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CASE REPORT

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Spontaneous remission and relapse of diabetes mellitus in a male dog

Mariola B. Rak[1] | Chen Gilor[2] | Stijn J. M. Niessen[3,4] | Eva Furrow[5]

[1]Department of Small Animal Clinical Sciences at the College of Veterinary Medicine, University of Tennessee, Knoxville, Tennessee, USA

[2]Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, Florida, USA

[3]Department of Clinical Science and Services, Royal Veterinary College, University of London, Hertfordshire, UK

[4]Veterinary Specialist Consultations & VIN Europe, Hilversum, The Netherlands

[5]Department of Veterinary Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, Minnesota, USA

Correspondence
Eva Furrow, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, University of Minnesota, 1352 Boyd Avenue, C339 Veterinary Medical Center, St. Paul, MN 55108, USA.
Email: furro004@umn.edu

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Abstract

An 8-year-old male neutered Miniature Schnauzer was diagnosed with diabetes mellitus based on fasting hyperglycemia and glucosuria after a 2-week history of polydipsia and periuria, in line with the Agreeing Language in Veterinary Endocrinology consensus definition. Treatment of insulin and dietary management was initiated. The insulin dose was gradually reduced and eventually discontinued over the next year based on spot blood glucose concentrations that revealed euglycemia or hypoglycemia. After discontinuation, the dog remained free of clinical signs for 1 year until it was again presented for polyuria/polydipsia with fasting hyperglycemia and glucosuria. Insulin therapy was resumed and continued for the remainder of the dog's life. Although diabetic remission often occurs in cats and humans, the presumed etiopathogenesis of pancreatic beta cell loss makes remission rare in dogs, except for cases occurring with diestrus or pregnancy. This case demonstrates that diabetic remission is possible in dogs, even in cases without an identifiable reversible trigger.

KEYWORDS
beta cells, glucotoxicity, insulin, obesity, pancreatitis, schnauzer

1 | CASE HISTORY

An 8-year-old male neutered Miniature Schnauzer presented to his primary veterinarian for a 2-week history of polydipsia and periuria. His appetite was normal, though he was fed table scraps in addition to commercial dog food in the preceding 2 weeks. He had a history of seasonal allergic rhinitis, obesity (maximum historic weight = 13.5 kg; body condition score [BCS] not reported), and thunderstorm-associated anxiety. The allergic rhinitis had been treated with 1-2 month tapering courses of methylprednisolone (Medrol, Pfizer, Inc, New York NY; 0.4 mg/kg every other day, PO), with the last dose given 18 months before. While receiving methylprednisolone, the dog had an increase in serum alkaline phosphatase activity (ALP; 1108 U/L; reference interval [RI] 20-150 U/L), mild fasting hyperglycemia (131 mg/dL; RI 60-110 mg/dL) and mild fasting hypercholesterolemia (311 mg/dL; RI 125-270 mg/dL). Six weeks after discontinuing methylprednisolone, ALP was 451 U/L and serum glucose concentration (unfasted) was 122 U/L; cholesterol was not measured. At the time of presentation, the dog was not receiving any medications, and biochemical data had not been obtained in the past year. Physical examination showed generalized dental calculus and gingivitis. No other physical examination abnormalities were noted, and the dog was reported to have a normal body condition (weight = 10.3 kg; BCS not documented). Serum biochemical abnormalities included hyperglycemia (401 mg/dL; RI 60-110 mg/dL) and an increase in ALP (1039 U/

Abbreviations: ALP, alkaline phosphatase; DM, diabetes mellitus; NPH, neutral protamine Hagedorn; RI, reference interval.

L). Complete blood count abnormalities were a mature neutrophilia (13.8 k/μL; RI 3-12 k/μL) and lymphopenia (0.66 k/μL; RI 1-4.8 k/μL). Urinalysis revealed a specific gravity of 1.004 and pH of 7.0 with glycosuria (1000 mg/dL) and proteinuria (30 mg/dL); no ketones were present, and urine sediment examination was unremarkable. The dog was diagnosed with diabetes mellitus (DM), in accordance with the Agreeing Language in Veterinary Endocrinology (ALIVE) consensus definition (www.esve.org/alive/search.aspx).[1] He was administered 6 U (~0.6 U/kg) of Neutral Protamine Hagedorn (NPH; Humulin-N, Eli Lilly and Company, Indianapolis IN) insulin SQ q12h in conjunction with a therapeutic weight management diet (Hill's Prescription Diet w/d Canine dry, Hill's Pet Nutrition, Inc, Topeka, KS).

On recheck with his primary veterinarian 5 days later, the dog's blood glucose concentration was 142 mg/dL on a point-of-care spot check 4 hours after insulin injection. Ongoing polydipsia was reported by the client, though not quantified. No changes were made to the insulin therapy. One week later, another point-of-care blood glucose spot check revealed hypoglycemia (55 mg/dL) 4 hours after insulin administration. No clinical signs were reported, but there was 0.45 kg weight loss from initial diagnosis. The insulin dose was decreased to 5 U (~0.5 U/kg) q12h. One week later, a spot check showed euglycemia (96 mg/dL). Two months later, the dog presented for a dental cleaning. Food and insulin were withheld that morning, and blood glucose concentration was 126 mg/dL on a point-of-care glucometer. The dog was maintained on 5 U (~0.5 U/kg) NPH insulin q12h. At a visit 1 month later, the owner reported that the dog's thirst and urination were normal.

Approximately 7 months after initial diagnosis of DM, the dog presented for urethral obstruction with a urethrolith and cystoliths noted on radiography. Insulin was administered several hours before presentation, and serum biochemistry revealed a glucose concentration of 138 mg/dL and an ALP of 280 U/L. A complete blood count revealed a lymphopenia (0.65 k/μL). A urinalysis showed a specific gravity of 1.025 and pH of 6.5 with hematuria, pyuria, and calcium oxalate dihydrate crystalluria; the urine was negative for glucose and ketones. A cystotomy was performed, with retropulsion of the urethrolith, for urolith removal (100% calcium oxalate composition). Postanesthetic blood glucose concentration was low (58 mg/dL). It was recommended that insulin be discontinued, but the owner continued therapy with no change in dose. The dog was prescribed carprofen (Rimadyl, Zoetis Services LLC, Parsippany NJ; 2.8 mg/kg q12h for 7 days) and cephalexin (generic; 28 mg/kg q12h for 14 days). When rechecked 3 days later, the dog's blood glucose concentration was 75 mg/dL on a glucometer 2.5 hours after insulin administration. The insulin dose was reduced to 4 U (~0.4 U/kg) q12h. There were no rechecks over the next 5 months, but the owner reported further dose reduction to 3 U (~0.3 U/kg) q12h during this time.

One year after diagnosis of DM, a blood glucose concentration was 95 mg/dL on a glucometer 4 hours after insulin administration. At that time, the dog had lost 1.7 kg, but records did not state if the weight loss was intentional or provide a BCS. Insulin therapy was discontinued. A blood glucose concentration 1 week later was 93 mg/dL. The dog continued to be fed the therapeutic weight management diet for the next 8 months and then presented for gross hematuria. Recurrence of cystolithiasis was diagnosed with radiography. A serum biochemistry panel revealed euglycemia (105 mg/dL), therefore meeting ALIVE criteria for remission of diabetes mellitus (www.esve.org/alive/search.aspx)[1]; ALP was not measured. A urinalysis showed a specific gravity of 1.014 and pH of 6.5 with hematuria and pyuria; the urine was negative for glucose and ketones. A second cystotomy was performed (urolith analysis declined by owner). The dog was prescribed amoxicillin/clavulanic acid (Clavamox, Zoetis Inc, Parsipanny, NJ; 14.5 mg/kg for 14 days) and a canned therapeutic urinary diet (Hill's Prescription Diet u/d Canine, Hill's Pet Nutrition, Inc, Topeka, KS). The owner discontinued this diet after an unspecified period and switched to an over-the-counter senior diet (Hill's Science Diet Senior, variety not specified, Hill's Pet Nutrition, Inc, Topeka, KS).

Nearly 2 years after initial diagnosis—11 months after insulin therapy was discontinued—the dog presented to his primary veterinarian for facial pruritus, panting, restlessness, and periuria. Laboratory analysis indicated hyperglycemia (486 mg/dL) and glycosuria (1000 mg/dL) without ketonuria; urine specific gravity was 1.033. He again met the ALIVE criteria for diabetes mellitus (www.esve.org/alive/search.aspx),[1] and NPH insulin was resumed at 5 U (~0.5 U/kg) q12h. The dog was also prescribed a 10-day tapering course of methylprednisolone (Medrol, Pfizer, Inc, New York NY; starting at 0.48 mg/kg q12h) for treatment of presumed atopy, and the diet was changed to a different over-the-counter food (Blue Buffalo Fish and Sweet Potato canned, Blue Buffalo Co, Ltd).

Over the next year, insulin doses were adjusted based on clinical signs and home glucometer readings (AlphaTRAK 2, Zoetis, Inc, Parsipanny, NJ), including multiple glucose curves (drawn every 2 hours for 12 hours) that documented persistent hyperglycemia with nadirs >200 mg/dL. A blood glucose concentration was also measured once at the University of Minnesota Veterinary Medical Center when the dog presented for a study on calcium oxalate urolithiasis and was increased at 148 mg/dL (RI = 81-125 mg/dL; i-STAT 1, Abbott Point of Care Inc, East Windsor, NJ). A urinalysis revealed a specific gravity >1.045 with no glucosuria but the presence of ketonuria (15 mg/dL) and proteinuria (300 mg/dL). The client received periodic phone consultations from her primary veterinarian on how to adjust therapy, and the dog's insulin dose was steadily increased to 17 U (~2.1 U/kg) q12h.

At 12 years of age (4 years after initial diagnosis of DM and 2 years after relapse), the dog had a cardiopulmonary arrest while under anesthesia for a dental cleaning. Preanesthetic bloodwork had been declined. A necropsy was not performed.

2 | DISCUSSION

This report documents spontaneous clinical DM remission in a male dog 1 year after initiation of insulin therapy. This case challenges the classic assumption that dogs invariably have a permanent, absolute insulin deficiency at the time of DM diagnosis,[2] and supports the presence of fluctuating contributors to beta cell function or peripheral

insulin resistance. Though an identifiable underlying condition to explain the dog's remission was lacking, he had historic (obesity and corticosteroid therapy), recent (feeding of table scraps, which might be high in fat), and ongoing (breed predisposition to hypercortisolism) risk factors for insulin resistance.[3-9] The dog's relapse 1 year after insulin discontinuation suggests that his pancreatic beta cell function did not fully recover, despite his apparent ability to maintain euglycemia during the intervening period.

Although diabetic remission is common in cats,[10-13] it is not expected in dogs due to differences in the pathophysiology of diabetes.[2,14] Though etiology is likely multifactorial, DM in dogs is often characterized by a partial or complete loss of beta cells resulting in an absolute insulin deficiency.[15] However, in humans with type 1 DM, which is also characterized by beta cell loss, a phase of remission can occur shortly after diagnosis, known as the "honeymoon period."[16] During this period, initiation of insulin therapy leads to a transient improvement in the function of remaining beta cell and restoration of euglycemia with reduced or no insulin therapy.[16] A major contributor to the honeymoon phase is theorized to be rapid achievement of glycemic control and resolution of glucotoxicity.[16-18] Glucotoxicity is the effect of persistent hyperglycemia on beta cells and leads to beta cell death and dysfunction with subsequent loss of endogenous insulin production. Glucotoxicity is documented in cats, humans, and dogs.[19-23] Humans with either type 1 or type 2 DM might be more likely to enter remission if there is limited beta cell loss at time of diagnosis and intensive insulin management is started early in the course of disease.[17,24] There is some evidence to suggest intensive insulin management also increases remission rates in cats.[11-13] The mean time to onset of the honeymoon phase in humans is 3-6 months after initiating insulin therapy and generally lasts <1 year.[16] In the dog reported here, the extent of beta cell damage at the time of diagnosis could not be determined, but insulin therapy was initiated soon (2 weeks) after the onset of owner-reported clinical signs.

Diet plays a role in glycemic control, though the role of diet in this dog's remission and relapse is unclear. Formulations lower in carbohydrates and fats and higher in insoluble fibers delay gastric emptying, slow carbohydrate absorption, reduce postprandial hyperglycemia, improve tissue sensitivity to insulin, and mitigate gastrointestinal endocrine response in dogs.[25-28] This dog's diet was transitioned from an over-the-counter maintenance diet (unreported type) to a therapeutic weight management diet upon initial diagnosis with DM. The therapeutic weight management diet fed is high in insoluble fiber (7.3 g/100 kcal) and might improve glycemic control in diabetic dogs over a diet with a similar nutrient profile except for lower insoluble fiber (4.6 g/100 kcal).[27] However, no difference in glycemic control is apparent in diabetic dogs fed diets differing in insoluble fiber (2.6-4.6 g/100 kcal), carbohydrate, and fat content.[29] It is difficult to confirm a contribution of diet to this dog's diabetic remission. This diet was continued for another 8 months after discontinuation of exogenous insulin therapy, before the dog was transitioned to a urinary diet, then to an over-the-counter senior diet before the diabetic relapse occurred. A limitation of interpreting the role of diet nutrient profiles in this dog's diabetic remission or relapse is that the quantity of the diets fed was inconsistently reported, and it was not possible to determine if caloric intake differed between diets.

Body condition also affects glycemic control. The patient was reported to be obese before his DM diagnosis and had lost >15% of his body weight at the time of his remission. Cellular sensitivity to insulin is diminished with obesity, leading to increased systemic insulin requirements.[3,30,31] Insulin sensitivity improves with weight loss and diet restriction in dogs.[31-33] Weight loss in this patient likely increased insulin sensitivity and thus glycemic control, contributing to diabetic remission. However, while improving insulin sensitivity might reduce the burden on remaining beta cells, it cannot restore them.

Glucocorticoids are another potential source of insulin resistance.[8] Exogenous glucocorticoid therapy is associated with DM risk in dogs,[34] and there is a report of a dog with DM remission after cessation of glucocorticoid therapy.[4] For the current case, the timing of glucocorticoid therapy did not coincide with initial DM diagnosis or relapse and was thus unlikely part of the pathogenesis. However, an excess of endogenous glucocorticoids (ie, hypercortisolism) could not be ruled out, as the dog was not screened for this disease.

Another important etiology of DM is disease of the exocrine pancreas. Histopathologic evidence of acute pancreatitis has been reported in up to a third of diabetic dogs.[35,36] The dog in this study had eaten table foods in the 2 weeks before onset of clinical signs and presentation to his veterinarian, which is a risk factor for pancreatitis in dogs.[37] While it is possible he had an episode of subclinical pancreatitis, significant dysregulation of glucose homeostasis and subsequent glucotoxicity are considered unlikely without concurrent acute clinical signs. Miniature Schnauzers are predisposed to hypertriglyceridemia, which is associated with insulin resistance and pancreatitis.[38-40] Mild fasting hypercholesterolemia was noted the year before the dog's diagnosis, but he did not have a triglyceride concentration measured at any time point.

Finally, DM remission occurs in female dogs with progesterone-controlled growth hormone overproduction DM (PGHDM).[41,42] However, this dog was a neutered male and did not have any known exogenous exposure to progesterone.

A limitation of this report is that neither glucose curves nor measurements of glycated protein concentrations, such as fructosamine or HbA_{1c}, were assessed during the initial period of DM. These diagnostics would have helped corroborate the state of chronic hyperglycemia at diagnosis and determine the extent and timing of glycemic control. Nevertheless, the dog met consensus criteria for the diagnosis of DM, both at first diagnosis and at the time of his relapse. The ALIVE definition for DM in dogs is a random blood glucose concentration ≥ 200 mg/dL with classic clinical signs of hyperglycemia (polydipsia in this case) without other plausible causes (www.esve.org/alive/search.aspx).[1] The dog also had marked glucosuria, supporting a hyperglycemic state. He additionally met the ALIVE criteria for diabetic remission, which is defined as absence of clinical signs and no evidence of DM for >4 weeks after cessation of exogenous insulin therapy. His clinical signs resolved, and a normal serum glucose concentration was documented both 1 week and 8 months after discontinuation of treatment. However, given the low frequency of these

glucose checks, we cannot rule out the possibility of ongoing, intermittent, subclinical hyperglycemia. Additionally, although the dog had received insulin therapy for 1 year, it is possible that he ceased needing insulin sooner than was recognized.

Another limitation is the lack of advanced abdominal imaging (ie, abdominal ultrasonography or computerized tomography) or postmortem examination. These diagnostics might have contributed to understanding the etiology of his DM and identified evidence of relevant comorbidities, such as pancreatitis or hypercortisolism. The dog's urine specific gravity at initial diagnosis was significantly more dilute (1.004) than what is typical for dogs with polyuria caused by DM alone,[43] suggesting that another disease process might have contributed to the polyuria.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Chen Gilor https://orcid.org/0000-0003-0393-4135
Stijn J. M. Niessen https://orcid.org/0009-0000-9667-6678
Eva Furrow https://orcid.org/0000-0002-7339-2354

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