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CLINICAL STUDY

Admission hypomagnesemia and hypermagnesemia increase the risk of acute kidney injury

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Abstract

Background: The association between admission serum magnesium (Mg) levels and risk of in-hospital acute kidney injury (AKI) is limited. The aim of this study was to assess the risk of developing AKI in all hospitalized patients with various admission Mg levels. *Methods*: This is a single-center retrospective study conducted at a tertiary referral hospital. All hospitalized adult patients who had admission Mg available from January to December 2013 were analyzed in this study. Admission Mg was categorized based on its distribution into six groups (less than 1.5, 1.5–1.7, 1.7–1.9, 1.9–2.1, 2.1–2.3 and greater than 2.3 mg/dL). The primary outcome was in-hospital AKI occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio of AKI of various admission Mg levels using Mg with lowest AKI incidence (1.9–2.1 mg/dL) as the reference group. *Results*: Of 9241 patients enrolled, AKI occurred in 1124 patients (12.2%). The lowest incidence of AKI was when serum Mg was within 1.7–1.9 and 1.9–2.1 mg/dL. A U-shaped curve emerged demonstrating higher incidences of AKI associated with both hypoMg (<1.7) and hyperMg (>2.1). After adjusting for potential confounders, both hypoMg (<1.5 mg/dL) and hyperMg (>2.3 mg/dL) were associated with an increased risk of developing AKI with odds ratios of 1.70 (95% CI 1.31–2.18) and 1.42 (95% CI 1.11–1.81), respectively. *Conclusion*: Both admission hypoMg and hyperMg were associated with an increased risk for in-hospital AKI.

Keywords

Acute kidney injury, dysmagnesemia, electrolytes, hypermagnesemia, hypomagnesemia, magnesium

History

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Introduction

Acute kidney injury (AKI) is a common clinical syndrome in hospitalized patients, independently associated with in-hospital morbidity and mortality.[1] Although, previous studies have attempted to identify effective interventions to prevent AKI events,[2–4] most were unsuccessful, and the mortality rate in patients with AKI remains very high. Therefore, further studies are required to identify patients at high risk of developing AKI during hospitalization.

Magnesium (Mg) serves as a catalyst for greater than 300 intracellular reactions and provides various functions in areas of energy generation, neurotransmitters release, intracellular calcium regulation and protein synthesis and degradation.[5] Experimentally, Mg reduces the arteriolar tone and counteracts the vasoconstriction, resulting in an increase in the renal blood flow by stimulating nitric oxide release.[6–9] Moreover, recent studies have demonstrated that hypoMg is associated with non-recovery of renal function after an AKI episode.[10,11] Therefore, it is possible that Mg provides protective effects on AKI. However, the effect of admission Mg levels on the risk of in-hospital AKI in the general hospital population has not been examined. The objective of this study was to evaluate the risk of developing AKI in all hospitalized patients across a spectrum of Mg levels.

Materials and methods

Study population

All research authorized adult (age 18 year or older) patients admitted to Mayo Clinic Rochester – a tertiary referral hospital – from 01/01/2013 through 12/31/2013 were enrolled. Exclusion criteria were patients with a history of end-stage renal disease (ESRD), patients who presented with AKI at the time of admission and patients who did not have serum creatinine (SCr) measurement during hospitalization. For patients with multiple admissions during this period, only the first hospital admission was analyzed. ESRD was identified based on ICD-9 (International Classification of Diseases, 9th) code assignment (Supplementary Table 1) or an eGFR of less than 15 mL/min/1.73 m^2. The local Institutional Review Board approved this study.

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Data collection

Clinical characteristics, demographic information and laboratory data were collected using manual and automated retrieval from the institutional electronic medical record system. The admission serum Mg level, defined as the first serum Mg level within 24 h of hospital admission, was collected. eGFR was derived using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[12] Chronic kidney disease (CKD) was defined as a calculated eGFR less than 60 mL/min/1.73 m^2. The Charlson Comorbidity score[13] was computed for co-morbidities at the time of admission. Principal diagnoses were grouped based on ICD-9 codes at admission (Supplementary Table 2).

Clinical outcomes

The primary outcome was AKI, based on the SCr criterion of the KDIGO definition.[14] AKI was defined as an increase in SCr, within 7 days after the admission date, of either $\geq$0.3 mg/dL or a relative change of $\geq$50% from the baseline. The baseline SCr was defined as the minimum SCr measured within one year before admission. If outpatient SCr was not available, the Modification of Diet in Renal Disease equation[15] was used to estimate baseline SCr level, assuming normal baseline GFR of 75 mL/min/1.73 m^2, in accordance with this guideline.[14] Pre-specified subgroup analysis for patients with and without CKD was also performed.

Statistical analysis

Continuous variables are reported as mean ± SD for normally-distributed data and median (IQR) for non-normally distributed data. All categorical variables are reported as count with percentage. Baseline demographics and clinical characteristics were compared among the admission Mg group, using ANOVA for continuous variables and the Chi-square test for categorical variables. We categorized admission Mg levels, based on 6-quantile percentiles (10% | 25% | 50% | 75% | 90%): less than 1.5, 1.5–1.7, 1.7–1.9, 1.9–2.1, 2.1–2.3 and greater than 2.3 mg/dL. The Mg level of 1.9–2.1 mg/dL was selected as the reference group for outcome comparison since it was associated with the lowest incidence of AKI (Table 1) and within normal plasma Mg concentration (1.7–2.1 mg/dL).[16] We performed univariate analysis and then multivariate logistic regression analysis to evaluate the independent association between admission Mg levels and AKI. Odds ratio (OR) with 95% confidence interval (CI) is reported. OR was adjusted for variables with statistically significant (p value less than 0.05) differences between groups in univariate analysis. The adjusting variables were age, sex, race, Charlson score, baseline GFR, principal diagnosis, comorbidities, medications and the need for vasopressor and mechanical ventilator at hospital admission. Comorbidities were coronary artery disease (CAD), hypertension (HTN), diabetes mellitus (DM) and congestive heart failure (CHF). Medications were angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs) and diuretics. A two-tailed p value of less than 0.05 was considered statistically significant. All analyses were performed using JMP statistical software, version 10 (SAS Institute, Cary, NC).

Results

A total of 11,734 hospital admissions with available Mg levels within 24 h were identified. After excluding 363 patients with ESRD, 2106 patients with AKI at presentation and 24 patients who lacked SCr measurement during hospitalization, 9241 unique patients were enrolled.

Baseline characteristics

Of 9241 patients, 8535 (92%) patients were Caucasian and 5206 (56%) were male (Table 2). Mean age was 61 ± 17 years. Patient age was positively correlated with admission Mg levels, while eGFR was inversely correlated with admission Mg levels. Patient comorbidities included HTN (49%), DM (19%), CAD (20%) and CHF (7%). Thirty-seven percent of the patients were taking diuretics, 35% were taking ACEIs or ARBs and 22% were taking NSAIDs before admission.

Admission Mg and the incidence of AKI

Of 9241 patients enrolled, AKI occurred in 1124 patients (12.2%). The lowest incidence of AKI (10.6%) was when serum Mg was within 1.7–1.9 and 1.9–2.1 mg/dL (Figure 1). A U-shaped curve emerged demonstrating higher incidences of AKI associated with both hypoMg (<1.7) and hyperMg (>2.1), $p < 0.001$. The incidences of AKI in patients with serum Mg <1.5 mg/dL and >2.3 were 17.1% and 17.2%, respectively.

Admission Mg and risk of AKI

To assess whether admission Mg levels contributed to the AKI development, logistic regression models were built, using 1.9–2.1 mg/dL as a reference range. Unadjusted, admission Mg levels of less than 1.5 mg/dL, 1.5–1.7 mg/dL, and greater than 2.3 mg/dL were associated with an increased risk of AKI with ORs of 1.75 (95% CI 1.37–2.21), 1.24 (95% CI 1.0–1.52) and 1.76 (95% CI 1.0–2.21),

Table 1. Outcomes.

		Serum magnesium level at hospital admission (mg/dL)						
Outcome	All	<1.5	1.5–1.7	1.7–1.9	1.9–2.1	2.1–2.3	>2.3	p
AKI	1124 (12.2)	114 (17.1)	155 (12.8)	232 (10.6)	279 (10.6)	213 (12.1)	131 (17.2)	<0.001
AKI stage								
Stage 1	949 (10.3)	84 (12.6)	129 (10.6)	193 (8.8)	243 (9.2)	189 (10.7)	111 (14.6)	<0.001
Stage 2	125 (1.4)	19 (2.8)	20 (1.6)	28 (1.3)	25 (0.9)	20 (1.1)	13 (1.7)	
Stage 3	50 (0.5)	11 (1.6)	6 (0.5)	11 (0.5)	11 (0.4)	4 (0.2)	7 (0.9)	

Table 2. Baseline clinical characteristics.

		Serum magnesium level at hospital admission (mg/dL)						
Variables	All	<1.5	1.5–1.7	1.7–1.9	1.9–2.1	2.1–2.3	>2.3	*p*
N	9241	667	1216	2189	2642	1767	760	
Age (year)	61 ± 17	59 ± 18	61 ± 17	61 ± 18	61 ± 17	62 ± 17	62 ± 18	<0.001
Male	5206 (56)	325 (49)	639 (53)	1190 (54)	1534 (58)	1063 (60)	455 (60)	<0.001
Caucasian	8535 (92)	606 (91)	1119 (92)	2025 (93)	2446 (93)	1640 (93)	699 (92)	0.66
Charlson score	1.9 ± 2.4	2.5 ± 2.8	2.2 ± 2.7	1.9 ± 2.5	1.7 ± 2.3	1.6 ± 2.1	1.6 ± 2.2	<0.001
Baseline serum creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.3	<0.001
GFR (mL/min/1.73 m^2)	80 ± 18	79 ± 19	79 ± 19	78 ± 18	78 ± 18	76	74 ± 18	<0.001
Comorbidities								
CAD	1807 (20)	115 (17)	206 (17)	395 (18)	517 (20)	410 (23)	164 (22)	<0.001
HTN	4517 (49)	350 (52)	647 (53)	1058 (48)	1216 (46)	886 (50)	360 (47)	<0.001
DM	1747 (19)	178 (27)	304 (25)	445 (20)	435 (16)	280 (16)	105 (14)	<0.001
CHF	693 (7)	33 (5)	62 (5)	133 (6)	191 (7)	161 (9)	113 (15)	<0.001
PVD	246 (3)	15 (2)	38 (3)	58 (3)	75 (3)	36 (2)	24 (3)	0.40
CVA	647 (7)	35 (5)	83 (7)	155 (7)	172 (7)	138 (8)	64 (8)	0.14
Principal diagnosis								
Cardiovascular	2839 (31)	103 (15)	276 (23)	562 (26)	845 (32)	700 (40)	353 (46)	<0.001
Hematology/Oncology	1599 (17)	224 (34)	304 (25)	435 (20)	380 (14)	175 (10)	81 (11)	
Infectious disease	321 (3)	41 (6)	56 (5)	77 (4)	77 (3)	51 (3)	19 (3)	
Endocrine/metabolic	269 (3)	22 (3)	48 (4)	69 (3)	70 (3)	44 (2)	16 (2)	
Respiratory	373 (4)	16 (2)	44 (4)	81 (4)	115 (4)	83 (5)	34 (4)	
Gastrointestinal	1027 (11)	89 (13)	157 (13)	296 (14)	273 (10)	155 (9)	57 (8)	
Injury and poisoning	1372 (15)	93 (14)	165 (14)	327 (15)	455 (17)	257 (15)	75 (10)	
Other	1441 (16)	79 (12)	166 (14)	342 (16)	427 (16)	302 (17)	125 (16)	
Medication								
ACEI/ARB	3275 (35)	273 (41)	461 (38)	764 (35)	887 (34)	626 (35)	264 (35)	0.006
NSAIDs	2008 (22)	166 (25)	298 (25)	505 (23)	537 (20)	361 (20)	141 (19)	0.001
Diuretics	3403 (37)	243 (36)	451 (37)	732 (33)	910 (34)	703 (40)	364 (48)	<0.001
Vasopressor use	753 (8)	72 (11)	111 (9)	142 (6)	155 (6)	144 (8)	129 (17)	<0.001
Mechanical ventilator	1674 (18)	159 (24)	225 (19)	332 (15)	345 (13)	348 (20)	265 (35)	<0.001

Note: Continuous data are presented as mean ± SD; categorical data are presented as count (percentage). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; HTN, hypertension; NSAIDs, nonsteroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GFR,

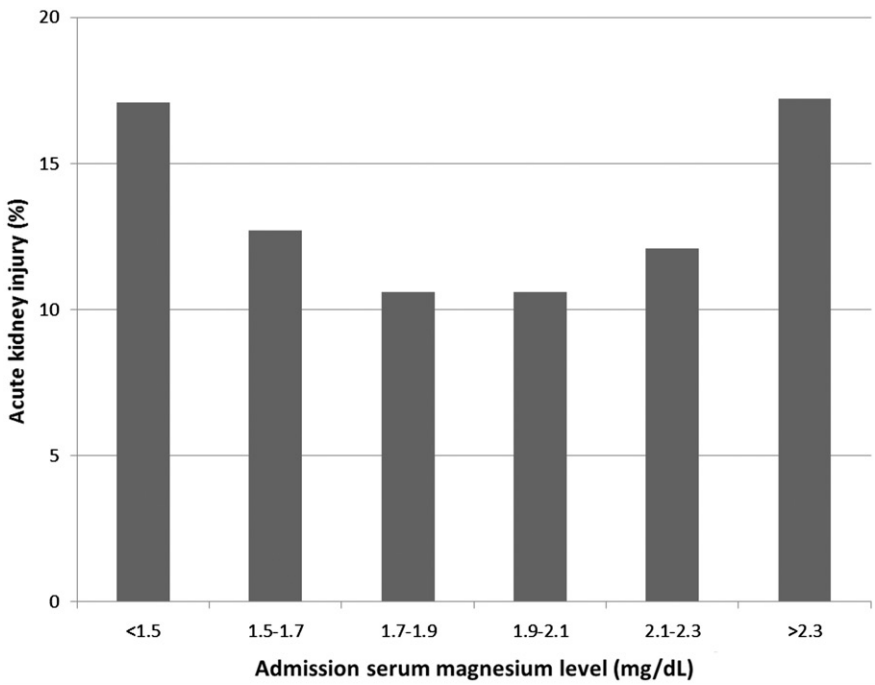

Figure 1. In-hospital acute kidney injury within 7 days between various admission serum Mg levels.

respectively (Table 3). When adjusted for all variables including age, sex, Charlson score, baseline GFR, comorbidities and medications, these associations remained statistically significant in Mg less than 1.5 mg/dL and greater than 2.3 mg/dL. Admission hyperMg (>2.3 mg/dL) was associated with increased risk of developing AKI (OR 1.42; 1.11–1.81). Admission hypoMg (<1.5 mg/dL) was higher associated with an increased AKI (OR 1.70; 1.31–2.18) (Table 3).

Table 3. Odds ratios for the association between admission serum magnesium levels and in-hospital acute kidney injury occurrence within 7 days.

	Univariate analysis		Multivariate analysis	
Serum magnesium level at hospital admission (mg/dL)	OR (95% CI)	*p*	Adjusted OR (95 % CI)	*p*
<1.5	1.75 (1.37–2.21)	<0.001	1.70 (1.31–2.18)	<0.001
1.5–1.7	1.24 (1.002–1.52)	0.048	1.18 (0.95–1.47)	0.14
1.7–1.9	1.00 (0.83–1.21)	0.97	1.00 (0.83–1.21)	0.98
1.9–2.1	1 (ref)		1 (ref)	
2.1–2.3	1.16 (0.96–1.10)	0.12	1.05 (0.86–1.28)	0.60
>2.3	1.76 (1.0–2.21)	<0.001	1.42 (1.11–1.81)	0.005

Note: Adjusted for age, sex, race, Charlson score, baseline GFR, history of coronary artery disease, hypertension, diabetes mellitus, congestive heart failure, principal diagnosis, use of ACEI/ARB, NSAID and diuretic, the need for vasopressor and mechanical ventilator at hospital admission.

Table 4. Odds ratios for the association between admission serum magnesium levels and in-hospital acute kidney injury occurrence within 7 days in subgroups of patients based on baseline GFR.

	Univariate analysis		Multivariate analysis	
Serum magnesium level at hospital admission (mg/dL)	OR (95% CI)	*p*	Adjusted OR (95 % CI)	*p*
Baseline GFR ≥60 mL/min/1.73 m^2 ($n = 8087$)				
<1.5	1.65 (1.26–2.14)	<0.001	1.62 (1.22–2.15)	0.001
1.5–1.7	1.24 (0.99–1.56)	0.06	1.19 (0.93–1.51)	0.16
1.7–1.9	0.98 (0.80–1.20)	0.85	1.00 (0.81–1.24)	0.97
1.9–2.1	1 (ref)		1 (ref)	
2.1–2.3	1.05 (0.85–1.30)	0.66	1.03 (0.82–1.28)	0.81
>2.3	1.65 (1.27–2.13)	<0.001	1.49 (1.13–1.95)	0.005
Baseline GFR <60 mL/min/1.73 m^2 ($n = 1154$)				
<1.5	1.88 (1.09–3.20)	0.02	1.93 (1.05–3.53)	0.03
1.5–1.7	1.10 (0.65–1.82)	0.72	1.10 (0.63–1.89)	0.74
1.7–1.9	1.02 (0.65–1.58)	0.94	1.00 (0.62–1.61)	0.99
1.9–2.1	1 (ref)		1 (ref)	
2.1–2.3	1.50 (0.98–2.32)	0.06	1.14 (0.72–1.82)	0.57
>2.3	1.80 (1.09–2.97)	0.02	1.22 (0.70–2.12)	0.48

Note: Adjusted for age, sex, race, Charlson score, baseline GFR, history of coronary artery disease, hypertension, diabetes mellitus, congestive heart failure, principal diagnosis, use of ACEI/ARB, NSAID and diuretic, the need for vasopressor and mechanical ventilator at hospital admission.

Risk of AKI based on baseline GFR

Subgroup analysis was performed to assess the risk of AKI in patients with various admission Mg levels based on baseline GFR as shown in Table 4. In multivariate logistic regression analysis for patients with CKD, admission hypoMg <1.5 mg/dL was significantly associated with increased risk of developing in-hospital AKI (OR 1.93; 1.05–3.53). Admission hyperMg (2.1–2.3 mg/dL and >2.3 mg/dL) was not significantly associated with an increased AKI in patients with CKD.

Discussion

In the present study, we demonstrated that admission Mg level was correlated with the incidence of AKI during hospitalization. The lowest incidence of AKI was when serum Mg was within 1.7–1.9 and 1.9–2.1 mg/dL and there was a U-shaped curve demonstrating higher incidences of AKI associated with both hypoMg (<1.7) and hyperMg (>2.1). Patients with both hypo (<1.5 mg/dL) and hyperMg (>2.3 mg/dL) at the time of admission had increased risk of developing AKI during hospitalization. In patients with CKD, admission hypoMg (<1.5 mg/dL) was associated with a 1.70-fold increased AKI risk.

There are several plausible explanations for the increased AKI risk in patients with dysmagnesemia at admission. Mg has been known to play an important role in the regulation of cardiovascular homeostasis.[17] It counteracts the vasoconstriction by endogenous catecholamines and potentiates the action of endogenous vasodilators.[6,7,18] In rats, hypoMg was shown to potentiate the post-ischemic renal injury.[19] In addition, an infusion of Mg has been shown to increase the renal blood flow *via* an endothelium dependent release of nitric oxide[8] and *via* its ability as a calcium channel antagonist.[9] Therefore, it is possible that dysmagnesemia, both hypoMg and hyperMg, may cause dysregulation of vascular tonicity homeostasis and result in higher risk of developing AKI *via* overstimulated vasoconstriction and vasodilation effects, respectively. In CKD patients, renal vasoconstriction can predispose patients to higher risk of AKI[20] as also demonstrated in our patients with hypoMg.

Although, previous reports have shown that hypoMg is a risk factor for non-recovery of renal function after an AKI episode in critically ill patients,[10,11] the investigators found no difference in Mg levels in patients with or without AKI. In the study by Alves et el.,[10] hypoMg was defined from any detected low Mg value during intensive care unit (ICU) stay. However, hospitalized Mg levels might not have represented the real patients' Mg status and patients might receive treatment to normalize Mg level, but they can still be Mg deficient.[21] In our present study, we used only the admission serum Mg for analysis, which is a reasonable indication of the patient's Mg status, and has been demonstrated to correlate best with Mg concentration in the bone.[22,23] Moreover, we

studied the effects of admission Mg on the risk of developing AKI in the general hospitalized patients, not only in ICUs. Therefore, the results presented in our study are the first to demonstrate that both hypoMg and hyperMg at time of admission is an important predictor of developing in-hospital AKI in the overall hospitalized patients.

This study has several limitations. Firstly, this is a single-center, retrospective study. Secondly, the patient population in this study is relatively homogeneous (predominantly Caucasian). Further studies with more heterogeneous population are desirable to ascertain the clinical effects of admission Mg on AKI in a broad patient population. Thirdly, there is potential selection bias, as those patients who had admission Mg measurements may have had different clinical characteristics from others who did not have admission Mg measurement. A multi-center, prospective study is ultimately required to address these limitations. Lastly, the effects of normalizing Mg levels and the risk of AKI were not the focus of our present study. Ritter and colleagues have recently completed an RCT comparing the incidence of AKI of Mg therapy to placebo in critically ill patients with hypoMg (ClinicalTrials.gov identifier – NCT01700998), which will elucidate if this intervention is effective to prevent AKI or shorten AKI recovery.

In conclusion, this study demonstrates that both admission hypoMg and hyperMg are associated with an increased risk for in-hospital AKI.

Declaration of interest

We do not have any financial or non-financial potential conflicts of interest.

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All authors had access to the data and a role in writing the manuscript.

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Supplementary material available online

Supplementary Tables 1 and 2.