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Editor's Choice

Hypomagnesaemia in patients hospitalised in internal medicine is associated with increased mortality

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SUMMARY

Background: Magnesium is the major intracellular divalent cation. Hypomagnesaemia is common among critically ill patients; it's prevalence is not known in patients admitted to general internal medicine. We sought to quantify hypomagnesaemia, and attempted to correlate it with clinical outcomes in internal medicine patients. **Materials and methods:** Retrospective chart review. Hypomagnesaemic patients admitted from 1 October 2010 through 18 November 2010 compared with normomagnesaemic patients. Laboratory tests, medical and demographic data were analysed. **Results:** In 627 consecutive admissions, overall frequency of hypomagnesaemia was 20.1% (87 patients). Hypomagnesaemic patients were a little older (mean age of 75) and more likely to be women (62%). There was a significant difference in mortality between the normomagnesaemic group (7.2%) and the hypomagnesaemic group (17.2%) ($p = 0.0067$). There was also a significant difference for length of stay (5.00 ± 5.3 vs. 7.0 ± 8.2, $p = 0.0001$). **Conclusion:** The prevalence of hypomagnesaemia in internal medicine is very high. It is associated with higher mortality and longer hospital stay in our population. It can be a useful tool in predicting morbidity and mortality. Although no causal role can be defined for it at present, the low cost and minimal discomfort of measuring magnesium justifies its routine measurement and replacement in patients hospitalised in internal medicine.

What's known

- Low magnesium is found in diabetics and people with cardiovascular disease.
- It is very common in critical care units, where it is associated with higher mortality.

What's new

- Prevalence of hypomagnesaemia in patients hospitalised in general medicine is over 20%.
- Mortality of patients with low magnesium is higher than those with normal levels.

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Introduction

Magnesium is the cation second only to potassium in intracellular concentration. In patients admitted to critical care units hypomagnesaemia was associated with mortality twice as high as compared with comparably ill normomagnesaemic patients (1). In this population, 41.4% of patients had low magnesium, much greater than the 3.5% prevalence reported in the chronic care population (2). Eleven per cent of randomly selected hospitalised patients have been reported to have hypomagnesaemia in 1983 (3), and nearly 53% of laboratory sera in another study published in 1990 (4).

Most data regarding magnesium abnormalities in hospitalised patients are not current, and are derived from either critically care units or laboratories. No one reports on the prevalence of hypomagnesaemia in internal medicine. Significant comorbidities, such as congestive heart failure, renal failure and diabetes mellitus, place this population at risk for hypomagnesaemia. Many patients also have elevated inflammatory markers, other electrolyte disturbances or take medications that cause hypomagnesaemia. However, magnesium is largely ignored outside critical care. Our aim is to assess frequency of hypomagnesaemia in general internal medicine in the modern era, and to try to discern differences between normomagnesaemic and hypomagnesaemic patients.

Materials and methods

The study was approved by the Helsinki Committee (ethics committee) at Rambam Health Care Campus; Haifa, Israel; informed consent was waived. Patients were anonymous. Data were collected from the computerised medical records system on consecutive admissions to Internal Medicine. Exclusion criteria included death within 24 h of admission, arriving mechanically ventilated, patients transferred or discharged within 24 h of admission, and admissions for elective procedures (e.g. endoscopy, MRI etc.). All others who had magnesium levels were included.

Other parameters collected were potassium, sodium, calcium, inorganic phosphate, creatinine, albumin, erythrocyte count, haemoglobin concentration, leukocyte count and platelet count. Inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate and ferritin were examined. Demographic data, primary reason for admission, presenting symptoms, as well as comorbidities and medications were also noted.

Free magnesium is measured in the biochemistry lab by SIEMENS Dimension® clinical chemistry set. (Reference range 0.65–1.2 mmol/l SI units, mean of 0.09 mmol/l with SD of 0.07 or 1.3–2.4 mEq/l). Ionised magnesium is measured in the gas lab by SIEMENS Dimension® clinical chemistry set as well. (Reference range 0.45–0.6 mmol/l SI units). In the assay Magnesium forms a complex with methylthymol blue (MTB). The amount of MG-MTB formed is proportional to the magnesium concentration and is measured using a bichromic end-point technique at 600 nm, then analysed by software. The barium salt of ethylenebis tetraacetic acid (Ba-EGTA) is used to reduce calcium interference. The MG method was evaluated for interference from haemolysis, icterus and lipaemia, when greater than 10%. The latter are potential confounders to magnesium levels, in particular red blood cells whose magnesium concentration is threefold that of plasma.

We included all hypomagnesaemics in our analysis. Of 87 individuals with low magnesium, 85 had whole magnesium, 68 had ionised magnesium measured and 66 had both.

Statistical analysis was performed using SPSS 18.0 (SPSS, Chicago, IL). The differences between the hypomagnesaemic and the normomagnaesemic patients in the quantitative parameters (i.e. lab values) were calculated with t-tests for independent groups or Mann–Whitney *U*-tests. Fisher exact test was used to determine prevalence of categorical variables (i.e. gender, medications). $p < 0.05$ was considered significant.

Results

Data were collected on 627 consecutive admissions, from 1 October through 31 December 2010. One hundred and ninety-four patients were excluded based on above criteria, leaving 433. Sixty nine patients did not have magnesium levels checked during their hospitalisation. Three hundred and forty-six patients had normal magnesium levels, while 87 (20.1%) had low magnesium. Of these 87 patients, 66 had both bound and ionised magnesium measured. Of these, 25 had both low, another 25 had low ionised levels, and the remaining 16 had low bound magnesium.

There were 217 women and 216 men. Table 1 shows demographics, comorbidities and medications. The only significant difference between the groups was that 62% of hypomagnesaemics were women vs. 47.1% of controls. The mean age in the control group was 72 and in the hypomagnesaemic group it was 75.

Length of stay was significantly different (Figure 1). The median number of days in the department was 5 (mean 6.3 ± 5.4 days, range 2–48) for the control patients and 7 (mean 8.6 ± 8.2 days, range 2–63) for the hypomagnesaemic patients ($p < 0.0001$). The most impressive difference between the two groups was in mortality (Figure 2). The overall mortality rate was 9.2%, with 17.2% ($n = 15$) in the hypomagnesaemic group and 7.2% ($n = 25$) in the normomagnesaemic group ($p = 0.0076$).

Some conditions predispose hypomagnesaemia, including malabsorption or malnutrition. 1.8% of the control patients and 2.3% of hypomagnesaemic patients had malnutrition/malabsorption, and 3.2% ($n = 11$) of the normals and 3.4% ($n = 3$) of the hypomagnesaemic patients were alcoholic. Renal failure was diagnosed in 101 (29.3%) of normals and in 31 (35.6%) of the hypomagnesaemic patients.

Medications that cause renal losses are commonly used. However, there was no difference between the groups for use of furosemide, thiazide or other diuretics. There was a statistically significant difference for calcineurin inhibitor use, however, only two patients, both in the hypomagnesaemic group, were taking these. Other medications such as antihypertensives, statins, anticoagulants, aspirin, bisphosphonates, Vitamin D, Calcium, potassium or magnesium supplements, antidepressants and antipsychotics, laxatives and insulin were used similarly by both groups. Significant differences were seen for use of oral hypoglycaemics (46% of hypomagnesaemics vs. 20.2% for normomagnesaemics $p = 0.0001$), anti-emetics (6.9% vs. 1.2% $p = 0.006$), for levothyroxine (17.2% of hypomagnesaemics vs. 8.1% of normomagnesaemics, $p = 0.016$) and for prednisone (12.6% vs. 3.5%, $p = 0.002$).

Table 2 shows some laboratory values. As expected, whole calcium (2.21 mmol/l vs. 2.1 mmol/l, $p < 0.001$), ionised calcium (1.17 mmol/l vs. 1.13 mmol/l, $p = 0.018$) and potassium levels (4.16 mmol/l vs. 3.78 mmol/l, $p < 0.0001$) were lower in the hypomagnesaemic group. Lastly, albumin was lower in the hypomagnesaemic group ($p < 0.0001$). There was no difference in phosphorus, creatinine, haemoglobin, CRP, ESR or ferritin.

Discussion

We observed hypomagnesaemia in 20.1% of patients admitted to general internal medicine. In addition,

Table 1 Patient demographics, comorbidities and medications

	Control (n = 346)	Hypomagnesaemia (n = 87)	p
Age*	72.4 ± 14.7	75.1 ± 15	ns
Gender			
Males	52.9% (183)	37.9% (33)	
Females	47.1% (163)	62% (54)	0.016
Renal Failure	29.3% (101)	35.6% (31)	ns
Congestive Heart failure	21.8% (75)	27.6% (24)	ns
Malnutrition/Malabsorption	1.8% (6)	2.3% (2)	ns
Alcoholism	3.2% (11)	3.4% (3)	ns
Other comorbidities	61.5% (112)	70.5% (31)	ns
Medications			
Furosemide	27.5% (95)	27.6% (24)	ns
Thiazide diuretics	9.5% (33)	10.3% (9)	ns
Other diuretics	5.2% (18)	10.3% (9)	ns
Calcineurin inhibitors	0% (0)	2.3% (2)	ns
Oral hypoglycemics	20.2% (70)	46% (40)	<0.0001
Insulin	7.8% (27)	10.3% (9)	ns
PPI	37% (128)	51/7% (45)	0.014
H2blocker	4.6% (16)	2.3% (2)	ns
Anti-emetics	1.2% (4)	6.9% (6)	0.006
Bisphosphonates	4.6% (16)	2.3% (2)	ns
Vitamin D	13.0% (45)	14.9% (13)	ns
Calcium	11.8% (41)	13.8% (12)	ns
Potassium	5.2% (18)	3.4% (3)	ns
Opiates	6.4% (22)	12.6% (11)	ns
Prednisone	3.5% (12)	12.6% (11)	0.002
Levothyroxine	8/1% (28)	17.2% (15)	0.016

*Mean and standard deviation.

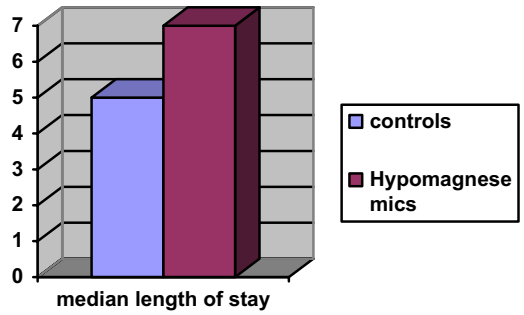

Figure 1 Length of stay in days $p < 0.0001$

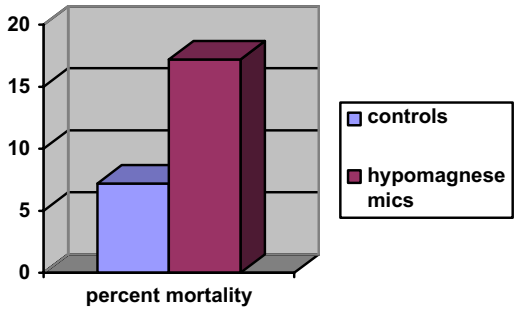

Figure 2 Mortality rates $p = 0.0067$

patients were more likely to have hypokalaemia and hypocalcaemia, and more importantly, hypoalbuminaemia, a well established prognostic marker. Our most striking finding is the greater mortality amongst our hypomagnesaemic patients.

Magnesium deficiency is caused by insufficient intake or absorption, or excessive loss. Losses in urine can be secondary to acidosis, increased aldosterone, antidiuretic hormone, thyroid hormone or catecholamine levels. Deficit is observed in athletes after exercise, which increases lipolysis, and when extremely intense, may increase loss in sweat (5).

Clinical findings in hypomagnesaemia are nonspecific. Complaints of weakness and fatigue are frequent. Tetany, positive Chvostek and Trousseau signs and general convulsions indicate neuromuscular irritability, which may occur despite normal calcium levels. Chvostek sign may be the most significant finding, reflecting intracellular magnesium levels. More severe depletion can cause vertical nystagmus,

Table 2 Salient laboratory findings, in Standard International and conventional units.

Lab value	Control Mean ± SD	HypoMagnesaemic Mean ± SD	p
K	4.16 ± 0.62 mmol/l	3.78 ± 0.68 mmol/l	< 0.0001
Ca	2.21 ± 0.225 mmol/l (8.85 ± 0.9 mg/dl)	2.21 ± 0.225 mmol/l (8.41 ± 1.36 mg/dl)	< 0.001
PO_4	1.15 ± 0.37 mmol/l (3.56 ± 1.14 mg/dl)	1.11 ± 0.28 mmol/l (3.44 ± 0.89 mg/dl)	ns
Albumin	39 ± 6.6 g/l (3.9 ± 0.66 g/dl)	27.7 ± 7.4 g/l (2.77 ± 0.74 g/dl)	< 0.0001
Creatinine	132.6 ± 99.9 μmol/l (1.5 ± 1.13 mg/dl)	123.8 ± 76 μmol/l (1.4 ± 0.86 mg/dl)	ns
Hgb	115 ± 2.1 g/l	111 ± 1.74 g/l	ns
CRP	800 ± 898 nmol/l (84.1 ± 94.3 mg/dl)	843 ± 795 nmol/l (88.5 ± 83.5 mg/dl)	ns
ESR	53.8 ± 94.3 mm/h	51.6 ± 30.9 mm/h	ns
Ferritin	853 ± 1849.3 pmol/l (380 ± 823 ng/dl)	773 ± 696.6 pmol/L (344 ± 310 ng/dl)	ns

Ns, non-significant; SD, standard deviation; K, potassium; Ca, calcium; PO_4, phosphorus; Hgb, haemoglobin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

tetany and seizure, followed by mild rhabdomyolysis. Cortical blindness has been reported and is reversible with correction (6). Depression, apathy and psychosis have also been described. Overt hypomagnesaemia usually signifies substantial depletion of body stores. Despite patients usually being asymptomatic at levels more than 1.2 mg/dl, symptoms do not necessarily correlate with measured levels. In addition, serum levels of magnesium may not reflect intracellular stores.

Low magnesium is common in clinical settings, such as heart disease, diabetes and inflammatory states. The Atherosclerosis Risk in Communities (ARIC) study found lower magnesium levels in men and women who developed coronary artery disease than disease free controls. Patients with acute myocardial infarction with mild hypomagnesaemia have a 2–3 fold increase in incidence of potentially fatal ventricular arrhythmias within the first 24 h, reduced by IV magnesium administration. In the weeks following, low magnesium can induce arrhythmias as well, secondary to lower threshold for depolarisation (7). Magnesium sulphate is the treatment for torsade de pointes or refractory ventricular fibrillation in cardiac resuscitation. In addition, sensitivity to digitalis toxicity may be enhanced, and mitral valve prolapse may be secondary to magnesium deficit as it influences collagen structure (8). In patients with congestive heart failure, an increased incidence of hypomagnesaemia has been found, due in part to treatment with diuretics. In a recent report from the Framingham heart study, hypomagnesaemia has been associated with atrial fibrillation in the community in people without cardiovascular disease (9). We did not observe more cardiovascular disease in our population with hypomagnesaemia, however, we looked at 433 patients, and these are common morbidities in our ageing population.

Hypomagnesaemia has also been associated with inflammatory states. In adults it increases the risk for metabolic syndrome, high blood pressure, diabetes mellitus type 2 and hyperlipidaemia (10). Low magnesium levels are strongly related to low grade systemic inflammation, oxidative stress and development of the metabolic syndrome. Subjects who consume magnesium below recommended daily doses are more likely to have elevated CRP levels. In diabetics hypomagnesaemia is very common, ranging from 13% to 47% in chronic care populations. In our population CRP and ESR, but not ferritin, tended to be higher in hypomagnesaemic patients, however, this difference was not significant. Regardless, markers of inflammation are elevated in many patients as a result of the illness that caused hospitalisation.

In conjunction with hypomagnesaemia, other laboratory perturbations are expected, such as low calcium, potassium and albumin. Our data showed significantly lower albumin levels in the hypomagnesaemic groups. Since albumin is the major protein carrier of magnesium in the blood, this finding is predictable (11). Severe hypomagnesaemia (< 0.5 mmol/l) is often

accompanied by hypocalcaemia. Low magnesium has a suppressive effect on PTH secretion, while parenteral magnesium supplementation leads to a rapid increase in plasma PTH. Calcium release from bone is significantly impaired when magnesium levels fall below 0.4 mmol/l, but for decreased PTH secretion, severe hypomagnesaemia is required (7). Hypocalcaemia is refractory to treatment until magnesium has been repleted.

Hypokalaemia and metabolic alkalosis are also commonly found alongside hypomagnesaemia. Magnesium inhibits potassium loss through channels in the renal tubules, partially explaining why repletion of magnesium is a prerequisite for adequate potassium repletion. Decreased intracellular magnesium slows ATP production, which has a negative effect on the Na-K ATPase, resulting in the loss of potassium from the cells. Loss of potassium and phosphorous, inhibition of glutathione synthesis and alterations in iron metabolism were all observed in animals with hypomagnesaemia. Hypocalcaemia and hypokalaemia were seen in our hypomagnesaemic population, and as expected were significantly lower than in the normomagnesaemic group. It is difficult to ascertain what proportion of clinical manifestations is caused by the hypomagnesaemia, or other abnormalities.

Diuretic use is a major cause for hypomagnesaemia. However, there was no difference between the normo- and the hypomagnesaemic groups when comparing use of major kaliuric and magnesuric diuretics. There was slightly more hypomagnesaemia for amiloride, spironolactone and indapamide, all of which are potassium sparing diuretics.

Another well known cause of hypomagnesaemia is use of calcineurin inhibitors, which increase fractional magnesium excretion (12). Cyclosporine reduces paracellin-1 expression in the thick ascending loop of Henle, resulting in decreased magnesium reabsorption (13). There were only two patients (4.5%) who were taking calcineurin inhibitors as well as magnesium supplements in the hypomagnesaemic group.

Bisphosphonates and Vitamin D affect magnesium metabolism. Magnesium exists in bone in two subcompartments. The slow compartment has firmly apatite-bound magnesium that cannot be mobilised even under conditions of severe deficiency. The mobile compartment has magnesium that is adsorbed to the surface of mineral crystals (14). Bisphosphonates prevent osteoclast-mediated mineral dissolution, and hypomagnesaemia has been described after pamidronate administration (15). However, in our patients, bisphosphonate usage was more common in the normomagnesaemic group (3.8% vs. 2.3%). Whether high doses of Vitamin D increase serum levels or increase magnesium excretion in the urine is controversial, but both phenomena have been reported (16). Only four patients (9.1%) in the hypomagnesaemic group were taking vitamin D vs. 20 patients (11.0%) in the control group.

Some causes of hypomagnesaemia are gastrointestinal. Dietary intake ranges from 58 to 148 mmol/day, 30–40% of which is absorbed, primarily in the jejunum and the ileum. Approximately 49 mmol are absorbed and 9 mmol are lost within GI secretions so net daily intake is 40 mmol. Intestinal absorption is stimulated by 1,25 $(OH)_2D$ and can rise to 70% in magnesium depletion states, or can be as low as 25% in magnesium rich states. Phosphates can inhibit magnesium absorption by forming insoluble complexes. Drinking water may be an important source of magnesium, better absorbed than dietary sources (14). Alcoholism and malabsorption/malnutrition often cause hypomagnesaemia, the most common electrolyte disturbance observed in 30% of patients (17). Alcohol stimulates inappropriate excretion of magnesium, also increased by metabolic acidosis and hypophosphataemia. Alcohol withdrawal syndrome and diarrhoea also contribute. Thiamine deficiency is common in alcoholism, partly because magnesium is needed for transforming thiamine into thiamine pyrophosphate. Counterintuitively, there were more alcoholics in the normomagnesaemic group (5.5% vs. 4.5%). Malabsorption/malnutrition, defined for this study as short bowel syndrome, chronic diarrhoea or those receiving total parenteral nutrition, causes increased magnesium loss in faeces. Again here, more patients had normal levels (1.6% vs. 0%).

In conclusion, our data indicate that hypomagnesaemia is very common in patients hospitalised in internal medicine, found in over 20% of our admissions. Most striking are the findings of increased length of stay and mortality in hypomagnesaemic patients. The relationship between serum magnesium levels and intracellular magnesium stores is poorly understood. In critically ill patients, mostly on mechanical ventilation with multiple organ involvement and with mortality near 50%, hypomagnesaemia is common, exceeding 40%. Since magnesium is required for cellular function, in particular respiratory and cardiac, it is reasonable to speculate that it's deficiency will contribute to organ system failure as a result of intracellular depletion. In our patients, a chronically ill population, it is possible that low serum levels may represent the tip of the iceberg, and in fact cellular levels are low as well. Regardless of whether magnesium was bound or ionised, outcomes were poorer. It is also unclear whether

symptoms are related to magnesium status, or to other abnormalities. Most patients have comorbidities or medications that cause magnesium deficiency, so causality could not be discerned. Most patients were in a state of inflammation, although we could not correlate measured inflammatory markers with low magnesium levels. Perhaps a larger group of patients are needed to detect these difference.

We believe low magnesium reflects the severity of illness and the depleted intracellular stores of magnesium in our patients. The increased use of analgesics and anti-emetics, as well as lower albumin levels in the hypomagnesaemic group support this. In addition, patients with renal failure had low magnesium. It is therefore plausible that magnesium could be a prognostic indicator. Studies are needed to elucidate it's role on a cellular level. In addition, prospective studies are necessary to see whether replacing magnesium could alter outcomes. Hypermagnesaemia is extremely uncommon and to induce toxicity, one would need to exceed recommended doses two or threefold. We believe the high prevalence, greater disease burden, longer hospital stay and greater mortality justify adding magnesium to routine chemistry panels, and if found low, should be replaced. The cost is minimal, the harm negligible, and the potential benefits huge.

Author contributions

Dr. Wolf is responsible for the study concept and design, overseeing data collection, data interpretation and writing/revising the manuscript. Dr. Hilewitz is responsible for data collection, literature search, drafting the manuscript and figures and tables.

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