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Reviews

Magnesium in Cystic Fibrosis—Systematic Review of the Literature

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Summary. Background: The metabolism of sodium, potassium, and chloride and the acid-base balance are sometimes altered in cystic fibrosis. Textbooks and reviews only marginally address the homeostasis of magnesium in cystic fibrosis. Methods: We performed a search of the Medical Subject Headings terms (cystic fibrosis OR mucoviscidosis) AND (magnesium OR hypomagnes-[a]emia) in the US National Library of Medicine and Excerpta Medica databases. Results: We identified 25 reports dealing with magnesium and cystic fibrosis. The results of the review may be summarized as follows. First, hypomagnesemia affects more than half of the cystic fibrosis patients with advanced disease; second, magnesemia, which is normally age-independent, relevantly decreases with age in cystic fibrosis; third, aminoglycoside antimicrobials frequently induce both acute and chronic renal magnesium-wasting; fourth, sweat magnesium concentration was normal in cystic fibrosis patients; fifth, limited data suggest the existence of an impaired intestinal magnesium balance. Finally, stimulating observations suggest that magnesium supplements might achieve an improvement in respiratory muscle strength and mucolytic activity of both recombinant and endogenous deoxyribonuclease. Conclusions: The first comprehensive review of the literature confirms that, despite being one of the most prevalent minerals in the body, the importance of magnesium in cystic fibrosis is largely overlooked. In these patients, hypomagnesemia should be sought once a year. Furthermore, the potential of supplementation with this cation deserves more attention. **Pediatr Pulmonol. 2016;51:196–202.**

Key words: aminoglycosides; cystic fibrosis; hypomagnesemia; magnesium; review.

INTRODUCTION

Since the discovery of the gene underlying cystic fibrosis, there has been tremendous progress in the care of cystic fibrosis lung disease.[1] New therapies have entered the market and are part of the standard treatment of these patients.[1] Now there are even more promising therapies directed at different components of the pathophysiology of the disease.[2,3]

Intriguingly, respiratory muscle weakness, inspissated mucus, increased airflow obstruction, and chronic pulmonary hypertension characterize both cystic fibrosis lung disease[1–3] and magnesium deficiency.[4,5] Nonetheless, textbooks and reviews only marginally address the possible association of magnesium deficiency with cystic fibrosis. To explore this issue, we reviewed the available literature.

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MATERIALS AND METHODS

Between May and September 2015, we performed a computer-based search with no date limits of the Medical Subject Headings terms (cystic fibrosis OR mucoviscidosis) AND (magnesium OR hypomagnes[a]emia) in the US National Library of Medicine and Excerpta Medica database. We used the principles established by the UK Economic and Social Research Council guidance on the conduct of narrative synthesis and on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[6] For the final analysis, we selected exclusively original reports available as full-length articles or letters, which explore the metabolism or the therapeutic potential of magnesium in cystic fibrosis patients of all ages. Dutch-, English-, French-, German-, Italian-, Portuguese-, or Spanish-language scientific reports were considered. Two of us (M. Santi and S. A. G. Lava) assessed articles for eligibility, and the Cohen's kappa index value, a measure of agreement between the investigators, was calculated. The data were independently extracted by the mentioned investigators and an agreement was reached on all items. Discrepancies were resolved through consensus discussion or adjudicated by a third author (G. P. Milani). If the same case was present in different publications, we retained the most complete description.

Smoothed simple regressions were calculated to estimate the effect of age on circulating magnesium level. For this purpose, we used the average and variability of magnesium level given in cross-sectional reports.

RESULTS

Search Results

The chance-adjusted agreement between the two investigators on the application of the inclusion and exclusion criteria was 0.88. Twenty-five original scientific reports published in English between 1964 and 2012[7–31] were retained for the final analysis, as depicted in Figure 1. They had been reported from the following countries: United States of America (N = 8), United Kingdom (N = 5), Germany (N = 3), Ireland (N = 2), Switzerland (N = 2), Australia (N = 1), Belgium (N = 1), Brazil (N = 1), Israel (N = 1), and Sweden (N = 1). Ten reports addressed circulating (or urinary) magnesium level,[7–16] 12 magnesium concentration in further body fluids or tissues,[17–28] and three the therapeutic potential of magnesium supplementation.[29–31]

Circulating Level

In healthy subjects, circulating magnesium levels do not vary with age.[4,5] Contrarily, the cumulated analysis of three rather large cross-sectional studies including a total of 451 patients (245 males and 206 females) affected with cystic fibrosis[9,11,16] suggests that in this disease magnesium level decreases with age, as depicted in Figure 2.

Four reports[7,8,12,13] document 15 cystic fibrosis-patients (seven male and eight female subjects aged from 15 to 30, median 24 years), who presented with signs of neuromuscular hyperexcitability such as positive Trousseau's or Chvostek's signs or muscle cramps while on treatment

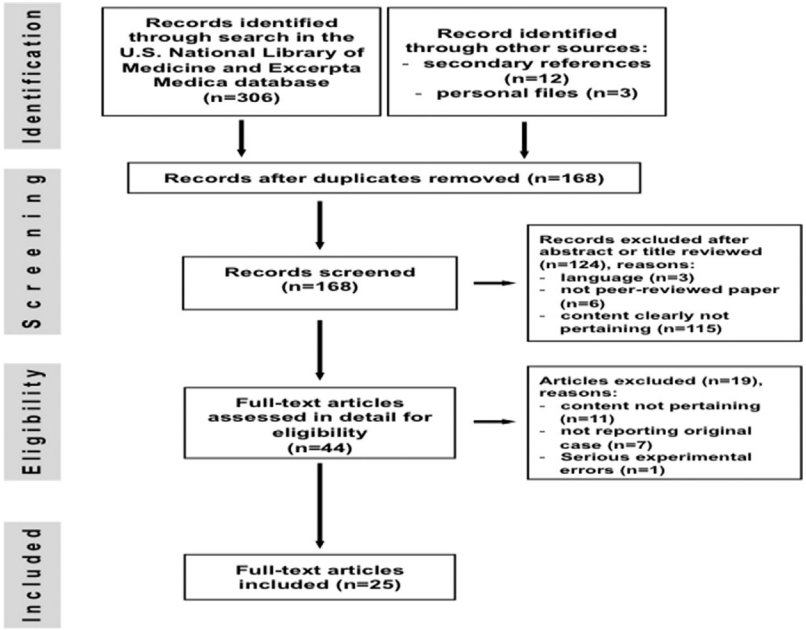

Fig. 1. Magnesium in cystic fibrosis. Flowchart of the literature search process.

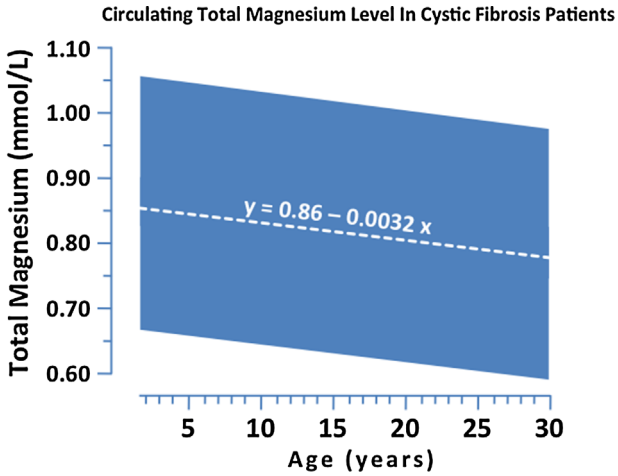

Fig. 2. Estimated age-related changes in magnesium level (mean ± 2 SD). Cumulated data from 451 patients (245 males and 206 females) affected with cystic fibrosis.[9,11,16]

with aminoglycoside antimicrobials. Severe hypermagnesiuric hypomagnesemia (≤0.50 mmol/L), associated with hypocalcemia (total level ≤2.20 mmol/L) in seven and hypokalemia (≤3.5 mmol/L) in five cases, was demonstrated in these patients. Further possible causes of hypomagnesemia were present in three of these cases: cystic fibrosis-related diabetes mellitus (N = 1) and management with either amphotericin B (N = 1) or furosemide (N = 1).

The interplay between aminoglycosides and magnesium metabolism was investigated in three studies.[11,14,15] In two reports, which addressed the acute effect of these antimicrobials, magnesium balance was measured immediately before and after a standard 14 days course of intravenous tobramycin 9 mg/kg daily[15] administered in three daily doses (N = 22; aged between 3.1 and 16 years) or amikacin 33 mg/kg daily[14] in three daily doses with ceftazidime 250 mg/kg daily in four daily doses (N = 24; aged between 9.0 and 19 years). The mentioned treatment regimens, which were not associated with any significant change in blood creatinine and urea level, markedly increased the urinary excretion of N-acetyl-β-D-glucosaminidase, a biomarker of proximal tubular dysfunction. Circulating and urinary magnesium levels were not influenced by the administration of tobramycin.[15] On the contrary, combined treatment with amikacin and ceftazidime[14] slightly (and transiently) but significantly decreased both plasma total (from 0.77 to 0.73 mmol/L; $P < 0.02$) and ionized (from 0.53 to 0.50 mmol/L; $P < 0.02$) magnesium concentration and increased the fractional urinary magnesium excretion (from 5.7 10^{-2} to 7.2 10^{-2}; $P < 0.05$). The long-term effect of tobramycin and gentamicin was investigated in a retrospective cross-sectional study.[11] Total magnesium level was significantly higher ($P < 0.001$) by 0.04 mmol/L in 98 patients who had never received aminoglycosides intravenously than in 85 patients, who had received these antimicrobials. Furthermore, the tendency towards hypomagnesemia was significantly ($P < 0.05$) correlated with the cumulative dose of aminoglycosides.

Finally, in a small case series of seven cystic fibrosis patients with distal intestinal obstruction syndrome,[10] oral and rectal administration of the mucolytic agent N-acetylcysteine and hypertonic solutions of sodium diatrizoate was followed by a decrease ($P < 0.05$) in total plasma magnesium that ranged from 0.02 to 0.30, median 0.14 mmol/L (a clinically relevant hypomagnesemia of ≤0.70 mmol/L was observed in four cases). No changes in plasma sodium, potassium or calcium were noted.

The tendency towards hypomagnesemia (total level <0.74 mmol/L) was also found to be common (N = 60; 57%) in a group of 106 cystic fibrosis patients aged between 16 and 56 years with advanced lung disease referred for assessment to a cardio-thoracic transplant unit.[16]

Concentration in Body Fluids and Tissues

In a small group of eight cystic fibrosis patients, the intraerythrocytic magnesium concentration was significantly ($P < 0.02$) lower by approximately 45% than in eight healthy controls.[26]

Sweat magnesium concentration was assessed in three studies. A pivotal but preliminary North American report published more than 50 years ago stated that sweat magnesium was, at most, marginally increased (regrettably, no quantitative data were provided) in four cystic fibrosis patients.[17] In Switzerland, this parameter was similar in 16 patients and 26 controls.[24] In Germany,[27] sweat magnesium was similar in 14 patients with mild to moderate lung disease (0.067 mmol/L) and 12 controls (0.053 mmol/L). In contrast, sweat magnesium was significantly ($P < 0.001$) higher in nine patients (0.123 mmol/L) with severe lung disease as compared with controls.[27]

Salivary magnesium was assessed in three studies including a total of 72 cystic fibrosis patients.[21,22,28] The level was found to be slightly but significantly ($P < 0.05$) lower by approximately 15% than in controls in a study including 22 patients.[28] On the contrary, salivary magnesium was similar in patients and controls in two studies including a total of 50 patients: these studies measured, in addition to the concentration of the ion, also the salivary flow rate.[21,22]

In three women with cystic fibrosis, cervical mucus magnesium was lower than in six controls.[23] Eighteen cystic fibrosis men had a threefold higher magnesium level ($P < 0.01$) in seminal plasma than 13 controls.[18]

The aforementioned North American study[17] stated that nail and hair magnesium are mildly increased in

67 cystic fibrosis patients (again, no quantitative data were provided). Nail sodium, calcium, and magnesium levels were also compared in 15 cystic fibrosis patients and 78 controls[20]: there was a significant ($P < 0.01$) increase in the mean value of sodium, calcium (both by 173%) and magnesium (by 37%) in the cystic fibrosis group. Similarly, hair sodium, potassium, calcium, and magnesium levels were found to be significantly ($P < 0.001$) higher by 220, 123, and 220%, respectively, 178% in 13 cystic fibrosis patients as compared with 34 controls.[19]

Finally, the total gastric secretion of sodium, potassium, calcium, chloride and magnesium was similar in 10 cystic fibrosis children and 10 healthy controls.[25] Duodenal fluid magnesium was found to be marginally increased in a single cystic fibrosis patient.[17]

Therapeutic Potential

Three reports investigated the possible usefulness of magnesium supplementation in cystic fibrosis.[29–31]

The effect of supplementation with magnesium 300 mg once daily for 8 weeks was investigated in a double-blind, randomized, placebo-controlled crossover study including 44 cystic fibrosis patients aged 7–19 years.[31] In these patients, magnesium supplementation achieved a significant improvement ($P < 0.001$) both in respiratory muscle strength and in the Shwachman-Kulczycki disease severity score.

In many cystic fibrosis patients, recombinant human deoxyribonuclease reduces the viscosity of sputum, which becomes easier to expectorate. A study[29] observed that the concentration of magnesium in sputum was on the average lower ($P < 0.03$) in nine cystic fibrosis patients (1.3 mmol/L) who do not benefit from this agent than in 13 responders (2.0 mmol/L). Furthermore, oral magnesium supplementation (162 mg three times daily) for 14 days was followed by an increase of the sputum magnesium concentration in five out of seven patients. Moreover, in vitro analysis demonstrated that sputum from clinical responders is degraded on incubation with recombinant deoxyribonuclease, while sputum from non-responders is degraded only after preincubation with magnesium. The positive effect of magnesium on deoxyribonuclease activity was mediated through inactivation of actin, an inhibitor of deoxyribonuclease.[29] Finally, the endogenous deoxyribonuclease activity, evaluated in bronchoalveolar lavage fluid from two adult cystic fibrosis patients, was found to increase after preincubation with magnesium.[30]

DISCUSSION

Hypomagnesemia, a rather common electrolyte abnormality, results from low intake, poor intestinal function or renal wasting.[4,5] In the presence of hypomagnesemia, the healthy kidney lowers magnesiuria. Hence, the diagnosis of hypomagnesemia caused by low intake or poor intestinal function is established by the demonstration of hypomagnesiuria. Conversely, the diagnosis of hypomagnesemia caused by renal wasting is established by the demonstration of inappropriately high urinary magnesium excretion.[4,5] The results of the first comprehensive review of the literature focusing on magnesium metabolism in cystic fibrosis may be summarized as follows: a) magnesemia, which is normally age-independent, decreases with age in cystic fibrosis (hypomagnesemia affects more than half of the patients with advanced disease); b) aminoglycosides frequently induce both acute and chronic renal magnesium-wasting, which is often associated with hypocalcemia and hypokalemia, two predictable consequences of this dyselectrolytemia[4,5]; c) contrary to sodium and chloride, which are drastically increased, magnesium concentration is usually normal in the sweat of cystic fibrosis patients but marginally increased in a small group of patients with advanced lung disease; d) very limited data suggest the existence of an impaired intestinal magnesium balance; e) stimulating observations that deserve confirmation indicate that magnesium supplements might achieve an improvement in respiratory muscle strength and mucolytic activity of both recombinant and endogenous deoxyribonuclease. The scientific soundness and the possible clinical relevance of the results are tentatively summarized in Table 1.

The results of this review and the current understanding of magnesium homeostasis[4,5] prompt us to speculate four main causes of magnesium deficiency in cystic fibrosis patients (Table 2). First, nutritional intake is often unsatisfactory in cystic fibrosis.[32] Second, poor intestinal uptake of magnesium is a well-known consequence of exocrine pancreatic insufficiency,[33] a major feature of cystic fibrosis.[31] In pancreatic insufficiency,[34] malabsorption results both from poor secretion of pancreatic enzymes as well as from insufficient bicarbonate secretion (without bicarbonate to neutralize gastric acidity, lipase cannot function optimally, and bile salt micellization of fat is impaired). Third, cystic fibrosis related diabetes mellitus, which is uncommon in children, occurs in approximately 20% of adolescents and 40–50% of adult patients.[35] Hypomagnesemia, which is quite frequent in diabetes mellitus, appears to be mainly associated with excessive urinary magnesium excretion that is reversed by correction of hyperglycemia.[4,5] Consequently, we hypothesize that diabetes mellitus also accounts for the tendency to hypomagnesemia observed in cystic fibrosis. Fourth, different drugs with a potential to cause renal magnesium wasting are prescribed in cystic fibrosis. These include β_2-adrenergic agonists, thiazide and loop diuretics, amphotericin B, bisphosphonates, calcineurin inhibitors, and especially

TABLE 1—Results, Scientific Soundness, and Possible Clinical Relevance of the Studies Addressing the Magnesium Homeostasis in Cystic Fibrosis

	Scientific soundness[1]	Possible clinical relevance[2]
Age-dependent decrease in circulating level	Good	High
Aminoglycosides antimicrobials cause renal wasting, both acutely, and chronically	Good	High
Sweat level usually normal but marginally increased in advanced lung disease	Satisfactory	High
Management of distal intestinal obstruction decreases circulating level	Poor	High
Supplementation improves respiratory muscle strength and disease severity score	Good	High
Supplementation enhances the mucolytic activity of deoxyribonuclease	Satisfactory	High
Intracellular level decreased	Poor	Low
Salivary and gastric fluid level normal	Satisfactory	Low
Duodenal fluid level increased	Poor	Low
Cervical mucus concentration decreased	Poor	Low
Seminal plasma level increased	Poor	Low
Nail and hair levels increased	Good	Low

[1]Scientific soundness was tentatively classified ex-post as follows: Poor (result supported by studies including a total number of patients $\leq$20). Satisfactory (result supported by studies including a total number of 21–39 patients or $\geq$40 patients if result of the quantitatively more important study is not confirmed in at least one report). Good (result supported by studies including $\geq$40 patients without reports not confirming the main result, or by studies including $\geq$100 patients if result of the quantitatively more important studies is not confirmed in at least one report).
[2]The possible clinical relevance was classified as either high or low in an ad-hoc consensus development conference among authors moderated by M. G. Bianchetti.

aminoglycosides.[4,5] Hypomagnesemia secondary to aminoglycosides, which is sometimes associated with alkalosis, hypokalemia or hypocalcemia but normal glomerular filtration rate, results from activation of the calcium-sensing receptors localized in the cortical ascending loop.[36] On the contrary, reduced glomerular filtration rate and De Toni-Debré-Fanconi tubulopathy induced by these antimicrobials result from drug accumulation and toxicity within the proximal tubule cells.[36] Finally, proton-pump inhibitors, which are often prescribed in cystic fibrosis, impair the intestinal magnesium absorption and tend to cause hypomagnesemia.[4,5,37]

Approximately 60–70% of circulating magnesium is in the free biologically active form, with 25% bound to albumin, and the remaining 5–10% complexed with bicarbonate, phosphate or citrate. Because most studies have shown good correlation between total and ionized magnesium, the latter is not routinely assessed in clinical practice.[4,5] However, in cystic fibrosis patients with severe hypoalbuminemia, total magnesium concentration may be slightly low despite a normal ionized magnesium concentration due to a decrease in the albumin-bound fraction.[5]

In cystic fibrosis, there is a tendency to chloride deficiency that results from excessive sweat production with an abnormally high content of this ion under conditions such as heat exposure.[38] In contrast, sweat magnesium level being usually normal, magnesium deficiency secondary to increased sweat magnesium loss is unlikely except in advanced lung disease.

The main limitation of the present systematic review results from the fact that the literature regarding magnesium in cystic fibrosis is scanty. The second limitation relates to the fact that we were not able to collect individual patient data to calculate the influence of age on magnesemia. The third limitation relates to the fact that no analysis of the association between the physical trait and the underlying genotype was performed, since none of the reports included data on genotyping. Finally,

TABLE 2—Main Causes Underlying Magnesium Deficiency in Cystic Fibrosis Patients

Poor intake
Exocrine pancreatic insufficiency
Management of distal intestinal obstruction syndrome
Cystic fibrosis related diabetes mellitus
Drugs frequently prescribed in cystic fibrosis
—increased renal loss: **aminoglycoside antimicrobials**, β_2-adrenergic agonists,[1] thiazide and loop diuretics, amphotericin B, bisphosphonates, calcineurin inhibitors[2]
—impaired intestinal absorption: proton-pump inhibitors

Causes of magnesium deficiency supported by the analyzed literature appear bold.
[1]These agents also cause a shift of magnesium from the extra- to the intra-cellular compartment.
[2]After lung transplant.

TABLE 3— Possible Therapeutic Benefits of Magnesium Supplementation in Cystic Fibrosis Lung Disease That Deserve Confirmation in Well Designed Trials

Benefit	Background
Improved respiratory muscle strength	Preliminary data in cystic fibrosis
Enhanced mucolytic activity of endogenous and exogenous deoxyribonucleases	Preliminary data in cystic fibrosis
Improved airflow obstruction	Preliminary data in chronic obstructive pulmonary disease of adulthood and asthma of childhood
Pulmonary vasodilatation in chronic pulmonary hypertension	Preliminary data in persistent pulmonary hypertension of the newborn

we classified the scientific soundness of published reports ex-post.

The present analysis confirms that, despite being the second most abundant intracellular cation, the fourth most abundant cation in the body and a relevant biochemical modulator involved in approximately 300 enzymatic reactions,[4,5] the importance of magnesium in cystic fibrosis is largely overlooked. Moreover, in this disease, the frequency of magnesium deficiency might increase as a consequence of improved survival and increased prevalence of cystic fibrosis related diabetes mellitus. It is concluded that in cystic fibrosis hypomagnesemia should be sought once a year. Finally, as shown in Table 3, the therapeutic potential of supplementation with this cation deserves more attention.

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