Serum total and ionized magnesium concentrations and urinary fractional excretion of magnesium in cats with diabetes mellitus and diabetic ketoacidosis

Carol R. Norris, DVM, DACVIM; Richard W. Nelson, DVM, DACVIM; Mary M. Christopher, DVM, PhD, DACVP

Objective—To determine magnesium (Mg) status in cats with naturally acquired diabetes mellitus (DM) and diabetic ketoacidosis (DKA), evaluate changes in Mg status after treatment for DKA, and correlate Mg status with systemic blood pressure and degree of glyceremic control.

Design—Case series and cohort study.

Animals—12 healthy cats (controls), 21 cats with DM, and 7 cats with DKA.

Procedure—Serum total magnesium (tMg) and ionized magnesium (iMg) concentrations and spot urinary fractional excretion of magnesium (FMg) were determined, using serum and urine samples obtained from all cats when they were entered in the study and from cats with DKA 12, 24, and 48 hours after initiating treatment. Indirect blood pressure and degree of glyceremic control were determined in 10 and 21 cats with DM, respectively.

Results—Initially, 2 and 13 cats with DM and 1 and 4 cats with DKA had serum tMg and iMg concentrations, respectively, less than the low reference limit (mean ± 2 SD) determined for controls. In cats with DKA, serum tMg concentration decreased significantly over time after initiating treatment. Urinary FMg was significantly higher in cats with DM or DKA, compared with controls. Systemic hypertension was not detected nor was there a correlation between Mg status and degree of glyceremic control in cats with DM.

Conclusions and Clinical Relevance—Hypomagnesemia was a common finding in cats with DM and DKA and was more readily identified by measuring serum iMg concentration than tMg concentration. The clinical ramifications of hypomagnesemia in such cats remain to be determined. (J Am Vet Med Assoc 1999;215:1455–1459)

Magnesium (Mg), the second most abundant intracellular cation, plays a key role in the mainte-
nance of transmembrane gradients, protein and nucleic acid synthesis, and signal transduction.1,12 Patients with hypomagnesemia are predisposed to a wide variety of cardiovascular, neurologic, and metabolic sequelae, including systemic hypertension, arrhythmias, muscle weakness, seizures, and refractory hypokalemia.1,5 Hypomagnesemia results from decreased intake, increased loss (renal or gastrointestinal tract), and alterations in transcellular distribution.8 In humans, hypomagnesemia is commonly associated with many diseases, including chronic diarrhea, short-bowel syndrome, pancreatitis, glomerulonephritis, postobstructive diuresis, hyperthyroidism, sepsis, and diabetes mellitus (DM).1,7 Hypomagnesemia has been described in dogs with traumatic and abnormal cardiopulmonary, gastrointestinal tract, endocrine, renal, and neuromuscular conditions,3,10 but reports evaluating Mg status in clinically ill cats are sparse.11,12

An association between DM and hypomagnesemia has been documented in humans.1,2,5 Concurrent hypomagnesemia and DM appear to play a role in the development of diabetic complications in humans, including systemic hypertension, diabetic retinopathy, thrombotic tendencies, dyslipidemias, and cardiac arrhythmias.2,5,11 In addition, Mg deficiency is speculated to cause insulin resistance12,14 and poor control of glycemia.15,19,26 Cats with DM suffer from many of the same complications. To our knowledge, there have been no studies done to evaluate associations between hypomagnesemia and DM, diabetic ketoacidosis (DKA), or complications arising from either condition in cats. The purpose of the study reported here was to evaluate Mg status in cats with DM and DKA by measuring serum total Mg (tMg) and ionized Mg (iMg) concentrations, spot urinary fractional excretion of Mg (FMg), and correlate hypomagnesemia with systemic arterial hypertension and control of glycemia in cats with DM.

Materials and Methods

Animals—Forty cats between 8 months and 19 years old were used for this study. The control group consisted of 12 cats that were selected from a specific-pathogen-free cat colony and determined to be healthy on the basis of physical examination and results of CBC and serum biochemical analyses. Twenty-one cats with naturally acquired DM, which was diagnosed by detecting typical clinical signs (eg, polyuria, polydipsia, polyphagia, weight loss) and persistent hyperglycemia and glucosuria, and 7 cats with DKA, which was diagnosed by detecting hyperglycemia, glucosuria, and ketonuria, were selected from those referred to the University
of California-Davis Veterinary Medical Teaching Hospital between September 1996 and September 1998. Cats with DKA had not been treated with IV administered fluids or insulin for at least 48 hours prior to entry into the study. All cats were fed 1 of 5 different diets replete in Mg (ie, diets meeting criteria recommended by the Association of American Feed Control Officials) prior to and throughout the study.\textsuperscript{21} Diets contained a mean (± SD) Mg concentration of 0.07 ± 0.009% (range, 0.05 to 0.11%) on a dry matter basis. Signalment, body weight, duration of DM, and prior insulin treatment were recorded for cats with DM or DKA. An initial minimum data base for these cats included a complete history, physical examination, and serum biochemical analyses.

**Determination of serum tMg and iMg concentrations**—Five milliliters of whole blood was collected into a tube without preservatives from cats with DM and DKA when they were entered into the study (time 0) and from cats with DKA 12, 24, and 48 hours after initiating treatment for the DKA. Collection tubes were filled to minimize loss of carbon dioxide from blood. Blood was allowed to clot for 15 minutes at 22 C, then centrifuged, and the serum was transferred into polystyrene tubes. Samples were stored at −70 C until assayed. Serum tMg concentration was determined by use of a spectrophotometric method that uses calgamin as a chromatic dye.\textsuperscript{22} Serum iMg concentration was determined, using an ion-selective electrode,\textsuperscript{23} and results were corrected for serum ionized calcium concentration and pH.

**Determination of FE\textsubscript{Mg}**—Three to 5 ml of urine was obtained by free catch or cystocentesis from 6 control cats and all cats with DM and DKA when they were entered into the study. Urine was assayed immediately or stored in plastic tubes at −20 C until analyzed. Frozen urine was thawed, and all urine samples were brought to room temperature (22 to 24 C), acidified with 0.2N hydrochloric acid to dissolve crystals, and mixed thoroughly. Serum and urine creatinine concentrations were determined by use of a kinetic method with the Jaffe reaction on an automated analyzer.\textsuperscript{24} Urine Mg concentration was determined in the same manner as described for serum Mg concentration. Urinary fractional excretion of Mg was calculated, using the formula:

\[
\text{FE}_{\text{Mg}} = \frac{\text{Scr} \times \text{Umg}/\mu\text{mol/L} \times \text{Ucr} / \mu\text{mol/L}}{\text{Scr} \times \mu\text{mol/L}}
\]

where Scr = serum creatinine concentration, Umg = urine Mg concentration, Smg = serum Mg concentration, and Ucr = urine creatinine concentration.\textsuperscript{22,24}

**Blood pressure determination**—Blood pressure (BP) was measured in the first 10 cats with DM entered into the study. Cats were kept in a quiet, secluded environment, and BP was measured, using a commercial indirect oscillometric machine.\textsuperscript{25} Pressure cuff size was calculated by multiplying the circumference of the limb by 0.4. Cats were positioned in sternal recumbency, and the cuff was placed over the radial or brachial artery. Ten readings of pulse pressure and systolic, diastolic, and mean BP were averaged. Systemic arterial hypertension was defined as a systolic BP > 180 mm Hg, diastolic BP > 100 mm Hg, or mean BP > 120 mm Hg.

**Glycemic control**—Degree of glycemic control in cats with DM was arbitrarily categorized as good or poor on the basis of blood glycosylated hemoglobin (GHB) and serum fructoseamine concentrations measured by use of affinity chromatography with a commercially available kit and a nitroblue tetrazolium reduction method,\textsuperscript{26} respectively. Glycosylated hemoglobin concentrations < 2.5% and > 3%, and serum fructoseamine concentrations < 450 μmol/L and > 500 μmol/L, were defined arbitrarily as indicative of good and poor glycemic control, respectively.\textsuperscript{26} Reference ranges for blood GHB and serum fructosamine concentrations were 1.0 to 2.2% and 180 to 360 μmol/L, respectively.\textsuperscript{26,27}

**Statistical analyses**—All analyses were performed, using an unpaired ANOVA and a commercial software package.\textsuperscript{28} A value of P < 0.05 was considered significant. Data are presented as mean ± SD.

**Results**

**Composition of groups**—Control cats comprised 8 castrated males and 4 spayed females between 2 and 10 years old (mean ± SD, 5.2 ± 2.9 years). All were domestic shorthair cats. Cats with DM comprised 16 males (2 sexually intact, 14 castrated) and 5 spayed females between 6 and 19 years old (10.8 ± 3.8 years). Sixteen were domestic shorthair or longhair cats, and 5 were Siamese. Cats with DKA comprised 2 castrated males and 5 spayed females between 8 months and 15 years old (9.8 ± 5.3 years). Five were domestic shorthair cats, 1 was a Siamese, and 1 was a Burmese. There were no significant differences in age, body weight, or duration of disease between cats with DM and DKA. Systemic hypertension was not detected in the 10 cats with DM for which BP was determined (systolic BP, 124 ± 10 mm Hg; diastolic BP, 85 ± 9 mm Hg; mean BP, 99 ± 9 mm Hg).

**Serum tMg and iMg concentrations**—The 12 control cats had serum tMg and iMg concentrations of 2.37 ± 0.31 mg/dL and 1.24 ± 0.09 mg/dL, respectively. For comparison with concentrations determined in the other groups, we used the mean concentration ± 2 SD determined for control cats as our reference range. Thus, reference ranges for serum tMg and iMg concentrations were 1.75 to 2.99 mg/dL and 1.06 to 1.42 mg/dL, respectively. Serum tMg and iMg concentrations in cats with DM were 2.14 ± 0.26 mg/dL and 0.98 ± 0.15 mg/dL, respectively, whereas in cats with DKA, values before treatment were 3.04 ± 0.75 mg/dL and 0.80 ± 0.30 mg/dL, respectively. Only 1 of 21 cats with DM and 1 of 5 cats with DKA had a serum tMg concentration less than the lower reference limit when they were entered into the study (Fig 1). In contrast, 13 of 20 cats with DM and 4 of 5 cats with DKA had a serum iMg concentration less than the lower reference limit (Fig 2). Serum iMg concentration was significantly lower in cats with DM and DKA, compared with controls.

![Figure 1](image-url)—Serum total magnesium (Mg) concentration in 21 cats with diabetes mellitus (DM) and 5 cats with diabetic ketoacidosis (DKA). Each point represents the value determined for an individual cat. The area within the box is the mean concentration ± 2 SD determined for 12 healthy adult cats.
Figure 2—Serum ionized Mg concentration in 20 cats with DM and 5 cats with DKA. Each point represents the value determined for an individual cat. The area within the box is the mean concentration ± 2 SD determined for 12 healthy adult cats.

Figure 3—Serum total Mg concentration in 7 cats with DKA before (time 0) and after IV administration of fluids and insulin. Each symbol represents values for an individual cat; values may overlap. *Mean serum total Mg concentration is significantly (P < 0.05) different from mean time-0 value.

Although serum tMg concentration in cats with DKA was significantly higher at time 0, compared with the other 2 groups, serum tMg concentration decreased significantly over time in these cats after initiation of treatment for DKA (Fig 3). At 48 hours, serum tMg concentration (1.7 ± 0.29 mg/dl) was significantly lower in these cats, compared with values determined for the other 2 groups at time 0.

Mean serum iMg concentrations in cats with DKA determined at all times after initiation of treatment were significantly lower, compared with mean serum iMg concentrations in control cats. Forty-eight hours after treatment, serum iMg concentration (0.77 ± 0.07 mg/dl) also was significantly less than values determined at time 0 for cats with DM. However, serum iMg concentration in cats with DKA did not decrease significantly over time, compared with the initial value obtained for that group. The 2 cats with DKA that had the lowest serum iMg concentrations (0.52 and 0.48 mg/dl) at time 0 died within the first 48 hours of hospitalization.

Urinary fractional excretion of Mg—Urinary fractional excretion of Mg in 6 of 12 control cats was 0.004 ± 0.002 (range, 0 to 0.01). Urinary fractional excretion of Mg was significantly greater in cats with DM (0.07 ± 0.12; range, 0.01 to 0.58) and DKA (0.10 ± 0.08; range, 0.01 to 0.21), compared with control cats. Significant differences in FEmg were not detected between cats with DM and DKA.

Glycemic control—There was no correlation between degree of glycemic control and serum tMg or iMg concentration in cats with DM. Poorly regulated cats had a significantly shorter duration of DM prior to entry into the study than well-regulated cats (5.1 months vs 14.7 months).

Discussion

Hypomagnesemia was common in cats with DM and DKA, which is similar to findings in humans. Approximately 30% of humans with DM and 55% of humans with DKA develop hypomagnesemia. Magnesium homeostasis is governed by a balance between gastrointestinal tract absorption, renal excretion, and transcellular shifts of Mg. Hypomagnesemia in patients with DM and DKA may be caused by hyperglycemia-induced osmotic diuresis and increased renal excretion of Mg, an insulin-induced shift of Mg from plasma into RBC, pancreatitis-induced malabsorption of Mg, and a renal tubular reabsorptive Mg defect. Hypomagnesemia in cats with DKA was more prevalent and severe than in cats with DM, presumably because of severe glucosuria, ketoaciduria, hypophosphatemia, and an insulin-mediated intracellular Mg shift.

Accurate determination of Mg deficiency can be difficult, because the majority of Mg is located intracellularly. Measurement of serum tMg concentration is the most common screening test currently available but is an insensitive measure of total body Mg stores. Consequently, serum tMg concentrations within reference limits can be detected in the face of total body Mg depletion, because <1% of total body Mg is in the extracellular fluid compartment. Serum iMg concentration reflects the physiologically active fraction of Mg, and intracellular iMg stores are believed to be in equilibrium with extracellular iMg stores. Measurement of serum iMg concentration should provide a more accurate assessment of total body Mg content than serum tMg concentration. Although measurement of serum tMg and iMg concentrations identified hypomagnesemia in cats with DM or DKA, low serum iMg concentrations were more commonly identified than low serum tMg concentrations. Initially, low serum tMg concentrations were detected in only 1 of 21 cats with DM and 1 of 5 cats with DKA, compared with low serum iMg concentrations, which were detected in 13 of 20 cats with DM and 4 of 5 cats with DKA. Thus, iMg appears to be a more sensitive indicator of hypomagnesemia in diabetic cats.

Serum tMg concentration can also be affected by dehydration, renal insufficiency, albumin concentration, and acid-base balance. These factors may have contributed to the decrease in serum tMg concentration over time in the cats with DKA that were treated with fluids and insulin, because dehydration (prerenal azotemia) and acidosis were presumably corrected with treatment. After 48 hours of treatment, serum tMg concentration was less than the lower reference limit in 2 of 5 cats with DKA, and serum iMg concentration...
was less than the lower reference limit in all of these cats. Although mean serum iMg concentrations in cats with DKA determined at all times before and after treatment were significantly lower than control values, serum tMg concentrations determined in 4 of 5 cats with DKA at entry into the study were greater than the upper reference limit. Therefore, interpretation of serum tMg concentration in cats with DKA prior to medical treatment must be done with caution, because total body Mg stores may be depleted despite high serum tMg concentration. A similar problem is faced when monitoring serum concentrations of other electrolytes (e.g., sodium, potassium, and phosphorus) in cats with DKA.26 Serial monitoring of serum tMg concentration is recommended to evaluate Mg status, especially when determination of serum iMg concentration is not possible.

The standard for measuring urine electrolyte concentrations is 24-hour urine electrolyte excretion.27 Because routine urinary catheterization is impractical in cats, we measured spot FEMg.21,22,26 As with measurement of urinary fractional excretion of any electrolyte, there are no reference range values, only expected values.28 We used 6 of our 12 control cats to determine a range of FEMg that was then compared with FEMg determined for cats with DM and DKA. All cats with DM or DKA had a higher FEMg than control cats; maximal renal Mg losses approached 100 times the magnitude of loss in control cats. On the basis of these findings, we believe that increased urinary Mg loss in cats with DM and DKA probably contributed to the development of hypomagnesemia. However, routine monitoring of FEMg is not recommended, because it is not a reliable indicator of total Mg status.

Hypertension is a complication of DM in humans.11,13,15 Magnesium deficiency has a direct vasocostrictive effect on vascular smooth muscle and indirectly leads to vasocostriction by increasing intracellular calcium concentration.29 Oral Mg supplementation may decrease systolic blood pressure in humans with type 2 DM.31 We did not detect systemic hypertension in cats with DM. One of these 10 cats had serum tMg concentrations less than the lower reference limit, and 3 had serum iMg concentrations less than the lower reference limit.

Insulin resistance, which results in poor control of glyceremia, is another effect of hypomagnesemia in diabetic humans.30,39 There is an inverse relationship between serum tMg concentration and blood glucose and GHb concentrations.6,17,20 Oral Mg supplementation decreases insulin requirements in humans with type 1 DM.30 Insulin resistance in Mg-deficient patients is believed to be attributable to alterations in insulin secretion, binding, and activity.13,14,16,17 Blood GHb and serum fructosamine concentrations are variables used to assess control of glyceremia in cats.24 We did not detect correlations between serum tMg or iMg concentrations and blood GHb or serum fructosamine concentration in cats with DM.

Hypomagnesemia can result in nonspecific abnormal cardiovascular and neuromuscular signs, including arrhythmias, weakness, ataxia, fasciculations, and seizures.5,6 Although these clinical signs were detected in a few of the 7 cats with DKA while they were hospitalized, it is not clear what role hypomagnesemia played in their development. Poorly controlled DM, concurrent diseases, and other electrolyte abnormalities can cause similar clinical signs. Many of the clinical signs resolved during the initial 48 hours of treatment, despite persistent or worsening hypomagnesemia. It is also unknown what role severe hypomagnesemia (iMg concentration < 0.5 mg/dL) may have played in the death of 2 of the 7 cats with DKA. Further studies are warranted to determine whether parenteral or oral supplementation with Mg would benefit cats with DKA and clinical signs of hypomagnesemia.

References
18. Nadler J, Buchanan T, Natarajan R, et al. Magnesium defi-


