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SUSPECTED HYPERVITAMINOSIS D IN RED-RUMPED AGOUTI (*DASYPROCTA LEPORINA*) RECEIVING A COMMERCIAL RODENT DIET

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Abstract: An 8 yr, intact male red-rumped agouti (*Dasyprocta leporina*) was evaluated for weight loss. Examination revealed poor body condition, hypercalcemia, elevated serum 25-hydroxyvitamin D, metastatic calcification of soft tissues, and hyperechoic kidneys. The diet, formulated for laboratory rodents, contained elevated levels of vitamin D_3. Histopathology from a female conspecific that died 5 mo prior identified dystrophic mineralization and nephrosclerosis, suggestive of a vitamin D_3 toxicity. The male agouti responded well to a dietary reduction in vitamin D_3 and calcium. Six months into therapy, progressive renal failure was identified and was further managed with enalapril, phosphorus binders, and dietary manipulation. Suspected vitamin D_3 toxicity has been reported in pacas (*Cuniculus paca*) and agouti and has been linked to exposure to New World primate diets. In this brief communication, an agouti developed suspected hypervitaminosis D after receiving a commercial rodent diet commonly fed to this species in captivity.

Key words: Agouti, *Dasyprocta leporina*, hypercalcemia, hypervitaminosis D, vitamin D.

BRIEF COMMUNICATION

An 8 yr, intact male (animal M80611) red-rumped agouti (*Dasyprocta leporina*) presented in April 2015 for weight loss. The agouti had a history of elevated total serum calcium levels (14.6 mg/dl)[13] 5 yr previously (Table 1).

The agouti was anesthetized for examination, identifying a cardiac arrhythmia, thin body condition, and marked callus formation on both hocks. Radiographs identified metastatic calcification of soft tissue structures (tendon and muscle). Serum biochemistry revealed hyperalbuminemia (>6.5 g/dl), hypercalcemia (>16.0 mg/dl),[13] and presumed hypervitaminosis D (397 nmol/L) when compared with other agouti specimens (median: 49 nmol/L, range 0–197 nmol/L, Michigan State University, Diagnostic Center for Population and Animal Health, Lansing, Michigan 48910, USA). Parathyroid hormone (PTH) levels were 0 (Table 1). The agouti received fluid therapy and began oral prednisone (0.8 mg/kg po q 12 hr for 7 days, then 0.8 mg/kg sid for 7 days, followed by 0.8 mg/kg po q 72 hr × 7 days, Qualitest Pharmaceuticals, Inc., Huntsville, Alabama 35811, USA).

Vitamin D_3 toxicity was suspected. Pest control in the building did not use vitamin D_3 analogs. The animal's diet had been changed in July 2012 from Mazuri® Rat and Mouse (no. 5663, Land O'Lakes, Inc., Arden Hills, Minnesota 55126, USA) to a breeder diet that was higher in vitamin D and calcium (Mazuri® Rodent Breeder, Purina Mills, LLC, Brentwood, MO 63144, USA, no. 5M30; Table 2). The diet was switched to Kaytee® Forti-Diet Mouse & Rat (Kaytee Products, Inc., Chilton, Wisconsin 53104, USA) for 2 wk until alternative diets could be delivered (Table 2).

The agouti was reexamined under anesthesia 2 wk later. A grade 3 (on a scale of 1 to 6) heart murmur with no arrhythmia was found. Serum calcium (15.5 mg/dl) and albumin (>6.5 mg/dl) remained elevated[13] (Table 1). Hyperechoic kidneys without cystic changes were noted on ultrasound. The diet was changed to a combination of Mazuri® Wild Herbivore High Fiber (Purina Mills, LLC, Brentwood, MO 63144, USA, no. 5V05) and Mazuri Rat and Mouse (Table 2).

The agouti was reexamined 3 wk later. Progressive weight loss and a grade 3 (on a scale of 1 to 6) cardiac murmur, with intermittent dropped beats were noted. Serum calcium was normal[13] (Table 1). Mazuri Wild Herbivore High Fiber was removed from the diet due to refusal.

An exam performed 6 wk later (July 2015) revealed no cardiac murmur or arrhythmia and an increase in body weight. Serum calcium and albumin were again elevated,[13] but 25(OH)D levels were presumed normal (108 nmol/L) with a PTH of 0 (Table 1).

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Table 1. Exam findings, diet, and serum calcium, 25(OH)D, parathyroid hormone (PTH),[a] and phosphorus in a male agouti (animal M80611) with presumed hypervitaminosis D.

Date	Clinical findings	Weight (kg)	Diet	Total Ca (mg/dl)[a]	Ionized Calcium (mmol/L)	25-Hydroxyvitamin D (nmol/L)	PTH[b] (pmol/L)	Phosphorus[c] (mg/dl)
Jul 2008		3.27		12.5	1.65	105	0	5.8
Jan 2010		3.27		14.6	—	137	—	4.1
Apr 9 2015	Arrhythmia, dystrophic calcification, hock callus, thin body condition	3.09	Mazuri Rodent Breeder	>16.0	1.92	397	0	5.5
Apr 20 2015	Heart murmur, hyperechoic kidneys	3	Kaytee forti-diet	15.5	2.01	204	0	4.9
May 2015	Heart murmur, arrhythmia, weight loss	2.82	Mazuri wild herbivore and Mazuri Rat and Mouse	10.9	—	—	0	6.4
Jun 2015	Improved body condition	3.36	Mazuri Rat and Mouse	14.1	—	108	0	5.8
Dec 2015	Weight loss, dehydration, cardiac murmur and arrhythmia	3.23	Mazuri Rat and Mouse	>16.0	2.21	116	0.6	5.5
Dec 2015	Hyperechoic, cystic kidneys, weight loss	3.18	Mazuri Rat and Mouse	15.5	2.04	—	—	8.9
Jan 2016	Calcium oxalate crystalluria, cardiac arrhythmia, weight loss	3.27	Mazuri Rat and Mouse	15.9	2.02	—	—	5.4
Feb 2016	Weight gain	3.27	Oxbow rabbit	15.1	2.03	42	0	3.1
Apr 2016	Stable weight	3.27	Oxbow rabbit	14.4	—	—	—	3.2
Aug 2016	Stable weight, thin body condition	3.18	Oxbow mouse and rat	13.8	2.12	57	0	2.2

[a] International Species Information System reference: (8.3–15.6 mg/dl).
[b] PTH results were frequently reported as 0, which implies that this assay may be inappropriate for agouti.
[c] International Species Information System reference: (3.1–11.5 mg/dl).

Table 2. Vitamin D_3, calcium, and phosphorus content of formulated feeds.[a]

	Vitamin D_3 (IU/kg)	% Calcium	% Phosphorus
Mazuri Rat and Mouse, no. 5663	1,425	0.95	0.65
Mazuri Rodent Breeder, no. 5M30[b]	2,700	1.1	0.65
Kaytee Forti-Diet Mouse and Rat	2,500	1.1	0.55
Mazuri Wild Herbivore High Fiber, no. 5V05	1,255	0.9	0.35
Oxbow Essentials Adult Rabbit Food	900	0.35–0.85	0.25
Oxbow Essentials Mouse and Young Rat	1,000	0.80–1.2	0.6

[a] As-fed basis, provided by the manufacturer.
[b] Formulated feed at time of presentation.

The agouti was maintained on Mazuri Rat and Mouse for the following 6 mo and had gained weight (0.18 kg) until December 2015, again presenting with weight loss and dehydration. An irregular cardiac rhythm and grade 2 (scale of 1 to 6) murmur were present, and the animal was profoundly hypercalcemic (>16 mg/dl).[13] It was administered prednisone at (0.8 mg/kg po q 12 hr for 14 days, then 0.8 mg/kg sid for 30 days, followed by 0.8 mg/kg po q 72 hr × 30 days) for calciuresis. Three weeks later, an exam found hypercalcemia (15.5 mg/dl), hyperphosphatemia (8.9 mg/dl), leukopenia (1,900 white blood cells/μl), and weight loss.[13] Ultrasonography showed hyperechoic and cystic kidneys (Table 1). The animal received fluid therapy and was started on enalapril (1.25 mg po sid, Valeant Pharmaceuticals, Bridgewater, New Jersey 08807, USA) for suspected proteinuria.

A recheck 10 days later revealed a persistent hypercalcemia (15.9 mg/dl), hyperalbuminemia (> 6.5 g/dl), and hyperphosphatemia (5.4 mg/dl; Table 1).[13] The cardiac murmur was absent, but skipped beats were noted. Urinalysis showed calcium oxalate crystalluria and proteinuria. The agouti was started on aluminum hydroxide powder (100 mg po bid, Rx Vitamins, Elmsford, New York 10523, USA) and received fluid therapy. The diet was changed to a lower calcium and vitamin D_3 rabbit pellet (Oxbow Essentials Adult Rabbit Food, Oxbow Animal Health, Murdock, Nebraska 68407, USA) in light of presumptive renal failure, causing persistent hypercalcemia (Table 2). Thirty days later, the agouti showed a weight gain (0.2 lbs), hyperalbuminemia (>6.5 g/dl), normophosphatemia (3.1 mg/dl), hypercalcemia (15.1 mg/dl), hyperglycemia (239 mg/dl), and presumed normal levels of serum 25(OH)D.[13] Prednisone was discontinued, and aluminum hydroxide and enalapril continued.

Two months later (April 2016), the agouti was castrated for population management. The animal had maintained a stable weight over the previous 60 days. Blood work revealed hypercalcemia (14.4 mg/dl), hyperglycemia (236 mg/dl), and normophosphatemia (3.2 mg/dl; Table 1).[13] Management was unchanged.

In August 2016, the male was reexamined prior to the introduction of a 4-yr-old female. The male had maintained weight but remained thin. Despite reductions in dietary vitamin D_3 and calcium, the male remained hypercalcemic (Table 1). The diet was transitioned to Oxbow's rodent diet (Oxbow Animal Health, Omaha, NE 68138, USA, Oxbow Essentials Mouse and Young Rat Food) to facilitate integration with the new female (Table 2). For comparison, the female was evaluated for calcium and vitamin D status, with results reported in Table 3 (animal 160619).

Histopathology for a conspecific female (animal 100640) housed with the male that died 5 mo prior to his initial presentation showed severe, end-stage nephrosclerosis and metastatic calcification (cardiac and splenic vessels and kidneys). Recent serum biochemistry was unavailable for this animal. Banked serum from a 7-yr-old female that died 5 yr prior to presentation indicated borderline hypercalcemia, azotemia, hyperproteinemia, and presumed increased serum 25(OH)D at time of death (Table 3, animal M81207). Histopathology identified mild lymphoplasmacytic interstitial nephritis and fibrosis and severe soft-tissue mineralization (splenic vessels and skeletal muscle and tendon). The sister of the dead female, who had also been housed at the institution for 5 yr, was shipped out 5 mo prior to the death of the other female. Historic banked serum for the sister (animal 100641) was unremarkable for 25(OH)D and calcium status (Table 3, animal 100641).

To determine whether vitamin D_3 toxicity was a concern for collection rodents being fed rodent breeder, serum samples were submitted for analysis for one coendu (*Coendu prehensilis*), one capybara (*Hydrochoerus hydrochaeris*), one Indian crested porcupine (*Hystrix indica*), and one beaver (*Castor canadensis*). Results are included in Table 3, with 25(OH)D_3 ranging from 23–207 nmol/L. None of these values appeared elevated.

Suspected vitamin D_3 toxicity has been reported in paca (*Cuniculus paca*) and agouti (*Dasyprocta aguti*).[7] In these cases, nine pacas and two orange-rumped agoutis died of extensive soft-tissue mineralization after exposure to New World primate diets.[7] Serum 25(OH)D levels were not reported in these cases. New World primate diets are high in calcium and vitamin D_3 and were theorized as the cause. Mazuri® New World Primate (Purina Mills, LLC, MO USA, no. 5MA5), for example, has 1.3% calcium and 7,940 IU/kg vitamin D.

The assay used detected ionized calcium and 25-hydroxyvitamin D in rodent samples but not PTH. Although PTH can be suppressed by hypercalcemia, it was also undetectable in animals with presumed normal calcium and serum 25-hydroxyvitamin D status. The PTH assay may not be suitable for some species and should be interpreted with caution.

Table 3. Total serum calcium, ionized calcium, 25-hydroxyvitamin D, parathyroid hormone (PTH), and phosphorus in agouti and other rodents housed at Cleveland Metroparks Zoo.

Animal	Date	Total calcium (mg/dl)	Ionized calcium (mmol/L)	25-Hydroxyvitamin D (nmol/L)	PTH[a] (pmol/L)	Phosphorus (mg/dl)
160619 4-yr-old female agouti	Aug 2016	12.6	1.54	37	0	4.9
M81207 7-yr-old female agouti[b]	Dec 2009	14.0	1.53	174	0	7.9
100641 5-yr-old agouti, female conspecific[c]	Jul 2014	10	1.32	77	0	—
10-yr-old prehensile-tailed porcupine, female[d]	May 2013	8.2	0.8	23	0	4.7
6-yr-old capybara, female[d]	Feb 2015	10.1	—	60	0	4.7
5-yr-old capybara, female[d]	Mar 2014	10.5	—	41	0	3.4
14-yr-old crested porcupine, male[d]	Jan 2013	11.2	—	86	0	3.3
10-yr-old crested porcupine, male[d]	Jun 2009	11.2	—	74	0	—
5-yr-old beaver, male[d]	May 2013	—	1.12	140	0.7	—
6-yr-old beaver, male[d]	Oct 2014	9.8	1.23	207	0	5.7

[a] PTH results were frequently reported as 0, which implies that this assay may be inappropriate for the rodent species listed here.
[b] Samples run 7 yr after collection.
[c] Samples run 18 mo after collection.
[d] Samples run August 2016.

Differentials for hypercalcemia include hypercalcemia of malignancy, hypoadrenocorticism, primary hyperparathyroidism, juvenile hypercalcemia, renal disease, pseudohyperparathyroidism, idiopathic, granulomatous disease, and hypervitaminosis D.[11] In agouti, polycystic kidney disease (PKD) associated with a mutation in the PKD1 gene has been postulated as a cause of hypercalcemia and appears to be hereditary.[3] PKD has also been linked to hypercalcemia in New Zealand White rabbits (*Oryctolagus cuniculus*).[8] In one study, PKD was a common finding for red-rumped agouti and was associated with metastatic calcification of arteries in four of seven animals examined, with secondary hyperparathyroidism postulated as the cause.[9] Polycystin-1 and polycystin-2 are the end products of the PKD gene and are involved in forming a calcium-sensitive channel in cells.[15] Though the precise mechanism is unknown, disorders in calcium signaling may contribute to hypercalcemia in these species.[8] Although cystic change was identified in the male agouti, it cannot be determined whether PKD was present without genetic testing.

For many zoo species, dietary vitamin D and calcium levels are unknown, and calcium metabolism can vary significantly among animals in the same taxonomic order. African mole rats (*Cryptomys hottentotus*) and naked mole rats (*Heterocephalus glaber*) have reportedly no dietary requirement for vitamin D, and calcinosis cutis and renal calcification have been linked in this species to excess dietary vitamin D.[2,12] Mole rats efficiently absorb calcium from the intestinal tract by using a nonsaturable diffusion mechanism independent of vitamin D_3.[1] In comparison, laboratory rats (*Rattus norvegicus*) have a reported dietary vitamin D requirement of 1,000 IU/kg diet.[10] Vitamin D deficiency has been linked to infertility in lab rats, increasing spontaneous abortions and death during parturition.[10] Many rodent species develop hypercalcemia secondary to renal disease from reduced excretion of calcium, similar to elephants (*Loxodonta africana*), rabbits, horses (*Equus caballus*), and hyrax (*Procavia capensis*).[4,6,14] In the serum samples evaluated as part of this brief communication, no other rodent species at this institution demonstrated elevated serum 25(OH)D after receiving the diet. After the diet change, persistent hypercalcemia was likely from nephrotoxicity and renal failure.

The dietary requirements for vitamin D in agouti are undetermined. The species either has a unique calcium metabolism or low dietary vitamin D requirements. In this case, a nearly 50% reduction of vitamin D_3 was sufficient to ameliorate the clinical signs of weight loss. The agouti developed renal failure characterized by cystic change and persistent hypercalcemia 6 mo into treatment, which was managed by further reduction of dietary vitamin D and calcium. Two

years later, the agouti remains under management for renal failure. Agouti diets should be carefully evaluated for dietary vitamin D.

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