Original Article

Association of hypermagnesemia and blood pressure in the critically ill

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Background: Although magnesium is important in the biology of blood pressure regulation, little clinical data exist on the association of hypermagnesemia and blood pressure.

Method: We examined the association of hypermagnesemia and SBP in a cross-sectional study of 10 521 ICU patients from a single tertiary care medical center, 6% of whom had a serum magnesium above 2.6 mg/dl at time of admission.

Results: In a multivariable analysis, hypermagnesemia was associated with SBP 6.2 mmHg lower [95% confidence interval (CI) −8.2, −4.2, $P < 0.001$] than in patients with admission values of serum magnesium 2.6 mg/dl or less. Each mg/dl increase in serum magnesium was associated with a decrease in SBP of 4.3 mmHg (95% CI −5.5, −3.1, $P < 0.001$). In addition, hypermagnesemic patients had a 2.48-fold greater likelihood (95% CI 2.06, 3.00, $P < 0.001$) of receiving intravenous vasopressors during the first 24 h of ICU care, independent of admission SBP.

Conclusion: Our findings add support to the biologic importance of magnesium regulation in blood pressure control.

Keywords: blood pressure, hypermagnesemia, hypotension, magnesium, vasopressor use

Abbreviations: BUN, blood urea nitrogen; ICU, intensive care unit; ESRD, end stage renal disease; TRPM, transient receptor potential melastatin; WBC, white blood cell count

INTRODUCTION

Magnesium, the fourth most abundant intracellular ion, has pleiotropic biologic effects, and has been linked to a wide range of diseases, including diabetes [1], insulin resistance [2,3], inflammatory states [4,5], and dyslipidemia [6]. Longstanding and emerging research suggests that magnesium also has an important role in vascular biology [7,8], regulating vascular tone [9], and cardiac rhythm [10] and contractility [11]. Hypomagnesemia has been linked to hypertension in some clinical studies [12,13], but not in others [14–18]. In contrast, magnesium infusion induces acute arterial vasorelaxation [19], and chronic magnesium supplementation interferes with the downstream effects of aldosterone [20] and attenuates development of hypertension [21]. The newly identified families of magnesium transporters, including transient receptor potential melastatin (TRPM) [22] expressed in the vasculature and the kidney, provide additional mechanistic links to the observed epidemiological association between magnesium levels and blood pressure [23].

Little is known about the effect of hypermagnesemia on blood pressure. Small clinical studies have suggested that hypotension ensues only at critically high magnesium concentrations (3–4 mg/dl), a level rarely seen outside of magnesium intoxication or renal failure [24]. In a typical intensive care setting, mild hypermagnesemia is seen in 5–10% of patients [25]. A possible relationship between these smaller increases in serum magnesium and altered blood pressure has not been previously evaluated.

To assess this question, we examined the association of serum magnesium concentrations with SBP and vasopressor requirement in a large sample of patients admitted to a single ICU.

METHODS

Study population

We used the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-II) research database, a joint venture of the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT) and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC) [26], a large, urban, academic medical center. The database contains data of high temporal resolution obtained from clinical computing systems, including lab results, electronic documentation, and bedside monitor trends and waveforms, for all patients admitted to BIDMC ICUs between 2001 and 2008. Use of the MIMIC II database has been approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the MIT.

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Of the 17 870 unique ICU admissions with an identifiable medication section of the discharge summary, 16 054 had documented magnesium concentrations obtained within the first 24 h of ICU care. Of these, 472 were missing documentation of SBP. Because of the marked effect of renal function on magnesium concentrations, we excluded patients who did not have a serum creatinine measurement on both the first and second day of ICU care ($n = 4910$), or for whom quantitative documentation of urine output over the first 24 h of ICU care was not available ($n = 139$). Because magnesium is routinely used to treat preeclampsia, we excluded all individuals with a diagnosis of preeclampsia or pregnancy-related complications ($n = 8$). An additional four individuals were excluded based on missing demographic information, leaving a final sample size of 10 521 unique admissions. Only first admissions were used in this analysis.

Exposure

Magnesium concentrations were taken from the first available laboratory measurement recorded within 24 h of admission to the ICU. To limit the effect of outliers, magnesium levels were winsorized at the 0.5 and 99.5 percentiles. In addition, we performed analyses with magnesium levels dichotomized at 2.6 mg/dl, which is the hospital clinical chemistry laboratory's definition of hypermagnesemia.

Outcome

The primary outcome was the first SBP measured upon arrival to the ICU. Blood pressure measurements obtained prior to ICU arrival were not available. As a secondary analysis, we examined whether magnesium concentrations were associated with use of vasopressors during the first 24 h of ICU care.

Covariates

Demographic information included age, sex, and ethnicity, coded as white, African-American, Asian, Hispanic, other, or unknown. All 30 comorbidities of the Elixhauser score were incorporated into the model as separate, independent measures, rather than a summary index score [27]. Individual predictors of illness severity included admission heart rate, temperature, and oxygen saturation. Values of serum calcium, phosphate, and hematocrit were included when obtained within 24 h of ICU admission. Imputed calculated means based on whole data were used for all variables with missing or implausible values: temperature ($n = 1372$), oxygen saturation ($n = 1$), white cell count (WBC) ($n = 13$), sodium ($n = 7$), blood urea nitrogen (BUN) ($n = 8$), calcium ($n = 1426$), phosphate ($n = 1332$), and hematocrit ($n = 59$). We also included admission serum creatinine, a follow-up creatinine within 24–48 h of ICU admission, and oliguria, defined as a urine output less than 500 ml/day during the first 24 h of ICU care. In order to describe diuretic exposure, we evaluated medications on admission using Natural Language Processing (NLP) of discharge summaries. We developed an NLP algorithm that searched for a discrete home medication section in the discharge summary and then processed the medications to find individual entries of any type of diuretic agent [28].

Statistical analysis

To assess whether SBP was related to magnesium concentrations, we developed sequential multivariable linear regression models. Binary indicator variables were created for all Elixhauser comorbidities and oliguria. Ethnicity was included as a multicategory variable. Age, vital signs, and laboratory values were all included as continuous variables. Prehospitalization diuretic exposure was included as a binary variable. We explored magnesium both as a continuous variable, and dichotomized at the 2.6 mg/dl threshold. Model I included age, sex, and ethnicity. Model II added vital signs, comorbidities, WBC, sodium, calcium, phosphate, and hematocrit. Model III added indicators of acute renal failure, including admission creatinine and BUN, creatinine within 24–48 h of ICU admission, oliguria, and diuretic exposure. We present the mean unadjusted and adjusted (model III) admission SBP, with confidence intervals (CIs), by mean serum magnesium concentrations on admission.

Given the dynamic effect of renal function on serum magnesium concentrations, we investigated if the association between serum magnesium concentration and blood pressure differed as a function of indices of renal function. Indicator variables were created for an admission serum creatinine 1.2 mg/dl or less, a creatinine change of above 30% between the admission and second day of ICU care, and oliguria. We tested multiplicative interaction terms between these variables and magnesium concentrations (defined categorically at 2.6 mg/dl). To further limit residual confounding by dynamic renal function, we then examined the association of hypermagnesemia and SBP in those with static renal function, as defined by a creatinine increase between the first and second ICU stay of less than or equal to 10%, as well as in those with end-stage renal disease (ESRD), who likely have minimal renal function. Chronic dialysis patients were identified by manual review of discharge summaries of 473 patients who had a dialysis billing code during their ICU stay, in order to distinguish acute from chronic renal failure. Because of the smaller number of ESRD patients, ethnicity was recoded into white/nonwhite/unknown, only congestive heart failure, hypertension, diabetes, pulmonary disease, and peripheral vascular disease were included as comorbidity variables, and diuretic use was not included in the analysis.

To assess whether magnesium concentrations on admission were associated with administration of intravenous vasopressors during the first 24 h of ICU care, we assessed vasopressor use, modeled as a binary variable, including all variables used in model III above. In addition, we included SBP at the time of ICU admission.

To test the specificity of our model, we also tested our models using admission temperature, a physiologic variable associated with critical illness but not hypothesized to relate to serum magnesium concentrations.

RESULTS

Admission characteristics

Approximately 6% of patients admitted to the ICU had hypermagnesemia (Table 1). Hypermagnesemic patients were older, had a higher prevalence of diuretic use, and

TABLE 1. Baseline characteristics

	Magnesium >2.6 ($n=664$)	Magnesium ≤2.6 ($n=9857$)	*P*-value
Age, mean (SD), (years)	68.1 (14.9)	64.2 (17.6)	<0.001
Male, no. (%)	404 (60.8)	5556 (56.4)	<0.001
Female, no. (%)	260 (39.2)	4301 (43.6)	<0.001
Ethnicity, no. (%)			
White	470 (70.8)	6997 (71.0)	<0.001
Black or African-American	50 (7.5)	702 (7.1)	
Hispanic or Latin	18 (2.7)	267 (2.7)	
Asian	13 (2.0)	221 (2.2)	
Other	13 (2.0)	237 (2.4)	
Unknown	100 (15.1)	1433 (14.5)	
Past medical history[1], no. (%)			
Hypertension	174 (26.2)	3312 (33.6)	<0.001
Congestive heart failure	156 (23.5)	2209 (22.4)	0.51
Cardiac arrhythmia	161 (24.3)	2065 (21.0)	0.05
End-stage renal disease	17 (2.6)	167 (1.7)	0.12
Diabetes	195 (29.4)	2464 (25.0)	0.02
Preadmission diuretic use	290 (43.7)	2935 (29.8)	<0.001
Vital signs, mean (SD)			
SBP (mmHg)	116.8 (23.9)	124.2 (26.5)	<0.001
DBP (mmHg)	58.8 (14.6)	63.1 (16.5)	<0.001
Heart rate, beats/min	69.8 (19.4)	69.3 (22.1)	0.52
Temperature (°C)	36.5 (0.78)	36.7 (0.95)	<0.001
Peripheral oxygen saturation (%)	94.3 (6.6)	93.0 (9.2)	<0.001
Admission laboratory values, mean (SD)			
White blood cell count (K/μl)	13.2 (6.8)	12.7 (9.9)	0.21
Hematocrit (%)	30.1 (5.9)	32.2 (6.0)	<0.001
Sodium (meq/l)	137.3 (5.9)	138.3 (4.8)	<0.001
Calcium (mg/dl)	8.4 (0.93)	8.2 (0.87)	<0.001
Phosphate (mg/dl)	4.0 (1.6)	3.6 (1.2)	<0.001
Urea nitrogen (mg/dl)	37.1 (31.7)	24.5 (19.7)	<0.001
Creatinine (mg/dl)	1.8 (1.8)	1.3 (1.3)	<0.001
24–48-h creatinine (mg/dl)	1.9 (1.7)	1.3 (1.2)	<0.001
Vasopressor use, no. (%)	277 (41.7)	6706 (68.0)	<0.001

[1]Past medical history as determined by Elixhauser coding.

had worse admission renal function. Both SBP (7 mmHg) and DBP (4 mmHg) were lower in hypermagnesemic patients. There was a trend towards a higher prevalence of ESRD amongst hypermagnesemic patients.

Association of magnesium with blood pressure

Table 2 presents sequential models of the association between SBP and magnesium, modeled categorically or continuously. After adjusting for age, sex, and race (model I), hypermagnesemia was strongly associated with lower SBP. The addition of Elixhauser comorbidities, vital signs, and other laboratory values slightly attenuated this effect, but it remained strong and significant. In the fully adjusted model (model III), SBP at admission was 6.2 mmHg lower in hypermagnesemic patients than in individuals with admission magnesium concentrations 2.6 mg/dl or less (95% CI −8.2, −4.2, $P<0.001$). When evaluated as a continuous variable, each 1 mg/dl increment in serum magnesium was associated with a 3.2 mmHg lower SBP (95% CI −4.3, −2.0, $P<0.001$) when adjusted for age, sex, and race ($P<0.001$), and a 4.3 mmHg lower SBP (95% CI −5.5, −3.3, $P<0.001$) in the final multivariable adjusted analysis (model III).

The association between magnesium and blood pressure did not seem to differ according to renal function. Using model III, we found no evidence of significant

TABLE 2. Cross-sectional association between magnesium concentration and SBP

	Mean difference in SBP associated with magnesium concentrations		
	Mg ≤ 2.6	Mg >2.6	Per 1 mg/dl increase in magnesium concentration
SBP			
Model 1[a]	1.00 (Ref.)	−7.7 (−9.7, −5.6) $P<0.001$	−3.2 (−4.3, −2.0) $P<0.001$
Model 2[b]	1.00 (Ref.)	−6.5 (−8.5, −4.5) $P<0.001$	−4.7 (−5.8, −3.5) $P<0.001$
Model 3[c]	1.00 (Ref.)	−6.2 (−8.2, −4.2) $P<0.001$	−4.3 (−5.5, −3.1) $P<0.001$

[a]Model 1 adjusts for age, sex, and race.
[b]Model 2 adjusts for age, sex, race, all 30 Elixhauser comorbidities, heart rate, temperature, oxygen saturation, WBC, hematocrit, sodium, calcium, and phosphate.
[c]Model 3 adjusts for age, sex, race, all 30 Elixhauser comorbidities, heart rate, temperature, oxygen saturation, WBC, hematocrit, sodium, calcium, phosphate, BUN, creatinine at admission and after 24 h, presence of oliguria, and prehospital diuretic exposure.

multiplicative interaction between magnesium above 2.6 mg/dl and the renal function parameters of admission creatinine above 1.2 mg/dl, more than 30% increase in serum creatinine between the first and second day of ICU care, or oliguria. The unadjusted and adjusted associations between magnesium and SBP are illustrated in Fig. 1.

Association of magnesium with blood pressure in patients with static renal function

Because the effect of renal function on magnesium concentrations is difficult to accurately quantify in those with dynamic renal function, we studied the association of magnesium with blood pressure in two populations whose renal function was static. There were 3497 patients whose serum creatinine changed 10% or less during the first 2 days of ICU care. There were 184 ESRD patients, who likely have minimal residual renal function. Baseline characteristics of each group are presented in Table 3. In patients with 10% or less change in creatinine, hypermagnesemia was associated with a 9.1 mmHg (95% CI −13.0, −5.2, $P < 0.001$) lower SBP in adjusted analysis. In those with ESRD, hypermagnesemia was associated with a 16.9 mgHg (95% CI −33.7, −0.60, $P = 0.04$) lower SBP in adjusted analysis.

Association of magnesium with intravenous vasopressor use

Hypermagnesemia was associated with vasopressor use, independent of admission SBP, as seen in Table 4. In a fully adjusted model that included admission SBP, hypermagnesemic patients had 2.48-fold increased odds of vasopressor administration (95% CI 2.06, 3.00, $P < 0.001$) than patients with magnesium concentrations 2.6 mg/dl or less. When analyzed as a continuous variable, each 1 mg/dl increase in serum magnesium was associated with a 1.82-fold adjusted increase in odds of vasopressor use (95% CI 1.62, 2.03, $P < 0.001$).

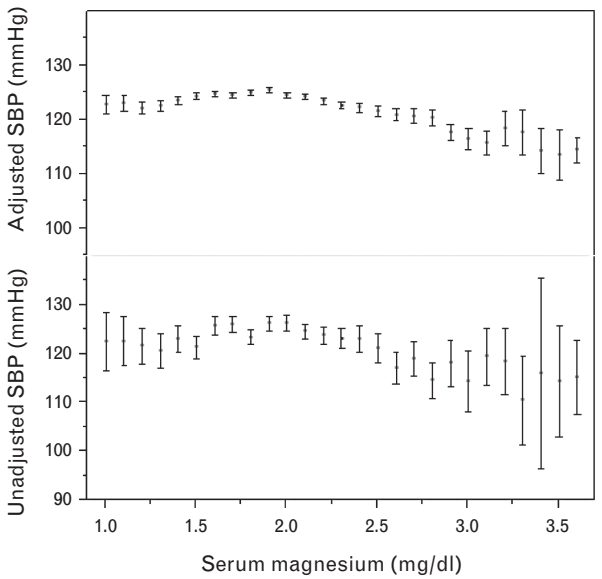

FIGURE 1 Unadjusted and model III-adjusted associations between admission serum magnesium concentration and initial ICU SBP. Mean, with 95% confidence intervals.

TABLE 3. Baseline characteristics of those with static renal function

	Creatinine change ≤10% ($n = 3497$)	End-stage renal disease ($n = 184$)
Age (years)	65.0 (17.5)	63.7 (15.0)
Male, no. (%)	2085 (60.0)	113 (61.0)
Admission creatinine (mg/dl)	1.3 (1.4)	6.3 (3.0)
24–48 h creatinine (mg/dl)	1.3 (1.4)	5.9 (2.6)
SBP (mmHg)	126.2 (26.3)	129.8 (33.5)
Hypermagnesemia, no. (%)	179 (5.1)	17 (9.2)

Mean values (SD).

Association with temperature as a control

To test the specificity of our analysis, we also evaluated the relationship between magnesium concentrations and body temperature at time of admission. No significant association was observed between magnesium concentrations modeled continuously and temperature.

DISCUSSION

In this large single-center sample of critically ill patients, hypermagnesemia was associated with lower SBP, independent of measured renal function. In addition, hypermagnesemia was associated with the administration of intravenous vasopressors during the first 24 h of ICU care, independent of admission SBP.

Hypermagnesemia-induced hypotension is well described, but thought to occur at levels of serum magnesium not frequently encountered in practice. In our study, mild hypermagnesemia was observed in 6% of ICU patients, and was associated with significantly lower SBPs. Most clinical trials on the effect of magnesium supplementation on blood pressure have studied the effect of magnesium intake, not achieved serum magnesium concentrations. Given that most study participants had normal renal function, magnesium supplementation would not be expected to produce frank hypermagnesemia. However, a magnesium dosage effect has been suggested [29], and the studies showing positive associations [12,14] usually administered higher daily magnesium doses than did the negative trials [30–33].

Renal function was, as expected, a strong predictor of serum magnesium concentration. Although we attempted to account for renal function in our analyses, without knowledge of baseline renal function prior to admission, it is impossible to fully characterize the presence of acute renal failure. Furthermore, the challenges of estimating glomerular function from serum creatinine, particularly in critical illness where renal function is dynamic, adds potential further confounding. By examining those with minimal change in serum creatinine during the first 48 h of ICU care, and those with minimal renal function (ESRD), we attempted to limit the confounding effect of dynamic renal function on the association of magnesium and blood pressure. In both groups, the association of hypermagnesemia with lower blood pressure remained robust.

The clinical significance of hypermagnesemia in ESRD has not previously been well characterized. In our analysis, almost 10% of ESRD patients were hypermagnesemic, and they had a 17 mmHg lower adjusted admission SBP than

TABLE 4. Association between serum magnesium concentration and intravenous administration of vasopressors during first 24 h of ICU care[a]

	Odds ratio for intravenous vasopressor administration		
	Mg $\leq$ 2.6	Mg >2.6	Odds increase per 1 mg/dl increase in magnesium concentration
Model 1[a]	1.00 (Ref.)	2.77 (2.38,3.25) $P<0.001$	1.65 (1.49, 1.81) $P<0.001$
Model 2[b]	1.00 (Ref.)	2.36 (1.97, 2.83) $P<0.001$	1.70 (1.53–1.90) $P<0.001$
Model 3[c]	1.00 (Ref.)	2.48 (2.06, 3.00) $P<0.001$	1.82 (1.62–2.03) $P<0.001$

[a]Model 1 adjust for age, sex, and race.
[b]Model 2 adjusts for age, sex, race, all 30 Elixhauser comorbidities, heart rate, temperature, oxygen saturation, admission systolic blood pressure, WBC, hematocrit, sodium, calcium, and phosphate.
[c]Model 3 adjusts for age, sex, race, all 30 Elixhauser comorbidities, heart rate, temperature, oxygen saturation, admission systolic blood pressure, WBC, hematocrit, sodium, calcium, phosphate, BUN, creatinine at admission and after 24 h, presence of oliguria, and prehospital diuretic exposure.

ESRD patients with magnesium concentrations 2.6 mg/dl or less. Hypomagnesemia has been associated with peripheral vascular disease in patients with renal failure [34], and magnesium supplementation prevents vascular smooth muscle cell calcification [35–37], suggesting that higher levels of magnesium may be beneficial in ESRD patients [38]. Conversely, whether hypermagnesemia contributes to intradialytic hypotension – a significant problem for many dialysis patients – has not been studied.

The ubiquitous distribution and activity of some TRPM magnesium transporters may play a role in the observed association of serum magnesium with lower blood pressure. Vascular TRPM7 serves as a kinase involved in vascular smooth muscle cell growth, apoptosis, and contractility, and as an ion channel that influences intracellular magnesium concentrations that suppress calcium channels, blocks inward K currents, and attenuates calcium-contraction coupling. TRPM6 modulates renal epithelial magnesium transport, and mutations have been associated with changes in serum magnesium [39,40]. Thus, although gain-of-function mutations or polymorphisms have not yet been described, serum magnesium concentrations might simply reflect activity of TRPM channels and/or other magnesium transporters and not a direct pathogenic role in blood pressure. In addition, since aldosterone and angiotensin II have been associated with decreased TRPM expression [41,42], systemic hypertension could itself induce renal magnesium wasting.

Extracellular magnesium has also been shown to alter responses to vasoconstrictor and vasodilator agents [43]. The absence of magnesium potentiates the contractile response to angiotensin II, whereas magnesium infusion inhibits endothelin-1 vasoconstriction [44]. Our findings that hypermagnesemic patients are more likely to receive intravenous vasopressors, independent of admission blood pressure, support a role for the vasoactive effects of magnesium.

Limitations of this study include lack of knowledge about over-the-counter medications that could influence magnesium concentrations, including magnesium-containing supplements. In addition, we had no method to assess for nutritional intake or gastrointestinal loss of magnesium. Since we used the first blood pressure entered into the bedside electronic medical record, we assume these were likely to be noninvasive measurements, and whether invasive measurements would lead to different findings is not known. Finally, since our sample is comprised of critically ill patients, generalizability to the outpatient population is uncertain.

In conclusion, in this large sample of critically ill patients, hypermagnesemia was associated with lower SBP and with the administration of intravenous vasopressors during the first 24 h of ICU care. These clinical findings add support to experimental data associating magnesium with blood pressure control. However, further well designed studies will be required to evaluate additional residual confounding factors that may have influenced the associations detected in this large single-center patient group.

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Conflicts of interest

There are no conflicts of interest.

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Reviewer's Summary Evaluation

Referee 1

This is a cross-sectional study reporting a negative association between systolic blood pressure and blood magnesium level in critically ill patients at the time of admission to an intensive care unit. Despite its retrospective and observational nature, this study has several strengths. First, the very large size (about 10 000 patients) allows reliable adjustments to be made simultaneously for an extensive number of covariates. Second, the statistical methodology is sound; an especially nice feature is the testing of the multivariable models for specificity, i.e. verifying the expected lack of relationship of magnesium level with temperature. Finally, the results have clinically relevant implications, cautioning intensivists against overzealous magnesium supplementation of their patients.