Magnesium Status and the Effect of Magnesium Supplementation in Feline Hypertrophic Cardiomyopathy

Lisa M. Freeman, Don J. Brown, Francis W.K. Smith, and John E. Rush

ABSTRACT

Magnesium deficiency has been associated with the development of cardiovascular disease in several species. Cats may be predisposed to alterations in magnesium status because of recent changes in the composition of commercial feline diets. The purposes of this study were 1) to examine the dietary history of cats with hypertrophic cardiomyopathy (HCM), 2) to study magnesium status of cats with HCM compared to normal cats, and 3) to determine the effects of magnesium supplementation in cats with HCM. In part 1 of the study, diets of 65 cats with HCM were examined retrospectively. Forty of the 45 cats for which diets could be determined (89%) ate a diet designed to be magnesium-restricted and/or to produce an acidic urine. In part 2 of the study, 10 cats with HCM were compared to 10 healthy control cats for serum creatinine and magnesium; urine creatinine and magnesium, urine specific gravity and pH, and fractional excretion of magnesium. Urine creatinine and specific gravity were higher in control cats than in cats with HCM. No other differences were found between the 2 groups. In part 3, cats with HCM were supplemented with either 210 mg magnesium chloride (n = 15) or 210 mg lactose (n = 15) for 12 wk. No differences between the 2 groups were found for changes in either magnesium status or echocardiographic parameters. However, the 30 cats with HCM, as a group, did show significant improvements in measures of cardiac hypertrophy over the 12-week period. This was likely the result of treatment with other medications, rather than the magnesium supplementation. The results of this study suggest that cats with HCM are likely to be fed magnesium-restricted diets, but that they do not appear to have altered magnesium status compared to healthy controls.

RÉSUMÉ

Il existe une association entre la déficience en magnésium et le développement de maladies cardiovasculaires chez plusieurs espèces. Les chats peuvent être prédisposés aux déséquilibres de l'état du magnésium à cause des changements récents dans la composition des diètes commerciales félines. Les objectifs de cette étude étaient les suivants : 1-d'évaluer l'histoire diététique des chats avec une cardiomyopathie hypertrophique (HCM), 2-d'étudier l'état du magnésium des chats avec HCM en le comparant à celui de chats normaux, et 3-de déterminer les effets d'un supplément en magnésium chez des chats avec HCM. Dans la partie 1 de l'étude, les diètes de 65 chats avec HCM ont été examinées de façon rétrospective. Quarante des 45 chats (89 %) pour lesquels les diètes ont pu être déterminées mangeaient des diètes conçues pour être restreintes en magnésium et/ou pour acidifier l'urine. Dans la partie 2 de cette étude, les taux de créatinine et de magnésium dans l'urine, la densité spécifique et le pH urinaire et la fraction d'excrétion du magnésium ont été comparés chez 10 chats avec HCM et 10 chats témoins en bonne santé. La créatinine et la densité spécifique de l'urine étaient plus élevées chez les chats témoins que chez les chats avec HCM. Aucune autre différence n'a été obervée entre ces deux groupes. Dans la partie 3, les diètes des chats avec HCM étaient complétées soit avec 210 mg de chlorure de magnésium (n = 15), soit avec 210 mg de lactose (n = 15) pendant 12 semaines. Aucune différence n'a été observée en ce qui concerne les modifications de l'état du magnésium ou les paramètres échocardiographiques. Cependant, dans le groupe de 30 chats avec HCM, des améliorations significatives des mesures de l'hypertrophie cardiaque ont été constatées sur la période de 12 semaines. Ceci était probablement la conséquence du traitement par d'autres médicaments plutôt que celle de la supplémentation en magnésium. Les résultats de cette étude suggèrent que les chats avec HCM ingérent souvent des diètes pauvres en magnésium mais qu'ils ne semblent pas présenter de déséquilibre de leur état du magnésium lorsqu'on les compare à des sujets témoins en bonne santé.

(Traduit par docteur Philippe Pibarot)

INTRODUCTION

Magnesium is an essential prosthetic group in hundreds of enzymatic reactions involving carbohydrate and fatty acid metabolism, protein and nucleic acid synthesis, the adenylate cyclase system, and cardiac and smooth muscle contractility. Thus, magnesium plays an important role in normal cardiac function. It also is clear that alterations in magnesium homeostasis in people are common, and can have deleterious effects in a variety of cardiovascular conditions, including hypertension (1), coronary artery disease (2), congestive heart failure (3), and cardiac arrhythmias

Department of Medicine, Tufts University School of Veterinary Medicine, 200 Westboro Road, North Grafton, Massachussetts 01536 USA.

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(4). Magnesium deficiency has been shown to cause a cardiomyopathy in a variety of species, including rats, hamsters, and puppies (5–7). In addition, numerous drugs used to treat cardiac conditions, including diuretics and digitalis, are associated with magnesium depletion (8).

Cats may be predisposed to hypomagnesemia as a result of diet formulation by the pet food industry. An increased awareness of feline lower urinary tract disease (FLUTD) and associations of this disease with various dietary components have caused pet food manufacturers to reformulate feline diets. Many commercial feline diets are now restricted in magnesium, often just meeting the Association of American Feed Control Officials (AAFCO) nutrient profile (9). In addition, maintenance of a low urine pH has been shown to decrease the risk of struvite urolithiasis (10). Therefore, most feline diets are now formulated to produce an acidic urine within a pH range of 6.0 to 6.8. Acidic urine, however, increases the urinary loss of several electrolytes and minerals, including magnesium (11). Therefore, recent changes in dietary formulation may predispose cats to magnesium deficiency, which has been shown in other species to cause cardiomyopathy. The purposes of this study were 1) to examine the dietary history of cats with HCM, 2) to study magnesium status of cats with HCM compared to normal cats, and 3) to determine the effects of magnesium supplementation on magnesium status and cardiac hypertrophy in cats with HCM.

MATERIALS AND METHODS

PART 1

In the first part of this 3 part study, dietary and other historical findings were recorded for cats with HCM. Cats were identified retrospectively from the medical records at the Foster Hospital for Small Animals at Tufts University for admissions between 1990–1992. Information was recorded on diet, environment, and medical history. Owners were contacted by telephone to gain information not available from the medical record. Diets were considered to be magnesium-restricted if they contained $\leq 0.10\%$ magnesium on a dry matter basis. Diets were considered to produce an acidic urine if the average urine pH produced by cats eating the diet was ≤ 6.8.

PART 2

In part 2 of the study, the magnesium status of cats with HCM was compared to that of healthy control cats. All cats were client-owned animals. A diagnosis of HCM was based on echocardiographic measurements of left ventricular free wall at end-diastole or interventricular septum measurement at end-diastole > 0.55 cm, and recognition of left atrial enlargement. Cats with renal failure, hyperthyroidism, and hypertension were excluded from the study. Cats were classified as healthy controls if they had a normal physical examination and normal echocardiographic parameters.

All measurements were taken after a 12 h fast. Additionally, furosemide was discontinued for 24 h prior to measurements in cats that received this medication. Following sample collection, serum was separated from red blood cells within 30 min, and both urine and serum were frozen at −80°C until the time of analysis. Serum and urine total magnesium were measured by flame atomic absorption. Serum and urine creatinine were measured by an automated chemistry analyzer (Roche Mira Analyzer, Roche Diagnostics Systems, Nutley, New Jersey, USA). Urinary fractional excretion of magnesium (FE_{mg}) was calculated based on the formula:

$$FE_{mg} = \frac{\text{serum creatinine} \times \text{urine magnesium}}{\text{serum magnesium} \times \text{urine creatinine}} \times 100$$

Urine pH was analyzed with urine dipsticks (Multistix, Miles Inc, Diagnostics Division, Elkhart, Indiana, USA) and urine specific gravity was measured by refractometry.

The means for the healthy control and HCM groups were compared using independent t-tests.

PART 3

Part 3 of the study included the 10 cats with HCM from Part 2, plus an additional 20 cats with HCM (selected according to the same criteria as in Part 2). Baseline measurements of serum magnesium and creatinine, as well as urine magnesium, creatinine, specific gravity, and pH were measured in the additional 20 cats. A baseline electrocardiogram, echocardiogram, arterial blood pressure measurement by Doppler technique, and a renal biochemical profile were performed on all 30 cats. A dietary history also was recorded. After baseline data were collected, cats were randomized to either the magnesium or placebo groups. Cats in the magnesium group were given 210 mg $MgCl_26H_20$ (magnesium chloride, Spectrum Chemical Manufacturing Corporation, Gardena, California, USA) orally once daily (to provide 25 mg elemental magnesium). The placebo group was given capsules containing 210 mg lactose (lactose, Humco Laboratory, Texarkana, Texas, USA). Investigators and cat owners were blinded as to the capsule formulation provided to each cat until that cat completed the study. Cardiac medications were prescribed as deemed appropriate in each case. Each cat was maintained on the diet on which it was previously fed.

All cats were reassessed after 12 wk of magnesium or placebo administration. At this time, measurements of serum magnesium and creatinine; urine magnesium, creatinine, specific gravity, and pH; as well as an electrocardiogram, echocardiogram, arterial blood pressure, and a renal biochemical profile were performed.

The mean baseline parameters of the experimental and placebo groups, as well as the changes over time between groups, were compared using independent *t*-tests. A *P*-value < 0.05 was considered statistically significant.

RESULTS

PART 1

Sixty-five cats with HCM were identified retrospectively from medical records for cats diagnosed with HCM between 1990–1992. Diets and adequate histories could be determined in 45 (69%) of the cats. Of this group, 15 (33%) had a past history of FLUTD. Thirty-three cats (73%) ate a diet designed to be

magnesium-restricted and 27 cats (60%) ate a diet which produced an acidic urine. Forty cats (89%) ate a diet with at least one of these properties and 20 cats (44%) ate diets that were both magnesium-restricted and acidic.

PART 2

Ten cats with HCM and 10 healthy control cats were enrolled prospectively in the study. No significant differences in age were found between HCM and control cats (Table I). In addition, there were no differences between groups in serum creatinine, serum magnesium, urine magnesium, urine pH, or FE_{mg} (Table I). Cats in the control group did have a significantly higher urine creatinine and higher urine specific gravity.

PART 3

Fifteen cats with HCM were randomized to receive magnesium capsules (magnesium group) and 15 cats with HCM were randomized to receive lactose capsules (placebo group). The magnesium dosage ranged from 2.5–9.2 mg elemental magnesium/kilogram body weight (mean = 4.3 mg elemental magnesium/kilogram body weight). At baseline, there were no significant differences in mean age, serum creatinine, serum magnesium, urine creatinine, urine magnesium, urine pH and specific gravity, or FE_{mg} between groups. The mean time from diagnosis of HCM to enrollment in the study, echocardiographic parameters, and medications also did not differ significantly between groups (Table II).

The groups also were compared for mean changes over the 12 wk supplementation period. No significant difference between the magnesium and placebo groups was found in serum creatinine, serum magnesium, urine creatinine, urine magnesium, urine pH and specific gravity, or FE_{mg}. While significant decreases in interventricular septum and left ventricular free wall thickness and increases in left ventricular cavity size were noted in the HCM cats as an entire group ($n = 30$), there were no significant differences between the magnesium and placebo groups in these parameters (Fig. 1). Possible confounding effects of other factors were examined, and it was found that cats taking enalapril had significant improvements in echocardiographic parameters compared to cats taking other medications. No significant effects of magnesium were found when the use of enalapril was controlled for.

TABLE I. Part 2. Baseline comparison between cats with hypertrophic cardiomyopathy (HCM) and healthy controls (mean ± SD)

	Controls ($n = 10$)	HCM cats ($n = 10$)	P value
Age (y)	6.10 ± 3.32	6.30 ± 4.24	NS
Serum creatinine (mg/dL)	1.44 ± 0.26	1.46 ± 0.20	NS
Serum magnesium (mg/dL)	2.28 ± 0.13	2.39 ± 0.25	NS
Urine creatinine (mg/dL)	519.25 ± 110.17	319.37 ± 105.29	0.001
Urine magnesium (mg/dL)	15.04 ± 9.51	12.20 ± 6.15	NS
FE_{Mg} (%)	1.89 ± 1.25	2.35 ± 0.99	NS
Urine pH	6.65 ± 0.78	6.50 ± 0.53	NS
Urine specific gravity	1.059 ± 0.002	1.044 ± 0.012	0.001

FE_{Mg} = fractional excretion of magnesium; NS = not statistically significant

TABLE II. Part 3. Baseline comparison between cats with hypertrophic cardiomyopathy (HCM) in the magnesium and placebo groups (mean ± SD)

	Placebo ($n = 15$)	Magnesium ($n = 15$)	P value
Duration of HCM (d)	424.07 ± 857.59	418.47 ± 562.87	NS
Heart rate (per minute)	198.67 ± 31.82	186.00 ± 25.01	NS
Systolic BP (mmHg)	141.87 ± 32.70	142.47 ± 29.77	NS
Left atrium (cm)	1.62 ± 0.17	1.76 ± 0.43	N S
MaxLA (cm)	1.72 ± 0.21	1.92 ± 0.51	N S
Right ventricle (cm)	0.23 ± 0.11	0.29 ± 0.18	NS
IVSd (cm)	0.75 ± 0.23	0.71 ± 0.14	NS
IVSs (cm)	1.03 ± 0.14	1.02 ± 0.14	NS
LVIDd (cm)	1.37 ± 0.21	1.39 ± 0.30	NS
LVIDs (cm)	0.64 ± 0.19	0.63 ± 0.15	NS
LVWd (cm)	0.76 ± 0.19	0.84 ± 0.18	NS
LVWs (cm)	1.01 ± 0.16	1.13 ± 0.19	NS
# cats in CHF	5	3	NS
# cats taking furosemide	8	4	NS
# cats taking diltiazem	9	9	NS
# cats taking β-blocker	2	4	NS
# cats taking enalapril	5	3	NS

NS = not statistically significant; BP = blood pressure; MaxLA = maximum diameter of the left atrium from short-axis 2-D directed M-mode echocardiographic measurement; IVSd/s = thickness of the interventricular septum in diastole/systole; LVIDd/s = left ventricular internal diameter in diastole/systole; LVWd/s = thickness of the left ventricular free wall in diastole/systole

The dietary histories of the cats in this part of the study also were examined. Ten cats in the placebo group (67%) and 11 cats in the magnesium group (73%) ate diets that were designed to be either magnesium restricted and/or to produce an acidic urine. Levels of dietary sodium, chloride, magnesium, and potassium were compared to echocardiographic parameters, as well as to serum creatinine and magnesium and urine creatinine and magnesium. No relationship was found between the dietary levels of sodium, chloride, magnesium, or potassium and the echocardiographic or laboratory parameters.

DISCUSSION

Magnesium deficiency has been implicated in the development of a variety of cardiovascular diseases. In rodents, magnesium deficiency is known to directly cause cardiomyopathy, with myocardial necrosis and calcification, as well as a mononuclear and giant cell infiltrate (5–12). It is postulated that this myocardial injury occurs as a result of increased production of free radicals and cytokines or that it occurs secondary to intracellular calcium overload (5,6,13). Although cardiomyopathy in people has not been shown to be caused by magnesium deficiency, an inverse relationship has been found between serum magnesium concentrations and left ventricular hypertrophy (14).

In the current study, 33% of cats with HCM studied retrospectively in part 1 had a history of FLUTD, while it has been reported that approximately one percent of the general feline population is affected per year with FLUTD (15). In addition, 89% of this group of cats with HCM ate a diet that was designed to be either magnesium-restricted and/or to

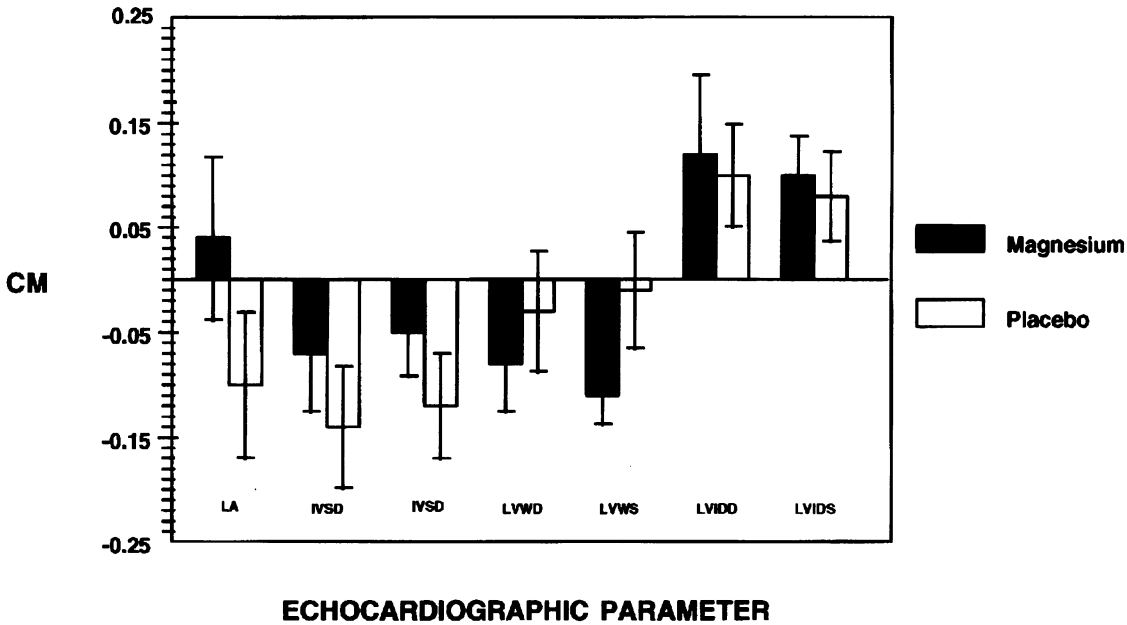

Figure 1. Mean changes in echocardiographic parameters for magnesium and placebo groups over the 12 wk study period (mean ± SEM).

produce an acidic urine. This is similar to the findings in HCM cats studied prospectively in part 3 of this study, as well, in which 67% and 73% of cats with HCM in the placebo and magnesium groups, respectively, ate this type of diet. Of interest, however, is the finding that 80% of the 10 healthy control cats also ate this type of diet.

Part 2 of this study showed no significant difference in measures of magnesium status between HCM and healthy cats. While this may suggest that there are truly no alterations in magnesium status in cats with HCM, it also may be the result of using techniques with inadequate sensitivities for assessing total body magnesium. Magnesium is distributed primarily in the bone (67% of total body magnesium) and the intracellular compartment (31% of total body magnesium), with only 1.3% of total body magnesium found in the extracellular fluid (8). Therefore, total body depletion of magnesium can exist in the presence of normomagnesemia. While urinary excretion of magnesium (FE_{Mg}) provided a crude functional measure of magnesium status in addition to the measurement of serum magnesium, intracellular magnesium would provide a more accurate assessment of magnesium status. Another important possibility is that the 10 healthy cats studied were not an ideal control group, as the majority also ate a magnesium-restricted diet.

The dosage of magnesium supplementation (210 mg magnesium chloride/day) was selected to provide 25 mg of elemental magnesium/day. This provides approximately the minimum level recommended in the AAFCO Nutrient Profile for cats and is the dosage extrapolated from a variety of human studies. Given the high prevalence of FLUTD in cats with HCM, this conservative dose of magnesium supplementation was selected to reduce the possibilities for the development of FLUTD in the study cases. In addition, magnesium chloride was selected to ensure the production of an acidic urine. At this dosage of magnesium supplementation, no differences in measures of magnesium status or echocardiographic parameters were found between cats with HCM given magnesium or placebo for 12 wk. It would be expected that magnesium supplementation would either increase serum magnesium concentration or increase urinary excretion of magnesium. Since neither of these parameters changed significantly with magnesium supplementation, it is possible that either the dosage was too low to affect magnesium status or that intracellular alterations could not be detected. The variability introduced by dietary differences between individual cats also may have overshadowed changes in magnesium status. The cats were maintained on their usual diets, however, to avoid any possible changes in magnesium status or echocardiographic parameters specifically due to dietary alteration. While there was a trend for the urine pH of magnesium-supplemented cats to decrease ($P = 0.11$), the mean urine pH of both groups was acidic before and after the 12-week study period.

In summary, retrospective analysis showed a high prevalence of FLUTD in cats with HCM and a large percentage of these cats ate a diet that was magnesium-restricted and/or produced an acidic urine. Despite these important findings, no demonstrable differences in magnesium status were found between cats with HCM and healthy controls when studied prospectively. Nor did magnesium supplementation at the selected dosage significantly alter magnesium status or echocardiographic parameters in cats with HCM. Therefore, the cause for the association between diet, FLUTD, and HCM remains unanswered, but remains a fruitful area for investigation.

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