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## The Association Between Admission Magnesium Concentrations and Lactic Acidosis in Critical Illness

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### Abstract

**Introduction**—Although magnesium plays an important role in aerobic metabolism and magnesium deficiency is a common phenomenon in critical illness, the association between magnesium deficiency and lactic acidosis in the intensive care unit (ICU) has not been defined.

**Methods**—This was a retrospective, cross-sectional study conducted at a 77 ICU bed tertiary medical center. Data pertaining to the first unique admission of any ICU patient between 2001 and 2008 were extracted from the Multiparameter Intelligent Monitoring in Intensive Care database. Hypomagnesemia was defined as serum magnesium <1.6 mg/dL. Mild and severe lactic acidosis were defined as lactate concentrations of >2 and > 4 mmol/L, respectively. Multivariate modeling was used to explore the association between magnesium and lactate concentrations.

**Results**—Of 8922 critically ill patients, 22.6% were hypomagnesemic. Hypomagnesemia was associated with an increased adjusted risk of mild lactic acidosis (odds ratio [OR] 1.71, 95% confidence interval [95% CI] 1.51–1.94,  $P < .001$ ) and severe lactic acidosis (OR 1.56, 95% CI 1.32–1.84,  $P < .001$ ) than the reference quartile. The association between hypomagnesemia and mild lactic acidosis was stronger in those at risk of magnesium deficiency, including diabetics (OR 2.02, 95% CI 1.51–2.72,  $P < .001$ ) and alcoholics (OR 1.92, 95% CI 1.16–3.19,  $P = .01$ ). As an internal model control, hypokalemia was not associated with an increased risk of lactic acidosis.

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#### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Conclusions**—Magnesium deficiency is a common finding in patients admitted to the ICU and is associated with lactic acidosis. Our findings support the biologic role of magnesium in metabolism and raise the possibility that hypomagnesemia is a correctable risk factor for lactic acidosis in critical illness.

### Keywords

magnesium deficiency; acidosis; lactic; critical illness; oxidative phosphorylation; nutritional deficiency

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## Introduction

Magnesium is an abundant intracellular cation that contributes to a range of physiologic processes including energy storage and utilization, protein metabolism, inflammation, and electrolyte homeostasis.<sup>1,2</sup> Hypomagnesemia is a common laboratory finding in the intensive care unit (ICU) setting with an estimated prevalence between 20% and 65%.<sup>3,4</sup> Among the total population of critically ill patients, those with alcoholism and diabetes have the highest rates of magnesium deficiency, presumably due to a combination of intracellular and extracellular magnesium depletion.<sup>4,5</sup> In the ICU, magnesium deficiency has been associated with worse outcomes including longer length of stay and increased mortality.<sup>6-8</sup>

Magnesium plays an important role in oxidative metabolism. The conversion of thiamine to its active triphosphate form is reliant on magnesium as a cofactor.<sup>9-11</sup> Thiamine pyrophosphate, in conjunction with pyruvate dehydrogenase, is critical in the metabolism of pyruvate to acetyl coenzyme A for entrance into the citric acid cycle.<sup>12</sup> In the absence of magnesium, disrupted oxidative phosphorylation shifts toward anaerobic metabolism, resulting in lactic acid production. Magnesium infusion attenuates lactate production during surgical procedures<sup>13</sup> and intense physical exercise,<sup>14</sup> but little information exists on the association of magnesium and lactate concentrations in the critically ill patients.

Given the prevalence of magnesium deficiency in critical illness and the morbidity associated with lactic acidosis, we investigated whether lower magnesium concentrations are associated with lactic acidosis in critically ill patients. We further hypothesized that the association between magnesium and lactate concentrations would be stronger in those at risk of intracellular magnesium deficiency and performed subgroup analyses in those with a history of diabetes and chronic alcoholism. In addition, we assessed whether the unbound fraction of extracellular magnesium was associated with lactic acidosis. Finally, we evaluated the association of magnesium concentrations in patients admitted with sepsis.

## Materials and Methods

### Study Population

The study population was drawn from the Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II) research database, a joint venture managed by researchers from the Laboratory of Computational Physiology at Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC). The MIMIC-II contains data from 24 581 adult patients who were admitted to surgical or medical ICUs at BIDMC. The

database contains high temporal resolution data from clinical systems, including laboratory results, electronic documentation, and bedside monitor trends and waveforms, for patients admitted to a BIDMC ICU between 2001 and 2008.<sup>15</sup> Use of the MIMIC-II database has been approved by the institutional review boards of BIDMC and the MIT.

Of 11 129 patients with a recorded admission lactate concentration, 9681 also had a serum magnesium concentration. Patients were excluded if they were missing admission Simplified Acute Physiology Scores (SAPs; n = 640), creatinine level (n = 48), or demographic information (n = 81), leaving 8922 unique first admissions. All laboratory data were determined by selecting the first measured value starting from 12 hours prior to ICU admission and extending until 12 hours after ICU admission.

### Outcome

The primary end point was lactic acidosis, defined as an admission serum lactate concentration >2 mmol/L in keeping with our hospital's laboratory normal range. Given that higher concentrations of lactic acid are more predictive of outcome in the critically ill patients, we also defined severe lactic acidosis as a concentration >4 mmol/L.<sup>16</sup>

### Exposure

The primary exposure was admission magnesium concentration, assessed as quartiles and continuously. Hypomagnesemia was defined as a serum magnesium concentration <1.6 mg/dL, in keeping with our hospital laboratory's definition, which was also the lowest quartile. To estimate the amount of unbound extracellular magnesium, corrected magnesium concentrations were determined using a previously defined formula: Corrected Magnesium = Serum magnesium + 0.005 × (40 – Serum albumin).<sup>17</sup> Magnesium concentrations were winsorized at the 0.5th and 99.5th percentiles to limit the effect of outliers.

### Statistical Analysis

We report baseline patient characteristics and laboratory data by quartiles. Sequential, multivariate models were created to define the association between magnesium concentrations, assessed as quartiles and as a continuous variable. For all analyses of cohort quartiles, the third magnesium quartile was used as reference. This reference value was chosen as it most closely reflects normal magnesium concentrations. Age, admission systolic blood pressure, admission SAPS, and admission serum creatinine were defined as continuous variables. Race and admission service type (medical, cardiac, surgical, or cardiothoracic ICU) were coded categorically. Oliguria was defined as a urine output less than 400 mL during the first 24 hours of ICU care.<sup>18</sup> We included all 30 Elixhauser comorbidities as individual variables rather than a summary score.<sup>19</sup> Model I presents the unadjusted association. Model II adds age, gender, ethnicity, and SAPS. Given the marked effect of renal function on magnesium concentrations, we included both SAPS and serum creatinine, along with Elixhauser comorbidities, ICU type, and blood pressure in model III. Separate regressions for lactic acidosis (>2 mmol/L) and severe lactic acidosis (>4 mmol/L) were performed.

In subgroup analyses, the *International Classification of Diseases, Ninth Revision* were used to identify patients with a history of chronic alcoholism or diabetes. A multiplicative interaction between serum magnesium and a binary term for either diabetes or chronic alcoholism, versus none, was tested ( $P = .03$ ), and further stratification was performed. Magnesium was examined in quartiles and continuously. A subgroup analysis of patients who were admitted to the ICU with sepsis was performed. Patients with sepsis were identified using the Martin criteria.<sup>20</sup> To better estimate unbound magnesium concentrations, a sensitivity analysis was performed using the corrected magnesium concentration.

As potassium is a primarily intracellular cation similarly affected by the balance of nutritional intake and renal excretion,<sup>21,22</sup> we tested the relationship between hypokalemia and lactic acidosis as a secondary outcome to ensure the specificity of observed associations. All statistical analyses were performed using JMP Pro, a component of SAS (Cary, North Carolina).

## Results

### Baseline Characteristics

The cohort mean magnesium concentration was 1.9 ( $\pm 0.54$ ) mg/dL. In all, 22.6% of the cohort was hypomagnesemic, who tended to be younger, with a higher prevalence of alcoholism and diabetes, and with better renal function, than those with elevated magnesium concentrations (Table 1).

### Association of Magnesium Concentration and Mild Lactic Acidosis

Overall, 4362 (48.9%) patients exhibited mild lactic acidosis with 58.6%, 49.5%, 43.4%, and 46.5% in the lowest to highest magnesium quartile, respectively. In unadjusted analysis (Table 2), the lowest magnesium quartile had an 85% increased odds of mild lactic acidosis (odds ratio [OR] 1.85, 95% confidence interval [95% CI] 1.64–2.08,  $P < .001$ ) compared to patients in the reference quartile. This relationship remained highly significant after adjustment (OR 1.71, 95% CI 1.51–1.94,  $P$  value  $< .001$ ). Patients in the second magnesium quartile were also more likely to have lactic acidosis (OR 1.29, 95% CI 1.13–1.47,  $P < .001$ ) in adjusted analysis. Each 1 mg/dL increase in magnesium concentration was associated with a 25% lower odds of lactic acidosis when evaluated continuously (OR 0.75, 95% CI 0.67–0.83,  $P < .001$ ).

### Association of Magnesium Concentration and Severe Lactic Acidosis

Lactate levels were  $>4$  mmol/L in 17.6% of patients in our cohort. In all, 23.0%, 16.5%, 14.8%, and 17.0% in the lowest to highest magnesium quartile, respectively, had severe lactic acidosis. Patients with hypomagnesemia were 72% more likely to have severe lactic acidosis (OR 1.72, 95% CI 1.48–2.00,  $P < .001$ ) when compared to the reference category (Table 3). This remained significant in adjusted analysis (OR 1.56, 95% CI 1.32–1.84,  $P < .001$ ). Each 1 mg/dL increase in magnesium concentration was associated with a 21% lower odds of severe lactic acidosis when evaluated continuously (OR 0.79, 95% CI 0.69–0.91,  $P < .001$ ).

### Association of Magnesium Concentration and Lactic Acidosis in Alcoholics and Diabetics

Of the 2022 (22.7%) patients with a history of diabetes, 17.6% were hypomagnesemic, which was associated with a 2-fold increased risk of mild lactic acidosis (OR 2.02, 95% CI 1.51–2.72,  $P < .001$ ), as seen in Table 4. Patients with diabetes and magnesium deficiency likewise had increased odds of severe lactic acidosis, although this did not reach statistical significance (OR 1.34, 95% CI 0.92–1.96). Of the 626 (7.0%) patients with a history of chronic alcohol use, 28.6% were hypomagnesemic, which was associated with 92% increased odds of mild lactic acidosis (OR 1.92, 95% CI 1.16–3.19,  $P = .01$ ) and a 2-fold increase in severe lactic acidosis (OR 2.09, 95% CI 1.11–4.00).

### Association of Corrected Magnesium Concentrations and Lactic Acidosis

Admission albumin measurements were available in 3897 (43.7%) patients in the cohort. The mean (standard deviation) magnesium and corrected magnesium concentrations in this subgroup were 1.91 ( $\pm 0.46$ ) and 1.96 ( $\pm 0.45$ ) mg/dL, respectively. In adjusted analysis, a corrected magnesium  $< 1.6$  mg/dL was associated with an 80% increased risk of mild lactic acidosis (OR 1.80, 95% CI 1.47–2.19,  $P < .001$ ).

### Association of Magnesium Concentration and Lactic Acidosis in Sepsis

There were 1765 patients admitted with sepsis. The mean lactate concentration was 2.76 mmol/L ( $\pm 2.33$ ). Hypomagnesemia in sepsis was associated with a 2-fold increased risk of lactic acidosis (OR 2.03, 95% CI 1.50–2.76,  $P < .001$ ) when compared to the reference quartile. Patients in the second and fourth magnesium quartiles also had increased rates of lactic acidosis when compared to reference category.

### Association of Hypokalemia and Lactic Acidosis

Hypokalemia was present in 614 (7.1%) patients in the cohort. In adjusted analysis, hypokalemia was not significantly associated with lactic acidosis (OR 1.05, 95% CI 0.89–1.26,  $P = .55$ ).

## Discussion

In this large, single-center analysis of critically ill patients, lower magnesium concentrations were associated with an increased risk of mild and severe lactic acidosis. The effect of magnesium on the risk of lactate acidosis was greater in those predisposed to intracellular and extracellular magnesium depletion.

Our findings extend an awareness of magnesium deficiency as a risk factor for anaerobic metabolism and lactate production, well described with the metabolic stress of intense physical exercise, to the metabolic stress of critical illness.<sup>14</sup> In adjusted analyses, including measurement of comorbidities, illness severity, blood pressure, and renal function, hypomagnesemia remained a significant predictor of lactic acidosis. Although lactic acidosis in critical illness is often assumed to reflect tissue hypoperfusion in response to a low-flow state and used to direct fluid resuscitation strategies, our analyses suggest that magnesium concentrations are an additional independent predictor.

Because magnesium is predominantly intracellular, and because the remaining extracellular component is highly protein bound, serum measurement may not accurately reflect biologically available magnesium.<sup>23–25</sup> Since neither intracellular nor free magnesium measurements are routinely available,<sup>26,27</sup> we studied patients known to be at risk of total body magnesium depletion, hypothesizing that the effect of serum magnesium on lactate production would be strengthened in those with both intracellular and extracellular magnesium depletion. Diabetics are considered particularly prone to magnesium depletion due to a combination of lower dietary magnesium intake and increased renal excretion as well as an alteration in transcellular transport.<sup>28–30</sup> Insulin deficiency may affect the Na<sup>+</sup>/H<sup>+</sup> antiporter in the renal proximal tubule leading to magnesium wasting.<sup>31</sup> Similarly, those with chronic alcoholism are at an increased risk of hypomagnesemia due to the diuretic action of alcohol coupled with decreased magnesium consumption.<sup>32</sup> In our cohort, the association between magnesium deficiency and lactic acidosis was strengthened in patients with either diabetes or chronic alcoholism.

To determine whether “free” magnesium concentrations were associated with lactic acidosis, we used a correction factor to assess the amount of unbound extracellular magnesium. Corrected magnesium concentrations remained significant predictors of lactic acidosis.

In addition to its critical role in oxidative phosphorylation, magnesium deficiency has been shown to have important immunomodulatory effects.<sup>1</sup> In a magnesium-deficient animal model, inflammatory cytokines including tumor necrosis factor  $\alpha$ , interleukin 1, substance P, and calcitonin gene-related peptide were elevated.<sup>33,34</sup> Further, hypomagnesemia may lead to impaired macrophage activation and leukocyte adherence to pathogens.<sup>35</sup> In experimental sepsis, magnesium deficiency is associated with increased mortality and magnesium replacement is protective.<sup>36</sup> In our analysis, patients with sepsis having hypomagnesemia had a more than 2-fold increased risk of lactic acidosis than the reference quartile. A combination of impaired glucose metabolism, coupled with a heightened inflammatory response, may account for the strong association between magnesium deficiency and lactic acidosis in those patients admitted with sepsis.

Our study has a number of limitations. The cross-sectional design prohibits conclusions about potential causality. In addition, our data set lacked the granularity to ascertain the time-lapse between magnesium and lactate measurements. Although we were able to calculate corrected magnesium, neither intracellular nor free magnesium concentrations were available. Information about dietary magnesium intake and over-the-counter dietary magnesium supplementations was not available. However, potassium, which is also largely dietary derived, was not associated with lactic acidosis when used as an internal model control, and the inclusion of albumin, a marker of general nutrition, did not attenuate the association between magnesium and lactic acidosis.

## Conclusion

Magnesium deficiency is a common finding in critical illness and is associated with lactic acidosis. Whether this association is due to residual confounding will require further well-designed interventional studies. Our findings support the biologic role of magnesium in

cellular metabolism and suggest that future studies should explore early magnesium repletion as a resuscitation goal.

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Table 1

## Admission Characteristics.

	Mg < 1.6	1.6	Mg < 1.8	1.8	Mg < 2.1	Mg 2.1	P Value
Total, n	2020	1617	2520	2765			
Demographics, mean (SD)							
Age, years	56.5 (19.5)	60.8 (19.9)	63.9 (18.0)	66.1 (17.3)			<.001
Male, %	52	55	56	57			.001
Ethnicity, %							
Caucasian	71	72	71	72			.57
African American	7	7	7	8			.67
Hispanic	3	4	3	2			.03
Comorbidities, %							
Congestive heart failure	14.0	20.0	24.7	28.0			<.001
Diabetes	31.6	22.0	23.3	26.4			<.001
Chronic alcoholism	9.0	7.8	6.6	5.6			<.001
Renal failure	4.8	4.3	4.7	6.8			<.001
Vitals, mean (SD)							
SBP, mm Hg	121.6 (29.8)	125 (28.2)	124.5 (27.2)	121.1 (26.6)			<.001
HR, bmp	94.0 (21.1)	92.6 (20.6)	90.7 (20.8)	91.0 (20.6)			<.001
Temp, °F	97.4 (5.8)	97.8 (4.8)	97.9 (3.9)	97.4 (5.2)			<.001
24 urine output, mL	2685 (2427)	2191 (1836)	2084 (1526)	1958 (1491)			<.001
ICU type, %							
Medical	38.9	41.7	44.1	47.7			<.001
Cardiac	4.2	8.1	9.0	10.4			<.001
Surgical	50.6	43.7	37.8	24.1			<.001
Cardiothoracic	6.4	6.5	9.1	17.8			<.001
Laboratory values, mean (SD)							
Calcium, mg/dL	7.8 (1.1)	8.2 (0.9)	8.5 (0.90)	8.7 (1.1)			<.001
Potassium, mEq/L	4.0 (0.8)	4.2 (0.8)	4.3 (0.8)	4.6 (1.0)			<.001
Creatinine, mg/dL	1.2 (1.1)	1.3 (1.2)	1.4 (1.4)	1.8 (1.8)			<.001
Hematocrit (%)	33.8 (6.2)	34.8 (6.4)	34.7 (6.4)	34.7 (5.6)			<.001

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	<b>Mg &lt; 1.6</b>	<b>1.6</b>	<b>Mg &lt; 1.8</b>	<b>1.8</b>	<b>Mg &lt; 2.1</b>	<b>Mg 2.1</b>	<b>P Value</b>
WBC, K/ $\mu$ L	13.7 (9.2)	13.9 (9.5)	13.0 (8.5)	13.8 (15.3)			.04
Disease severity score, no. (SD)							
SAPS	15.1 (5.3)	14.2 (5.5)	14.6 (5.7)	15.9 (5.6)			<.001

Abbreviations: HR, heart rate; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SBP, systolic blood pressure; SD, standard deviation; WBC, white blood cell.

Table 2

Association Between Magnesium Concentration and Mild Lactic Acidosis.

Odds Ratio for Lactic Acidosis (Lactate > 2 mmol/L)							
	Mg < 1.6	1.6	Mg < 1.8	1.8	Mg < 2.1	Mg 2.1	Per 1 mg/dL Increase in Mg
Model #1 <sup>a</sup>	1.85 (1.64–2.08) <.001	1.28 (1.13–1.45) <.001	Reference	Reference	1.14 (1.02–1.27) .02	0.75 (0.69–0.83) <.001	
Model #2 <sup>b</sup>	1.72 (1.53–1.95) <.001	1.29 (1.13–1.46) <.001	Reference	Reference	1.07 (0.96–1.20) .21	0.74 (0.67–0.82) <.001	
Model #3 <sup>c</sup>	1.71 (1.51–1.94) <.001	1.29 (1.13–1.47) <.001	Reference	Reference	1.09 (0.97–1.23) .16	0.75 (0.67–0.83) <.001	

Abbreviations: ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SBP, systolic blood pressure.

<sup>a</sup> Includes unadjusted magnesium.

<sup>b</sup> Adjusts for age, gender, ethnicity, and SAPS.

<sup>c</sup> Adjusts for age, gender, ethnicity, SAPS score, comorbidities, ICU type, admission serum creatinine, SBP, and oliguria during first 24 hours of ICU care.

**Table 3**

Association Between Magnesium Concentration and Severe Lactic Acidosis.

Odds Ratio for Lactic Acidosis (Lactate > 4 mmol/L)							
	Mg < 1.6	1.6	Mg < 1.8	1.8	Mg < 2.1	Mg 2.1	Per 1 mg/dL Increase in Mg
Model #1 <sup>a</sup>	1.72 (1.48–2.00) <.001	1.14 (0.96–1.35) .14	Reference	Reference	1.18 (1.02–1.37) .03	0.87 (0.76–0.98) .02	
Model #2 <sup>b</sup>	1.56 (1.37–1.83) <.001	1.16 (0.97–1.38) .10	Reference	Reference	1.03 (0.89–1.21) .65	0.83 (0.72–0.93) .001	
Model #3 <sup>c</sup>	1.56 (1.32–1.84) <.001	1.15 (0.95–1.38) .14	Reference	Reference	0.99 (0.85–1.17) .94	0.79 (0.69–0.91) <.001	

Abbreviations: ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SBP, systolic blood pressure.

<sup>a</sup>Includes unadjusted magnesium.<sup>b</sup>Adjusts for age, gender, ethnicity, and SAPS score.<sup>c</sup>Adjusts for age, gender, ethnicity, SAPS score, comorbidities, ICU type, admission serum creatinine, SBP, and oliguria during first 24 hours of ICU care.

Table 4

Adjusted Association of Magnesium Concentration and Mild Lactic Acidosis in Those at Risk of Magnesium Deficiency.<sup>a</sup>

	Mg < 1.6	1.6	Mg < 1.8	1.8	Mg < 2.1	Mg 2.1	Per 1 mg/dL Increase in Mg
Diabetics	n = 356 2.02 (1.51–2.72) <.001	n = 349 1.37 (1.03–1.82) .03	n = 588 Reference	n = 729 0.96 (0.76–1.21) .71	n = 155 0.65 (0.42–0.99) .05	0.63 (0.5–0.79) <.001	
Alcoholics	n = 179 1.92 (1.16–3.19) .01	n = 126 1.54 (0.90–2.64) .12	n = 166 Reference	n = 1776 1.25 (0.74–2.10) .40	n = 1912 0.79 (0.70–0.89) <.001		
Nondiabetic, nonalcoholic	n = 1501 1.63 (1.41–1.90) <.001	n = 1153 1.25 (1.07–1.46) .01	n = 1776 Reference	n = 1912 1.12 (0.99–1.29) .11			

Abbreviations: ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SBP, systolic blood pressure.

<sup>a</sup>Adjusts for age, gender, ethnicity, SAPS score, comorbidities, ICU type, admission serum creatinine, SBP, and oliguria during first 24 hours of ICU care.