 22) for 8 wk with a 4-wk washout period between trials. All patients were undergoing conventional treatment of CF. The experimental protocol included clinical evaluation, assessment of urinary concentration of magnesium, and manuvacuometric measurements [maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP)]. MIP was the primary outcome.

Results: Urinary magnesium increased after the administration of magnesium (change: 36.38 mg/d after magnesium compared with 0.72 mg/d after placebo; P < 0.001). Moreover, MIP and MEP significantly improved only after magnesium administration (change in MIP: 11% predicted after magnesium compared with 0.5% predicted after placebo; change in MEP: 11.9% predicted after magnesium compared with 0.8% predicted after placebo; P < 0.001 for both). Magnesium administration had a beneficial effect on clinical variables assessed by the SK score (change: 4.48 points after magnesium compared with −1.30 points after placebo; P < 0.001).

Conclusion: Oral magnesium supplementation helped improve both the SK score and respiratory muscle strength in pediatric patients with CF. This trial was registered at www.ufmg.br.bioetica/coep as CAAEO 559.0.203.000-07. Am J Clin Nutr 2012;96:50–6.
Although the mechanism of action of magnesium in pulmonology is not fully understood, inhaled, intravenous, and oral administration of magnesium has proven efficient in the treatment of pulmonary pathology in both children and adults (12–15).

Over the past decade, interest in magnesium has increased with biochemical studies on magnesium, its nutritional relevance, its potential roles in human diseases, and particularly its association with the pathogenesis of pulmonary disorders (16, 17).

Moreover, magnesium is a low-cost mineral, and no serious side effects have been found after magnesium supplementation in several studies.

We hypothesized that CF patients have low body magnesium storage and that magnesium supplementation could improve respiratory muscle strength. This study aimed to evaluate the effects of oral magnesium supplementation on the respiratory musculature.

SUBJECTS AND METHODS

Enrollment and follow-up for this crossover study were performed between January 2007 and December 2010. Forty-four children and adolescents from a single center were included. The patients were recruited and followed up at the university hospital’s CF clinic (Federal University of Minas Gerais, Brazil). Inclusion criteria were as follows: age of 7–19 y, 2 positive sweat tests (≥60 mmol/L) according to the Gibson and Cook method (18), and stable clinical condition (ie, no need for oral or intravenous antibiotic treatment in the 4 wk before testing).

Smokers and patients receiving any treatment likely to affect magnesium absorption or excretion, such as diuretics, digoxin, or calcium-containing medications, were excluded from the study.

All children were undergoing conventional treatment of CF, including respiratory medications, pancreatic enzyme, and supplementation of water-soluble and fat-soluble vitamins at Recommended Dietary Allowance (RDA) doses (2, 19).

After an initial screening and run-in period of 4 wk, the 44 patients were randomly assigned to the study treatments. Each participant received 300 mg oral magnesium-glycine (n = 22) or a placebo control (n = 22) once daily for 8 wk, with a washout period of 4 wk between trials (Figure 1). Magnesium amino acid chelate (taste free; lot number 251755) from Albion Laboratory was used. The magnesium dose used for each participant ranged from 5 to 12 mg·kg⁻¹·d⁻¹ according to the RDA. In the initial phase of the study we evaluated the average weight of the group to perform a stratified randomization. Thus, we arbitrarily chose the dose of 300 mg/d on the basis of the median weight of the children and adolescents included in the study (40 kg × 7.5 mg/kg = 300 mg/d). Patient compliance with the prescribed magnesium therapeutic regimen was assessed in a monthly follow-up by questionnaire.

Investigators and patients were blinded to randomization, drug manipulation, and dispensing, which were performed independently from the recruitment and assessment of participants. The magnesium and placebo powders were similar in appearance and were prepackaged by a pharmacist in identical containers that were coded according to a randomized sequence. Stratified randomization was performed by using a computer-generated table of random numbers, and participants were randomly assigned to the intervention or placebo group. The randomization code was revealed at the end of the study (20). The magnesium powder was provided in a single-dose packet. The same researcher provided the packages containing either magnesium or placebo at each appointment to ensure accuracy. Glycine was used as a placebo, so the difference between the 2 groups was only the presence or absence of magnesium. The magnesium and placebo had a similar taste and appearance. Participant adherence was evaluated at each appointment by checking the empty used packages brought in by the parents or legally responsible member of the family. If the patients used <80% of the monthly doses of magnesium or placebo, they were excluded.

FIGURE 1. Flowchart of study enrollment and design.
The experimental protocol included clinical evaluation and assessment of urinary magnesium and strength of respiratory musculature. All of these assessments were performed at the beginning of the trial as well as after 60 d of magnesium or placebo administration during both trial periods. Maximal inspiratory and expiratory pressures (MIPs and MEPs, respectively) were measured as indexes of respiratory muscle strength. The primary outcome was MIP, and secondary outcomes were MEP and respiratory disease severity assessed by the Shwachman-Kulczycki (SK) score.

Written informed consent was obtained from each participant and/or his or her parents before the study. The research committee approved both the informed consent and the experimental protocol in accordance with the Brazilian Ministry of Health/Brazilian National Committee on Ethics in Research, resolution no. 196/1996. All procedures were conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Maximal respiratory pressures

The measurement of maximal respiratory pressures generated at the mouth is an accepted noninvasive clinical method for evaluating the strength of respiratory muscles (21, 22). The MIP reflects the strength of the diaphragm and other inspiratory muscles, whereas the MEP reflects the strength of the abdominal muscles and other expiratory muscles. The detection of a change in respiratory muscle strength can be useful in identifying improvement or progression of the disease (23). MIP and MEP were measured by using an analog manuvacuometer (Imebra’s), with operating intervals of 0–300 cm H2O. All of the tests were performed according to American Thoracic Society/European Respiratory Society statements (23) by the same member of the research team. Inspiratory and expiratory muscle strength was measured before and immediately after each treatment period by using maximal static pressures produced at the mouth. MIP was measured at residual volume, and MEP was measured at total lung capacity with the subject seated in a hard-backed chair while wearing a nose clip and keeping a mouthpiece held firmly between the lips. Because of the volitional character of the test, the researcher carefully instructed and encouraged motivation for each maneuver (24). Each pressure attempted was measured at 1-min intervals at least 3 times until there was <10% difference between the 2 highest values. The maximal MIP and MEP values were described and analyzed as percent-predicted values for the study subjects. The predicted values were based on those reported by Wilson et al (25).

Clinical assessment

The SK score was calculated by 2 pediatric pulmonologists with expertise in CF. The pediatric pulmonologists were blinded to each other and to subject treatment and order of treatment. The SK score is divided into 4 domains: general activity, physical examination, nutrition, and radiologic findings. Each of these domains has 5 possible subscores based on the degree of impairment. The scores of the 4 domains are summed to obtain the final score, from which the condition of the patient is categorized as excellent (86–100 points), good (71–85 points), average (56–70 points), poor (41–55 points), or severe (≤40 points) (26).

Anthropometric measurements

Anthropometric measurements included weight, height, and BMI. They were performed according to the WHO recommendations (27) by the same member of the research team. Weight (in kg) was measured by using an anthropometric platform scale (Filizola SA), and height (in cm) was measured by using a stadiometer attached to the same scale. BMI was calculated as weight divided by height squared. Values of weight, height, and BMI were standardized by age and sex according to the WHO growth curve (28) and expressed as z scores.

Urinary concentration of magnesium

The urinary concentration of magnesium was assessed in all patients before and after each study period. Concentrations were determined by using the VITROS magnesium slide method with the Mg Slides and Chemistry Products Calibrator Kit 1 in VITROS 250/350/950/5, the 1 FS (shading coefficient) and 4600 Chemistry Systems, and the 5600 Integrated System (Johnson & Johnson).

Statistical analyses

On the basis of our previous pilot study (data not published), a sample size of 19 patients was determined for each group, with consideration of appropriate calculations for randomized clinical trials and the possibility of a type II error. With an SD of 6.46 base units of MIP (percent predicted) used as the primary outcome, we calculated that 19 subjects in each group would be required for 85% power at the 5% level of significance. Descriptive statistics were assessed accordingly.

Student’s t test was used to compare age, weight, and BMI in both groups. The Mann-Whitney U test was used to compare height. Chi-square and Fisher’s exact tests were used to analyze sex and race, respectively. Because the urinary concentrations of magnesium were normally distributed, a single paired Student’s t test was used.

Normality was tested for all outcomes. Because a crossover design was used and the results were not normally distributed, the Wilcoxon signed-rank test was used. All data were entered before the treatment codes were revealed and were analyzed by using the Statistical Package for Social Sciences (version 17 for Windows; SPSS); P values <0.05 were considered significant. Data are presented as means ± SDs (29).

RESULTS

Forty-four patients screened for participation in this study met the study criteria. There were no dropouts. No carryover effect was seen in the groups that started with either magnesium or placebo. Although it is impossible to accurately test for the presence of a carryover effect (ie, whether the effect of treatment “carries over” and affects results while the patient is receiving placebo) in a traditional 2 × 2 crossover design (2 groups, 2 periods) such as this one, we have tested the effects of sequence and period-by-treatment interaction, which are possible indicators of a carryover effect. The effects of sequence and period-by-treatment interaction were not significant for any outcomes (P > 0.05 for all outcomes, ANOVA). No adverse effects of magnesium toxicity such as vomiting, double vision,
TABLE 1
Characteristics of the patients with cystic fibrosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 44)</th>
<th>Magnesium group (n = 22)</th>
<th>Placebo control group (n = 22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>12.86 ± 3.72</td>
<td>12.68 ± 3.73</td>
<td>13.05 ± 3.79</td>
<td>0.75</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>20:24</td>
<td>10:12</td>
<td>10:12</td>
<td>1.00</td>
</tr>
<tr>
<td>Race (white:black)</td>
<td>39:5</td>
<td>19:3</td>
<td>20:2</td>
<td>1.00</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>39.63 ± 12.81</td>
<td>39.22 ± 12.86</td>
<td>40.04 ± 13.04</td>
<td>0.83</td>
</tr>
<tr>
<td>z Score</td>
<td>-1.13 ± 1.37</td>
<td>-1.08 ± 1.3</td>
<td>-1.18 ± 1.47</td>
<td>0.60</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.46 ± 0.17</td>
<td>1.46 ± 0.18</td>
<td>1.47 ± 0.18</td>
<td>0.94</td>
</tr>
<tr>
<td>z Score</td>
<td>-1.10 ± 1.34</td>
<td>-1.10 ± 1.25</td>
<td>-1.20 ± 1.44</td>
<td>0.29</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.95 ± 2.52</td>
<td>17.68 ± 2.24</td>
<td>18.21 ± 2.69</td>
<td>0.49</td>
</tr>
<tr>
<td>z Score</td>
<td>-1.15 ± 1.37</td>
<td>-1.09 ± 1.31</td>
<td>-1.20 ± 1.46</td>
<td>0.43</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>75 ± 23</td>
<td>69 ± 25</td>
<td>80 ± 18</td>
<td>0.26</td>
</tr>
<tr>
<td>PI [n (°)]</td>
<td>7/44 (15.9)</td>
<td>3/22 (13.6)</td>
<td>4/22 (18.2)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

1 FEV₁, forced expiratory volume in 1 s; PI, children and adolescents with pancreatic insufficiency.
2 Mean ± SD (all such values).
3 Student’s t test.
4 Chi-square test.
5 Fisher’s exact test.
6 Mann-Whitney U test.

Feeling of warmth, flushing, or hypotension were reported from patients in either group.

Random assignment resulted in a well-balanced equivalent distribution of patients with respect to age, sex, race (self-reported), height, weight, BMI, forced expiratory volume in 1 s, and pancreatic insufficiency at baseline. These results are shown in Table 1. Both groups showed appropriate compliance.

Urinary concentrations of magnesium and SK score data at baseline and at the end of follow-up for both groups are shown in Table 2. As shown in Figure 2, after the intervention period MIP showed an 11 ± 7.8% predicted increase (from 98.3 ± 29.7% to 109.3 ± 31.8% predicted) in the magnesium group, with a slight 0.5 ± 6.3% predicted increase (from 99.2 ± 28.6 to 99.7 ± 29.3% predicted) in the placebo group. MEP also showed an 11.9 ± 7.7% predicted increase (from 97.5 ± 27.8 to 109.4 ± 27.3% predicted) after magnesium administration and a slight 0.8 ± 6.5% predicted increase (from 97.4 ± 26.6% to 98.2 ± 27.3% predicted) after placebo administration. The differences between the intervention and placebo periods were significant (P < 0.001 for both MIP and MEP).

DISCUSSION

Our results showed that after 2 mo, children and adolescents with CF who were receiving conventional therapy for CF and oral magnesium supplementation achieved a significant improvement in the functional status of the respiratory musculature, as assessed by manovacuometry. Significant clinical improvements, shown by means of the SK score, were also observed.

To the best of our knowledge, the current study is the first performed in pediatric CF subjects to investigate the effects of oral magnesium administered on a regular basis. Up to the time of the study outline, there was a lack of data that could be used as parameters for improved planning in CF pediatric subjects in terms of effective doses of magnesium, length of treatment period, and possible side effects. Some of the available data were based on studies performed in adult patients and in those with other respiratory diseases (10, 14). Other data were obtained from updated reviews of the physiologic, clinical, and analytic aspects of the use of magnesium in different diseases (6).

Assessment of age, weight, height, race, and sex indicated that our population was homogeneous. Moreover, the characteristics of our population were similar to those of CF children in other studies. Even after random assignment, the 2 groups retained similar demographic characteristics without any statistically significant differences.

The assessment of serum magnesium concentrations is not an accurate reflection of the magnesium status of muscle, bone, and other tissues. There is a poor correlation between serum and intracellular magnesium concentrations, most probably because only 1% of total body magnesium reserves can be found in whole blood (6). We therefore decided to analyze the urinary
concentration of magnesium before and after each period of magnesium or placebo administration (30).

Many factors may be responsible for magnesium deficiency in CF patients. First, current dietary surveys show that the average magnesium intake in Western countries is often below the RDA (280 and 350 mg/d for women and men, respectively) (31). Second, gastrointestinal malabsorption, a common symptom of CF, may cause hypomagnesemia (32). Third, certain antibiotics and chemotherapeutic agents such as amphotericin B, cyclosporine, aminoglycosides, and tobramycin used by CF patients also induce hypomagnesemia (33). Magnesium supplementation is therefore a promising strategy for improving clinical symptoms and respiratory musculature strength in CF patients, as was shown by this trial.

Interestingly, only those patients who received oral magnesium in the study period presented with better clinical symptoms as assessed by the SK score. In a study by Stollar et al (34), the SK score was reported to be a useful and simple tool for monitoring the severity of CF.

The proposed action of magnesium in CF patients is not completely understood. ATP regulates the opening and closing of the CFTR Cl channel, and magnesium plays a role in many crucial enzyme systems, especially those involving ATP metabolism (35). Moreover, magnesium acts as a cofactor in the enzymatic degradation of DNA by rhDNase I, so a minimum concentration of magnesium is required to obtain optimal rhDNase I activity (36). The addition of magnesium to sputum samples that cannot be degraded by rhDNase I enables these samples to be degraded by that enzyme (36). Sanders et al (8) showed that the effect of magnesium on rhDNase I is mediated through actin and that oral intake of magnesium enhances its concentration in the sputum of CF patients. The failure of rhDNase I may therefore be overcome by combining rhDNase I with oral magnesium supplements.

In the analyses of the functional status of the respiratory musculature, our findings were similar to those reported that used the SK score because, at the end of the follow-up period, we observed significant improvement in MIP and MEP values. MIP reflects the strength of the diaphragm and other inspiratory muscles, whereas MEP reflects the strength of the abdominal muscles and other expiratory muscles (23). Magnesium plays an important role in muscle tissue (6). The skeletal muscle cells contain long complex fibers made up of the proteins actin and myosin. These proteins work together to promote contraction and relaxation of muscle fibers. Magnesium helps to provide these contractile fibers the energy they require to function (6).

In addition, maximal voluntary ventilation is a test of the overall function of the respiratory system (24). The respiratory system exists in an oxygenated milieu and is continuously exposed to both endogenous and exogenous oxidants and irritants.
A variety of diet-dependent defenses have evolved to protect the lungs. These comprise vitamins, proteins, polyphenols, fatty acids, and cofactors (16, 37). Magnesium has a variety of functions, including acting as a cofactor for sodium and potassium ATPase, which is responsible for maintaining muscle membrane potential and action potential propagation. Magnesium deficiencies can result in muscle weakness and cramping (6).

Inflammation is a major pathophysiologic feature of the lung disease in CF, and the abnormal CFTR function is probably also involved in this inflammatory process (38). Recently, oxidative stress has been increasingly recognized as one of the major factors contributing to the chronic inflammatory process in CF (39).

Magnesium is closely related to the immune system in both nonspecific and specific immune responses (ie, innate and acquired immune responses) (40). Furthermore, magnesium is also a cofactor in >300 enzymatic reactions, and its deficiency is linked to inflammation and oxidative stress (41). For example, it is a cofactor for glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, 2 pentose-cycle enzymes that catalyze the production of NADPH from NADP+. Thus, a deficiency of dietary magnesium reduces glutathione reductase activity and results in radical-induced protein oxidation and marked lesions in tissues such as the skeletal muscles, brain, kidneys, and lungs (42).

In conclusion, our double-blind, randomized, crossover study showed that children and adolescents with CF who receive conventional treatment in combination with oral magnesium supplementation achieve significant improvement in functional status of the respiratory musculature and better clinical results. Further large-scale studies should include other well-established pulmonary function tests to further assess the potential role of magnesium supplementation in the management of CF in children and adolescents.

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The authors’ responsibilities were as follows—CG-A, PC, and EVG: designed the research (ie, project conception, development of overall research plan, and study oversight); CG-A: undertook data collection, wrote the manuscript, and had primary responsibility for the final content of the manuscript; and EVG: supervised the research. All authors assisted in the interpretation of analyses and revision of the manuscript and read and approved the final manuscript. The supporting research agencies had no influence in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the manuscript for publication. The authors had no personal or financial conflicts of interest.

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