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Source: Journal of Avian Medicine and Surgery, 38(1) : 21-33

Published By: Association of Avian Veterinarians

URL: https://doi.org/10.1647/AVIANMS-D-22-00057

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Journal of Avian Medicine and Surgery 38(1):21–33, 2024
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Original Study

Avian Diabetes Mellitus: A Review

Yannick Van de Weyer and Stamatios Alan Tahas

Abstract: Diabetes mellitus (DM) is an uncommon, poorly documented metabolic disorder of birds. Extrapolating knowledge from DM in mammals is challenging because of marked differences in avian physiology and metabolism. A literature review from December 1991 to January 2022 identified 14 publications covering 16 diabetic birds, 63% (10/16) of which belonged to the order Psittaciformes with *Ara* as the predominant genus. No sex predilection was noted, but males generally presented at a younger age. Commonly reported clinical signs included polyuria 94% (15/16), polydipsia 88% (14/16), weight loss 75% (12/16), lethargy 63% (10/16), and polyphagia 38% (6/16). Diagnosis of DM was based on the presence of clinical signs and persistent hyperglycemia 100% (16/16), often with glucosuria 93% (13/14), response to insulin therapy 80% (8/10), and pancreatic pathology 90% (9/10). Specific treatment for DM was initiated in 14 patients, but blood glucose regulation for 6 months or longer was only achieved in 6 birds. Five of the regulated birds were managed with injectable long-acting insulin and 1 with oral glipizide combined with dietary modifications. However, glipizide yielded poor results in other cases, likely attributable to a lack of functional beta cells. Three diabetic birds progressed to remission. Treatment proved unsuccessful for 7 patients with a mean survival time of 36 days from diagnosis. One patient was lost to follow-up, and 2 were euthanized immediately following diagnosis. Histological examination of the pancreas frequently (90%, 9/10) revealed abnormalities including atrophy, fibrosis, and vacuolization of the endocrine islets with or without lymphoplasmacytic pancreatitis. Comorbidities, including hemosiderosis and infection, were common. This review suggests that birds diagnosed with DM are primarily affected by a type I diabetes as observed in dogs and humans. In contrast to mammalian species, avian DM is often associated with underlying disease and a complete clinical workup is essential to diagnose and address secondary disease conditions prior to initiating long-term insulin therapy.

Key words: diabetes mellitus, polyuria, polydipsia, glucose, glucagon, hyperglycemia, avian, psittacine

INTRODUCTION

In humans and other mammals, diabetes mellitus (DM) is defined as a persistent hyperglycemic state caused by a relative or absolute insulin deficiency.[1,2] Avian glucose homeostasis, however, is not regulated by insulin alone. Contrary to its effect in mammals, insulin appears to have a weaker hypoglycemic effect in studied avian species, whereas glucagon has a potent hyperglycemic effect.[3] Therefore, it has been suggested by previous authors that the pathophysiology of diabetes in birds is more dependent on the glucagon-to-insulin ratio rather than an absolute lack of or low sensitivity to insulin as in mammals.[4,5] The following definition for avian DM has been proposed based on current knowledge of the disease: "A pathological or experimental dysfunction of the islets of Langerhans as a whole."[4]

Insulin and glucagon, together with somatostatin, are produced in the endocrine islets of the pancreas and are the dominant hormones responsible for glucose homeostasis.[3,6,7] Avian insulin has anabolic effects that support glucose uptake from the blood into cells, whereas glucagon is a catabolic hormone that promotes glycogenolysis and gluconeogenesis, thereby increasing the available glucose in the circulation.[7] In practical terms, insulin plays an important role in the postprandial bird, whereas glucagon is crucial to maintain energy provision in the fasted bird.[8] Additionally, somatostatin acts as a regulator

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by inhibiting both insulin and glucagon secretion while also modifying the glucagon/insulin ratio.[4,5,7] Nonetheless, the exact interaction between these hormones and other factors in the development of a chronic hyperglycemic state have not been elucidated in birds.

Avian species naturally have much higher blood glucose concentrations compared with mammals.[7,9] It is not entirely clear how birds are able to cope with persistent glucose concentrations that would induce oxidative stress in other taxa, but mechanisms such as increased glycation resistance of proteins and the antioxidative properties of uric acid have been inferred.[7,9] The relatively rare occurrence of avian DM, together with obvious differences in glucose homeostasis, metabolic rates, and dietary preferences, make it difficult for clinicians to extrapolate information from the literature that is primarily focused on mammals. The purpose of this retrospective review was to compare published case reports and identify patterns in the signalment, diagnosis, treatment, prognosis, and pathology of DM in birds.

MATERIALS AND METHODS

A systematic literature review was conducted to identify case reports of birds diagnosed with DM published in English between December 31, 1991, and January 1, 2022. The search terms used were "avian," "diabetes mellitus," "polyuria," "polydipsia," "hyperglycemia," "hyperglycaemia," and "case report," and they were entered into the following databases: Google scholar, PubMed, *The Journal of Avian Medicine and Surgery*, ScienceDirect, and *The Journal of Avian Pathology*. Additionally, conference proceedings from the Association of Avian Veterinarians were manually surveyed. For case reports stating reference intervals of relevant hematological and biochemical parameters but without disclosing their source, values were cross-referenced when species-specific data was available.[10] Bird ages were recorded and allocated into 3 categories: juvenile, subadult, and adult based on species-specific reference intervals for sexual maturity.[11,12] A Fisher exact test was used (R-project 4.1.0 Software, Boston, MA, USA) to determine if there were associations between these age groups and sex. A $P < 0.05$ was used to determine statistical significance. In this study, hyperglycemia was defined as serum or plasma glucose concentrations >800 mg/dL,[6] whereas a successful outcome was considered as survival ≥6 months from the initial diagnosis with amelioration of clinical signs.

RESULTS

The search for published avian DM case reports yielded 8 peer-reviewed case reports and 6 conference proceedings, representing 16 birds.[13–26] The majority (63%, 10/16; 95% confidence interval: 39–87) of DM cases were recorded in the order of Psittaciformes (5 macaws [2 blue and gold macaws, *Ara ararauna*; 1 chestnut-fronted macaw, *Ara severus*; and 1 military macaw, *Ara militaris*], 2 cockatiels [*Nymphicus hollandicus*], 1 eclectus parrot [*Eclectus roratus*], 1 nanday conure [*Nandayus nenday*], and 1 grey parrot [*Psittacus erithacus*]), followed by 2 in Piciformes (keel-billed toucan, *Ramphastos sulfuratus*; toco toucan, *Ramphastos toco*) and 1 case each in Accipitriformes (red-tailed hawk [*Buteo jamaicensis*]), Passeriformes (Bali mynah [*Leucopsar rothschildi*]), Anseriformes (domestic goose [*Anser anser domesticus*]), and Sphenisciformes (emperor penguin [*Aptenodytes forsteri*]) (Table 1). The majority (75%, 12/16) of the birds were presumably privately owned, 19% (3/16) belonged to a zoological collection, and 1 bird (6%) was a wild animal in rehabilitation. There were 7 females (44%, 7/16) and 9 males (56%, 9/16). All diabetic animals in this review were subadults or adults. No association between age and sex was found ($P = 0.09$) albeit this comparison approached significance. Males appeared to develop DM at a younger age than females because 44% (4/9) of males were subadults and all (100%, 7/7) female birds were adults (>7 years old) at the time of diagnosis.

In some cases, diagnostic assessments were too inconsistent to provide complete results, and therefore, results are provided in percentages as well as number of cases in which each laboratory variable was evaluated. Comorbidities were recorded in 63% (10/16) of cases and included hemosiderosis (31%, 5/16), fungal or viral infection (19%, 3/16), glomerulopathy (13%, 2/16), obesity (6%, 1/16), hepatic lipidosis (6% 1/16), and zinc toxicosis (6%, 1/16); infection was also suspected in 19% (3/16) of the birds. The most commonly reported clinical signs included polyuria (PU) (94%, 15/16) and polydipsia (PD) (88%, 14/16), followed by weight loss (75%, 12/16), lethargy (63%, 10/16), and polyphagia (38%, 6/16) (Table 1). Two birds (13%, 2/16) were so debilitated that they were unable to fly or perch, and another 2 patients (13%, 2/16) suffered from melena. Clinical signs were first observed, on average, 59 days (median 14, range 1–366) before consultation with a veterinarian. An initial diagnosis of DM was made based on persistent hyperglycemia (100%, 16/16) combined with a history of PU–PD (88%, 14/16) and the presence of glucosuria (93%, 13/14) and/or

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Table 1. Clinical signs reported in avian patients diagnosed with diabetes mellitus in the scientific literature from December 31, 1991, to January 1, 2022.

Common name (species)	Polyuria	Polydipsia	Polyphagia	Weight loss	Lethargy	Other
Domestic goose (*Anser anser domesticus*)[25]	Yes	Yes	Yes	Yes	Yes	Ataxia, Head tremors, Emaciation
Emperor penguin (*Aptenodytes forsteri*)[18]	Yes	na	na	Yes	Yes	Dehydration
Blue and gold macaw (*Ara ararauna*)[17]	Yes	Yes	No	Yes	na	Feather plucking, Ovarian activity
Blue and gold macaw (*Ara ararauna*)[23]	Yes	Yes	na	Yes	na	
Military macaw (*Ara militaris*)[21]	Yes	Yes	Yes	Yes	Yes	Reduced vocalization
Chestnut-fronted macaw (*Ara severus*)[21]	Yes	Yes	na	Yes	Yes	
Chestnut-fronted macaw (*Ara severus*)[19]	Yes	Yes	na	Yes	Yes	Melena, Dehydration
Red-tailed hawk (*Buteo jamaicensis*)[15]	Yes	Yes	Yes	na	Yes	Paresis, Inability to fly
Eclectus parrot (*Eclectus roratus*)[26]	Yes	Yes	na	Yes	Yes	Recent ovipositioning
Bali myna (*Leucopsar rothschildi*)[24]	na	na	Yes	Yes	Yes	Cataract, Underweight
Nanday conure (*Nandayus nenday*)[22]	Yes	Yes	No	na	Yes	Melena, Not perching
Cockatiel (*Nymphicus hollandicus*)[18]	Yes	Yes	Yes	na	Yes	Open-mouthed breathing, Overweight
Cockatiel (*Nymphicus hollandicus*)[20]	Yes	Yes	na	Yes	na	
Grey parrot (*Psittacus erithacus*)[14]	Yes	Yes	No	Yes	No	Emaciation
Keel-billed toucan (*Ramphastos sulfuratus*)[16]	Yes	Yes	Yes	Yes	na	Diarrhea
Toco toucan (*Ramphastos toco*)[13]	Yes	Yes	na	na	na	

Abbreviation: na, not available or assessed.

ketonuria (60%, 6/10) when urinalysis was performed (Table 2). For cases in which insulin treatment or histology were pursued, initial response to insulin therapy (80%, 8/10) and pancreatic pathology (90%, 9/10) were also used to confirm diagnosis. Hematologic and biochemistry testing revealed that at least 54% (7/13) of birds had a low packed cell volume, and 33% (3/9) of birds had elevated uric acid concentrations, respectively. A majority of birds with blood test results also had low serum or plasma insulin concentrations (86%, 6/7) and ketonemia (100%, 2/2) (Table 3).

When stated in the case description, initial treatment included supportive care (44%, 7/16), including fluid and/or antibiotic therapy, and specific treatment for DM was initiated in 88% (14/16) of the cases (Table 4). Forty-three percent (6/14) of these cases had a successful outcome, meaning survival for at least 6 months from the diagnosis of DM and start of treatment. Euglycemia and abatement of clinical signs were achieved with glipizide (0.05 mg PO q12h; Glucotrol, Pfizer Inc., New York, NY, USA) in 1 cockatiel and with protamine zinc insulin (PZI) (various dosages and formulations as detailed in Table 4; Neutral Protamine Hagedorn insulin; Iletin, Eli Lilly & Co., Indianapolis, IN, USA) or glargine insulin (0.25 IU IM q12–24h; Lantus, Sanofi-Aventis, Bridgewater, NJ, USA) in the other 5 birds. These treatments were combined with dietary adjustments, such as transition from a seed- to a pellet- and vegetable-based diet (Table 4). Two macaws survived for >2 years and showed signs of remission with a gradual PZI dose reduction.[21] Regulation without the need for insulin therapy was achieved for a toco toucan 4 months after transitioning from a diet of dog food and fruits to a low-iron pellet.[13] Treatment proved unsuccessful for 7 patients with a mean survival time of

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Table 2. Biochemistry and hematologic findings of birds diagnosed with diabetes mellitus from published case reports from 1992 to 2022.[a]

Common name (species)	Glucose, mg/dL	Insulin, μU/mL	PCV (%)	Ketonemia, μmol/L	Glucosuria, mg/dL	Ketonuria, mg/dL
Domestic goose (*Anser anser domesticus*)[25]	**838**	na	**30**	na	na	na
Emperor penguin (*Aptenodytes forsteri*)[18]	**614–908**	**1.9**	WRR	na	**Yes**	na
Blue and gold macaw (*Ara ararauna*)[17]	**905–1067**	3.6–10.3	37–41	na	**Yes**	No
Blue and gold macaw (*Ara ararauna*)[23]	**>1000**	**Low**	**Low**	na	**Yes**	na
Military macaw (*Ara militaris*)[21]	**1008**	na	**28**	**11 126**	**>500**	**Yes**
Chestnut-fronted macaw (*Ara severus*)[21]	**1015**	na	WRR	**7136**	**>500**	**Yes**
Chestnut-fronted macaw (*Ara severus*)[19]	**902–987**	na	**17**	na	**Yes**	**Yes**
Red-tailed hawk (*Buteo jamaicensis*)[15]	**977**	na	na	na	**749**	**15**
Eclectus parrot (*Eclectus roratus*)[26]	**1161–1500**	na	na	na	na	na
Bali myna (*Leucopsar rothschildi*)[24]	**898–910**	**2.9**	**28**	na	**>2000**	No
Nanday conure (*Nandayus nenday*)[22]	**920–1081**	**<3**	**24–38**	na	**>500**	**Yes**
Cockatiel (*Nymphicus hollandicus*)[18]	**1500–1800**	na	WRR	na	**Yes**	No
Cockatiel (*Nymphicus hollandicus*)[20]	**1872**	na	WRR	na	**>500**	No
Grey parrot (*Psittacus erithacus*)[14]	**885**	**<3**	45.4	na	**458**	**46**
Keel-billed toucan (*Ramphastos sulfuratus*)[16]	**1107–1252**	na	na	na	1	na
Toco toucan (*Ramphastos toco*)[13]	**1587**	2.0	35–40	na	**Yes**	na

Abbreviations: PCV, packed cell volume; na, not available or assessed; WRR, within published reference interval.

[a] 'Glucose' is the value or range of blood glucose concentrations before initiating treatment and where possible, after fasting. Ketonemia values are based on beta-hydroxybutyrate measurement, whereas ketonuria is based on acetic acid values. Abnormalities, according to the author(s) of the respective peer- reviewed publication, are denoted in bold. One exception to this is PCV for the Toco toucan,[13] which was considered WRR by the author, but not according to a more recent reference ranges for this species.[10]

36 days (range 4–120) following the DM diagnosis and treatment. Administration of glipizide (0.5–1.25 mg/kg PO q12–24h) or somatostatin (3–10 μg/kg SC q12h) yielded poor results in 86% (6/7) and 100% (2/2) of the cases, respectively. One penguin responded favorably to initial treatment but was lost to follow up.[18] The remaining 2 birds were euthanatized immediately following diagnosis of DM.[14,15]

Histologically, pancreatic pathologies were identified in 90% (9/10) of birds that had a postmortem examination (Table 5). The most common findings were degenerative changes of the endocrine islets, including atrophy (60%, 6/10), fibrosis (30%, 3/10), and vacuolization (30%, 3/10); moderate-to-severe lymphoplasmacytic pancreatitis (50%, 5/10); and hyperplasia of the exocrine tissue (30%, 3/10).

DISCUSSION

Although DM appears to be an uncommon disease condition in avian species, for this study, it was most often diagnosed in psittacine birds, which is consistent with the findings of previous authors.[6,27] Former reports on avian DM not included in this study because of the source (eg, textbook) or because they were conducted prior to the defined study period, predominantly involved budgerigars (*Melopsittacus undulatus*) and cockatiels,[27,28] whereas most cases in this review belonged to *Ara* species and *Ramphastos* species. Although we did have 2 cases attributed to cockatiels in our findings, the difference in reporting for the other species was likely attributed to the novelty of DM in these species. It is important to identify new species reports of DM to ensure this disease is included in appropriate differential diagnoses lists for clinicians and to improve our understanding of DM in captive avian species.

A clear sex or age predisposition for DM in birds has not been previously established. Although male and female avian patients with DM are equally represented in the literature, in this review, male birds presented at a younger age than females, and several of these males were subadults at the time of diagnosis. Studies in mammals have found that estradiol can increase the survival time of pancreatic islet cells challenged with metabolic or proinflammatory injuries, suggesting a transient protective effect against DM type I in subadult females.[29] However, no such studies are currently available in birds and this finding may be incidental because of the small sample size.

The clinical signs of avian DM reported in this study are comparable to those in mammals, and DM should be considered a differential diagnosis in birds suffering from PU–PD. Other differentials for PU–PD include stress, renal disease, adrenal disease, liver disease, hyperthyroidism, paramyxovirosis, intracranial neoplasia, diabetes

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Table 3. Species-specific ranges for insulin, glucagon, and fructosamine in multiple bird species as reported in the literature.[a]

Common name (Species)	Sample size (n)	Insulin, μIU/mL	Glucagon, pg/mL	Fructosamine, μmol/L	Reference
Amazon parrot (*Amazona* sp.)	10	5.9–12.3*			58
Orange-winged (*Amazona amazonica*), blue-fronted (*Amazona aestiva*), yellow-crowned (*Amazona ochrocephala*), and yellow-headed Amazon parrots (*Amazona oratix*)	24			60.0–154 (122)	43
Domestic goose (*Anser anser domesticus*)	10–12	15.5 ± 1.8	1230 ± 60		4
Blue and gold (*Ara ararauna*), scarlet (*Ara macao*), and hyacinth macaws (*Anodorhynchus hyacinthinus*)	19	4.2–12.4~	299–1801		17
Chicken (*Gallus gallus domesticus*)	40	30.0–44.4 (fed) 13.7–24.8 (fasted)	152–450		2, 45
Bald eagle (*Haliaeetus leucocephalus*)	13	1.4–5.4	229–1239		44
Budgerigar (*Melopsittacus undulatus*)	61			46.6–134.8* (90.7 ± 22.1)	59
Budgerigar (*Melopsittacus undulatus*)	6			74–142 (82)	43
Cockatiel (*Nymphicus hollandicus*)	2–4	5.8–8.6~	780–964		60
Cockatiel (*Nymphicus hollandicus*)	11			80–172 (108)	43
Psittacine birds (unspecified)	19			113–238*	21
Keel-billed toucan (*Ramphastos sulfuratus*)	2		758–1327~		16
Toco toucan (*Ramphastos toco*)	2	7.0–8.2*	90.7–109.5*		13

[a] All values were measured in plasma unless stated otherwise by means of "~" (serum) or "*" (unknown if plasma or serum). Based on variation in methodology and numerous factors between studies, consultation of the original publication for more information regarding the applied technique and study population is highly recommended prior to pursuing diagnosis or therapy based on these values.

insipidus, psychogenic polydipsia, lymphoplasmacytic ganglioneuritis, and iatrogenic and dietary factors.[30–33] In theory, a water-deprivation test and blood arginine vasotocin concentration can be used to differentiate between DM and diabetes insipidus;[34–36] however, diabetes insipidus is rare, and the use of these tests in practice can be challenging because of the cost of the test and limitations in obtaining true urine from the droppings or directly from the ureters.

In order to diagnose DM, multiple blood glucose measurements are required to distinguish between DM and transient stress–induced hyperglycemia, which is common in birds.[37] Blood should be analyzed in a timely manner by an accredited laboratory and, ideally, include a full complete blood count and plasma biochemistry panel. Persistent serum or plasma glucose concentrations >800 mg/dL are considered diagnostic in companion birds.[6] Although the use of a glucometer is possible, it is not currently recommended because commercial glucometers are not calibrated for birds and results can be unreliable.[38,39]

A urinalysis provides a worthy secondary diagnostic test to blood glucose measurements for diagnosing DM, and a urine dipstick can be used to quickly measure urine for glucosuria and ketonuria. A urinalysis can be particularly useful in small birds (eg, budgerigars) for which sufficient blood volume is challenging to obtain. The urine of healthy birds should not contain ketones but may contain trace amounts of glucose.[37] Nonetheless, renal glucose thresholds can vary between species, and with average values of approximately 600 mg/dL in birds, glucosuria may also be observed with stress-related hyperglycemia.[40] Therefore, single readings should be interpreted with caution. The use of ketonuria in the diagnosis of DM in birds is controversial. When tested, 60% (6/10) of cases were positive for ketones on a dipstick, and half had concurrent liver pathology;[19,21] histopathology was not available for most others. Therefore, it is possible that ketonuria in these cases was associated with liver disease rather than DM. It would be prudent to suggest that ketonuria is only suggestive of DM in the presence of persistent hyperglycemia and glucosuria and in the absence of concurrent hepatic disease or a fasted state given the versatile process of ketogenesis in birds.[41] Furthermore, retroperistalsis of ureteral urine into the rectum and breakdown of glucose and ketones by colonic

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Table 4. Treatments and outcomes for birds diagnosed with diabetes mellitus in the scientific literature from December 31, 1991, to January 1, 2022.

Common name (species)	Supportive care and dietary changes	Antidiabetic/hormonal treatment	Outcome
Domestic goose (*Anser anser domesticus*)	Fluid therapy and gavage feeding	Glipizide (1 mg/kg PO q12h)[a]	Died <48 hours after presentation[25]
Emperor penguin (*Aptenodytes forsteri*)	Fluid therapy, antibiotics, and itraconazole	Glipizide (5 mg PO q12h)[b] was started but caused poor regulation by itself. Neutral Protamine Hagedorn Insulin (4–12 IU SC/IM q12h)[c] reduced serum glucose concentrations and clinical signs	Regulated, but lost to follow-up after 13 days[18]
Blue and gold macaw (*Ara ararauna*)	Dietary change from seed-based diet to pellets and vegetables	Somatostatin (3–10 μg/kg SC q12h)[d] did not lead to regulation. Neutral Protamine Hagedorn Insulin (0.1–0.2 IU/kg SC q12h)[e] appeared more successful	Regulated for >7 months with resolution of clinical signs[17]
Blue and gold macaw (*Ara ararauna*)	na	Insulin therapy (unspecified brand and dose)	Died after 4 days[23]
Military macaw (*Ara militaris*)	Phlebotomies and transition to a low-iron pelleted diet	Successful use of bovine protamine zinc insulin (0.3–0.5 IU/kg IM q12h)[f]. Gradual dose reduction was possible after treatment (0.1–0.15 IU/kg IM q 12h)	Regulated for >29 months[21]
Chestnut-fronted macaw (*Ara severus*)	Deferoxamine mesylate and transition to a low-iron pelleted diet	Glipizide (1.25 mg/kg PO q24h)[b] did not regulate. Managed for 22 months with porcine protamine zinc insulin (0.50-0.67 IU/kg IM q12h)[g] and gradual dose reduction was possible after treatment. Bovine protamine zinc insulin (Unknown dose)[f] was initiated after lack of response to porcine PZI	Regulated for 24 months, then died during anesthesia[21]
Chestnut-fronted macaw (*Ara severus*)	Fluid therapy, gavage feeding, metoclopramide, sucralfate, antibiotics, and blood transfusion	Intermediate-acting human Neutral Protamine Hagedorn Insulin (1 IU q12h)[m] was initiated	Died 5 days after diagnosis[19]
Red-tailed hawk (*Buteo jamaicensis*)	"Supportive care"	Specific hormonal treatment was not initiated because this was a wild animal	Euthanized after diagnosis[15]
Eclectus parrot (*Eclectus roratus*)	na	Administration of Glipizide and Metformin did not achieve regulation. Human long-acting Glargine Insulin (0.25 IU IM q12–24h)[h] did	Regulated for >12 months[26] but hypoglycemic episodes reported

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Table 4. Continued.

Common name (species)	Supportive care and dietary changes	Antidiabetic/hormonal treatment	Outcome
Bali myna (*Leucopsar rothschildi*)	Fruit removed from diet. Sodium sulfachlorpyridazine	Glipizide (0.5 mg/kg PO q12h)[i] did not achieve regulation. Human long-acting protamine zinc insulin (0.2–8 IU/kg q12h)[j] achieved partial regulation. Transition to human protamine zinc insulin (5.3 IU/kg q12h)[k] achieved regulation for about 50 days.	Euthanized after 4 months because of hypoglycemic episodes and lack of reliable treatment[24]
Nanday conure (*Nandayus nenday*)	Fluid therapy and antibiotics. Transition from a diet of seeds, fruits, and fruit juices to pellets and vegetables	Rapid-acting human insulin (0.1 IU/kg IM q unspecified; Humulin-R) resolved clinical signs, but euglycemia was not achieved. Intermediate-acting porcine protamine zinc insulin (0.4 IU/kg IM q12h)[g] resulted in euglycemia for <4 hours. Long-acting human insulin (0.25-0.35 IU/kg IM q12)[l] achieved regulation for 3 weeks.	Presented one month after diagnosis with acute dyspnea, depression, and died[22]
Cockatiel (*Nymphicus hollandicus*)	Fluid therapy, antibiotics, medroxyprogesterone, and lactulose. Transition to a pelleted diet	Successfully regulated with Glipizide (0.05 mg PO q12h).[b] Treatment was discontinued after 1 year.	Regulated for >1 year[18]
Cockatiel (*Nymphicus hollandicus*)	na	Glipizide (1 mg/kg PO q24h)[b] did not achieve regulation.	Euthanized 9 days after diagnosis[20]
Grey parrot (*Psittacus erithacus*)	Antibiotics	No treatment for DM initiated.	Euthanized on diagnosis[14]
Keel-billed toucan (*Rhamphastos sulfuratus*)	na	Somatostatin (3 μg/kg SC q12h)[d] was initiated and clinical signs improved, but this did not result in euglycemia.	Initial improvement but died after 4 months[16]
Toco toucan (*Ramphastos toco*)	Transition from dog food and fruits to a pelleted diet. Probiotics	Oral aloe vera–derived polysaccharides (PO q2-3d; Acemannan)[m] without regulation. Protamine zinc insulin (0.25-2 IU IM q2-3d)[m] was initiated and discontinued after 4 months.	Regulated for >9 months[13], possibly due to dietary changes

Abbreviation: na, not available.

[a] Sandostatin, Sandoz Inc., Princeton, NJ, USA.
[b] Glucotrol, Pfizer Inc., New York, NY, USA.
[c] Humulin N, Eli Lilly & Co., Indianapolis, IN, USA.
[d] Sandostatin, Sandoz Pharmaceuticals Corp., East Hanover, NJ, USA.
[e] Iletin, Eli Lilly & co., Indianapolis, IN, USA.
[f] PZI, Summit Veterinary Pharmacy, Aurora, Ontario, Canada.
[g] Caninsulin, Intervet, Whitby, Ontario, Canada.
[h] Lantus, Sanofi-aventis, Bridgewater, NJ, USA.
[i] Glipizide, Accord Healthcare Inc, Durham, NC, USA.
[j] PZI, Taylors Pharmacy, Winter Park, FL, USA.
[k] ProZinc, Boehringer Ingelheim, St Joseph, MO, USA.
[l] Humulin-U, Eli Lilly Canada, Toronto, ON, Canada.
[m] Manufacturer information not specified.

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Table 5. Pancreas histopathology and comorbidities for birds diagnosed with diabetes mellitus from published case reports from December 31, 1991, to January 1, 2022.

Species	Pancreatic pathology	Comorbidity	Reference
Domestic goose (*Anser anser domesticus*)	Moderate lymphoplasmacytic pancreatitis with severe atrophy, fibrosis, and islet vacuolization	Zinc toxicosis	25
Emperor penguin (*Aptenodytes forsteri*)	Not assessed	Infection (fungal) suspected	18
Blue and gold macaw (*Ara ararauna*)	Not assessed	Hepatic lipidosis Oral candidiasis	17
Blue and gold macaw (*Ara ararauna*)	Severe hyperplasia and hypertrophy of islet cells with foamy cytoplasm and vesicular nuclei	Hemosiderosis (liver) Glomerulosclerosis	23
Military macaw (*Ara militaris*)	Atrophy of endocrine islets with fibrosis. Mild hemosiderosis	Iron storage disease (liver, marked)	21
Chestnut-fronted macaw (*Ara severus*)	Atrophy of endocrine islets with hypertrophy of exocrine part. Mild hemosiderosis	Iron storage disease (liver, marked)	21
Chestnut-fronted macaw (*Ara severus*)	Lymphocytic pancreatitis with marked islet cell vacuolization and exocrine hyperplasia	Zygomycosis Hemosiderosis (liver)	19
Red-tailed hawk (*Buteo jamaicensis*)	Severe vacuolization of islet (beta) cells with normal exocrine tissue	Infection suspected Hallux fracture	15
Eclectus parrot (*Eclectus roratus*)	Not assessed	None found	26
Bali myna (*Leucopsar rothschildi*)	Mostly normal. Few cysts, mild multifocal nodular acinar cell hypoplasia, and focal mild islet cell hyperplasia	Glomerulopathy Cataracts Hemosiderosis (liver)	24
Nanday conure (*Nandayus nenday*)	Moderate lympho-plasmocytic pancreatitis with atrophy of endocrine islets and normal exocrine tissue	Secondary infection suspected	22
Cockatiel (*Nymphicus hollandicus*)	Not assessed	Obesity	18
Cockatiel (*Nymphicus hollandicus*)	Severe lymphoplasmacytic pancreatitis with atrophy, fibrosis, and inclusion bodies	Psittacid herpesvirus 1	20
Grey parrot (*Psittacus erithacus*)	Severe lymphoplasmacytic pancreatitis with atrophy	Infection suspected	14
Keel-billed toucan (*Ramphastos sulfuratus*)	Not assessed	None found	16
Toco toucan (*Ramphastos toco*)	Not assessed	None found	13

and cecal microbiota has been proposed as a possibility in avian species.[42] Conversely, fecal contamination of urine can cause trace readings or false positive results.[37] To avoid this, the clear liquid part of the urine should be aspirated with a pipette when possible. In theory, cloacoscopy and aspiration of urine from the urodeum could be possible but is not reported in a clinical setting. Whereas urine analysis is a useful, ancillary tool that can be used to help diagnose DM, it comes with limitations, and results should always be interpreted based on additional patient-specific diagnostic information and clinical disease signs of DM.

Long-term diagnostic markers for DM, such as fructosamine and glycosylated hemoglobin, are currently less useful tools in birds because reliable reference intervals are lacking for most avian species, birds produce relatively few glycosylated products, and these products have short half-lives.[9,43] Moreover, poor consensus regarding the use of plasma versus serum for fructosamine analysis further complicates interpretation. Nevertheless, it has been suggested that fructosamine

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concentrations >300 μmol/L may indicate DM in psittacine birds (Table 3).[21,22]

Low insulin concentrations are defined as values <3 μU/mL for psittacine birds.[17] In the literature, multiple birds suffering from DM were found to have insulin concentrations <3 μU/mL;[13,14,18,22,24] however, similarly low values are also reported in healthy conspecifics.[13,18,23] In fact, 1 clinically healthy emperor penguin had a lower serum insulin concentration (1.04 μU/mL) than a diabetic conspecific (1.87 μU/mL).[18] Conversely, glucagon was elevated in 2 diabetic toucans (toco and keel-billed) when compared with healthy conspecifics.[13,16] This further supports that an excess of glucagon as opposed to a lack of insulin could be the pathophysiological mechanism for at least some cases of DM in avian species; this has been previously suggested for granivorous and frugivorous birds.[6] Although it has been suggested that carnivorous birds are more dependent on insulin, these conclusions were made from a limited number of cases.[15] Despite being insufficiently documented, interspecific differences in glucose homeostasis are to be expected given the large variety of avian species and the diversity of their respective diets. Furthermore, considerable fluctuations in both insulin and glucagon concentrations can occur between individuals of the same species depending on the individual bird's needs.[44,45] For example, plasma insulin concentrations of chickens after 6 hours of fasting were reduced by approximately 50% compared with those recently fed.[45] Apart from preprandial and postprandial states, various factors such as age, reproductive status, stress, diet, and pancreatic pathology may also affect concentrations of insulin, glucagon, and somatostatin at any given time.[3,44] Despite limitations, it may be useful to measure insulin and glucagon for species with available reference intervals to obtain a better understanding of an individual's diabetic state prior to the initiation of insulin therapy. If a bird is PU–PD and hyperglycemic, low insulin and/or high glucagon may reflect pancreatic islet pathology and further support a diagnosis of DM. However, recent dietary intake history should be recorded at the time of blood sampling and taken into consideration when interpreting these results.

Most confirmed DM cases suffered from mild-to-moderate anemia, and 1 patient was administered a blood transfusion.[19] Anemia is a common complication in human cases of DM and is often caused by impaired production of erythropoietin.[46] Erythropoietin deficiency is a result of nephropathy that is thought to be induced by the oxidative stress of persistent hyperglycemia.[47] Alternatively, gastrointestinal blood loss associated with severe pancreatitis may contribute to anemia as suggested by the presence of melenic feces in 2 cases from this review.[19,22] Similar clinical signs were observed in an eclectus parrot with malignant pancreatic neoplasia.[48] Elevated serum uric acid concentrations were noted in 3 cases, including 2 cockatiels, and could be explained by nephropathy or dehydration.[14,18,20] For 1 of the cockatiels, increased total solids suggest prerenal hyperuricemia,[20] whereas azotemia, hyponatremia, and hypocalcemia suggested renal compromise in the other cockatiel.[18] Insufficient information was available to make a distinction for the African grey parrot. In summary, birds with DM may be anemic or hyperuricemic, and it is important to monitor these parameters. Hemoconcentration from dehydration and hemodilution from extensive fluid therapy have been reported in diabetic birds. Consequently, serum biochemical parameters should always be interpreted in conjunction with total solids and total protein. For avian patients with a low packed cell volumes (<15%) and hypoproteinaemia, a blood transfusion may be necessary.

Ketoacidosis is a life-threatening complication in avian patients that predominantly occurs in type I DM as described in mammals.[1,2] It is caused by an overload of toxic ketones in the body that are mobilized from fat when it is utilized as an alternative energy source to glucose. Several birds in this study had ketonuria, and the only 2 birds from which blood beta-hydroxybutyric acid (BOHB) concentrations were available[21] demonstrated values exceeding the 450–1422 μmol/L range reported for psittacine birds (Table 2). However, our current knowledge about avian ketogenesis is limited, and liver disease rather than primary DM may have contributed to the elevated BOHB concentrations in the 2 birds mentioned previously.[21] Data (n = 1505) from a commercial laboratory demonstrated poor correlation between hyperglycemia and ketonemia in avian species.[49] Furthermore, none of the birds with glucose concentrations potentially suggestive of DM (1%, 12/1505) in the cited study had elevated plasma BOHB,[49] questioning if BOHB is the primary ketone involved in ketoacidosis of birds or whether these birds exceeded the hyperglycemia threshold due to DM or another disease process. Regardless, hyperglycemia should not be used as a synonym for DM in avian patients, and it may be prudent for the clinician to attempt a diagnosis by first excluding other inciting causes of hyperglycemia prior to reaching a diagnosis of DM based on a combination of clinical signs and thorough diagnostic testing.

Of 7 birds treated with glipizide, only an obese cockatiel was successfully managed with this drug and dietary changes.[18] Glipizide is an oral compound used for the treatment of DM type II in humans, and its effect depends on the presence of functional

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pancreatic beta cells.[50] The fact that most cases in this review had severe pancreatic lesions may explain the lack of a response to glipizide treatment. Five birds were successfully managed for at least 6 months with twice daily injections of long-acting PZI or glargine insulin, combined with dietary changes when appropriate.[13,17,21,26] In all cases, establishing the correct dose was challenging, and euglycemia was often maintained for a shorter duration than would be expected in mammals. This is likely a result of the higher metabolic rate of avian species and differences in glucose metabolism compared with mammals.[7] Moreover, the type of injectable insulin was changed at least once for 4 cases due to inadequate response, and in some instances, this resulted in severe hypoglycemia.[21,22,24] This illustrates that, despite the reportedly less potent hypoglycemic effect of insulin in birds compared with mammals, administration of insulin is not without risk and should only be done after thorough clinical justification. Any avian patient receiving a novel insulin treatment regimen should be monitored closely following administration.

Dietary changes that aim to reduce nonstructural carbohydrate intake are often an important component in the management of DM in mammals.[2] Dietary changes were undertaken for 8 patients in this review. These included a change from seeds to pellets, discontinuation of fruit juice supplementation, and introduction of low-iron pellets for patients predisposed to or diagnosed with iron storage disease (ISD).[13,16–18,21,22,24] Dietary changes could be considered the crucial factor in the clinical improvement of the toucans, which were originally fed dog food, a diet high in iron.[13] As such, dietary changes can be an important consideration for the management of DM in birds, depending on the underlying etiology and the species involved.

Degenerative changes of the pancreatic islets were the most common histopathological feature in diabetic birds. In dogs and humans, a gradual reduction in the size of the pancreatic islets with vacuolization, degeneration, and atrophy of the beta cells are changes characteristic of type I DM.[2] Whether this is a result of idiopathic atrophy, autoimmune-mediated disease, or chronic pancreatitis, this multifactorial condition eventually leads to a depletion of beta cells, causing an absolute insulin deficiency.[2] Several authors performed pancreatic immunohistochemistry with avidin-biotin immunoperoxidase to assess the presence of insulin, glucagon, and somatostatin in situ. Pilny and Luong demonstrated an absence of insulin immunopositivity in vacuolized islet cells from a chestnut-fronted macaw compared with controls.[19] Desmarchelier and Langlois[22] noted the same, also observing immunopositivity for glucagon in a nanday conure. Shivaprasad and Bonda[23] noted immunopositivity for glucagon in a blue and gold macaw, especially in hyperplastic and hypertrophic islet cells, whereas fewer islet cells stained positive for insulin compared with a control.[23] Stains for somatostatin appeared unrewarding for avian species. The reduced or absent immunopositivity for insulin in pancreatic islets from affected birds most closely resembles DM type I in mammals (insulin-dependent diabetes).

The fact that comorbidities were confirmed or suspected in most recorded cases of avian DM suggests that the avian patient may develop DM secondary to another underlying disease process. Historical reports on avian DM established associations with pancreatic islet cell carcinoma, female reproductive tract pathology, and pancreatitis of infectious or unknown etiology.[27,32]

Pancreatic and/or hepatic hemosiderosis was diagnosed in 5 cases included in this review (Table 5). Of these cases, a military and a chestnut-fronted macaw showed marked improvement and required lower insulin dosages following treatment of underlying ISD.[21] Studies in mice demonstrated that iron can accumulate and cause oxidative stress in pancreatic beta cells, resulting in impaired insulin secretion.[51] This implies that hemosiderosis may be an underlying cause of avian DM, and hyperglycemia could normalize after this is resolved. Additionally, remission was achieved in a toco toucan after implementing dietary changes, which led to the discontinuation of insulin therapy.[13] Toucans are highly susceptible to ISD,[52] and a study in mice has shown that dietary iron restriction can protect against DM-related disease.[53] Hence, it may be possible that several diabetic toucans recorded in the literature actually suffered from ISD though this was not investigated at the time.[13,16] This illustrates the importance of a full diagnostic workup to investigate comorbidities with pancreatic and/or hepatic biopsies potentially being valuable in the management of avian DM, especially in species that are susceptible to ISD.[21]

Of particular interest is the finding of lymphoplasmacytic pancreatitis in 5 cases.[14,19,20,22,25] In a cockatiel, the lymphoplasmacytic pancreatitis was associated with Psittacid herpesvirus-1, and lesions were confined to the pancreas.[20] However, in an African grey parrot, a nanday conure, and a chestnut-fronted macaw, lesions were identified in localities such as the kidneys and the peripheral and central nervous system, which is reminiscent of lesions induced by avian bornavirus infection.[54] Although atypical, avian bornavirus has been associated with lymphoplasmacytic pancreatitis of experimentally infected cockatiels.[55] Although a noncytopathic virus,

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bornavirus-associated autoimmune destruction of pancreatic islet cells or vagal neuritis could theoretically contribute to pancreatic pathology and subsequent DM. In the anseriform case, zinc toxicity was confirmed and was correlated to the patient's pancreatic insufficiency.[25]

As DM can compromise the immune system and presumably predispose an avian patient to infection, it may be difficult to distinguish cause from effect for some comorbidities. *Candida* species and *Zygomyces* species infection were recorded in 2 macaws, but these pathogens are typically considered opportunistic.[56]

Traditionally, DM has been classified either as type I, characterized by an absolute deficiency of insulin (often) caused by islet cell destruction, or as type II, in which the insulin deficiency is relative because of insulin resistance.[1,2] The majority (90%, 9/10) of patients with available histology suffered from pancreatic islet pathology with degenerative changes. This, combined with the fact that several animals had absent or reduced insulin immunopositivity in their pancreatic islets when tested (100%, 3/3) and responded well to parenteral insulin treatment when this was initiated (80%, 8/10), indicates that companion birds may suffer predominantly from type I DM. However, a cockatiel resembled type II DM based on the fact that it was suffering from obesity and responded well to glipizide and dietary changes.[18] Also worth noting is that the cockatiel received an injection of medroxyprogesterone, a possible confounder.[18] Unfortunately, pancreatic histopathology was not performed for this bird. Islet amyloidosis, a characteristic feature of type II DM in certain mammalian species, such as felids and humans,[2] was not reported in any of the diabetic birds. Although avian patients in this review displayed similarities to type I DM as described in dogs and humans,[2] labeling DM is sometimes difficult even in human medicine, and ultimately, understanding the underlying pathogenesis of the persistent hyperglycemic state is more important when contemplating treatment options.[1]

A major limitation of this study is publication bias associated with case reports, whereby cases that received a full diagnostic workup and those that involved interesting comorbidities are more likely to be published. This may have contributed to the relatively high representation of large, valuable birds, such as macaws, for which the owners may agree to all recommended diagnostic tests. It is worth noting that major avian textbooks, which may base some observations on the anecdotal experience of knowledgeable avian practitioners, often cite cockatiels as the most common psittacine species affected by DM.[27,28] This is also the experience of the authors. Moreover, toucans are prone to ISD, a confounding condition. Despite the high proportion of psittacine birds among birds diagnosed with DM, most research has been conducted in granivorous poultry and waterfowl. These findings may not accurately reflect pathophysiology in psittacine pet birds, and more research is required in these species. The findings regarding the prevalence of disease based on age and sex may be incidental because of the small sample size of this study. Studies with larger sample sizes, ideally considering the glucagon/insulin ratio too, are also required to obtain reliable reference ranges for insulin and glucagon and to elucidate their role in avian DM. To avoid confusion and facilitate comparison, a consensus should be reached regarding the use of plasma versus serum for the analyses of glucose, insulin, glucagon, and fructosamine. Based on established reference intervals, the authors suggest plasma as the preferred sample.

Based on published cases, DM is most commonly reported in psittacine birds with most individuals within this order belonging to the genus *Ara*. Males may develop the disease at a younger age than females though this may be incidental given the small sample size of published reports included in this review. Whereas clinical signs appear similar to those observed in mammals, the potential underlying etiologies responsible for the diabetic state appear more complex and varied in avian patients.

This study suggests that DM may be a secondary disease process in companion birds with no collective identifiable etiology. As such, individual birds suspected of DM should have diagnostic tests performed that include a complete blood count, plasma biochemistry panel, urinalysis, and diagnostic imaging. A presumptive diagnosis of avian DM can be made by establishing persistent hyperglycemia and potentially glucosuria. Fructosamine, insulin, and glucagon concentrations can be measured and used to assist with a diagnosis; however, availability of reference intervals for many species may be limited. Depending on the underlying etiology, the disease may be successfully managed with twice daily injections of long-acting insulin and dietary modification when appropriate. Diabetes mellitus can be transient in birds, and addressing concurrent pathologies may result in remission of the diabetic state. Therefore, regular monitoring is essential for patients receiving insulin treatment. The prognosis may be more reserved for patients in which euglycemia cannot be achieved.

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When basic diagnostic techniques have been explored and for cases that are nonresponsive to treatment, advanced diagnostic imaging modalities and pancreatic and liver biopsies could be useful tools to investigate underlying disease conditions. Avian bornavirus polymerase chain reaction and indirect immunofluorescence for the detection of avian bornavirus-specific antibodies in serum may be valuable diagnostics to exclude this virus as a cause of lymphoplasmacytic pancreatitis and subsequent DM.[57] Most patients in this review resembled type I DM as observed in humans and dogs. However, much has yet to be learned from the pathophysiology of avian DM, and further research is required to tailor diagnostic parameters and medications used for the treatment of this condition in companion birds.

Acknowledgments: The authors thank all clinicians involved in publishing individual diabetes mellitus case reports and sharing their findings, thereby enabling this review. Special thanks to the *Journal of Avian Medicine and Surgery* reviewers for providing outstanding suggestions, which significantly improved the quality of the manuscript. In an era in which predatory publishing is highly prevalent, it is invigorating to be exposed to challenging yet thought-provoking peer review. This study was carried out in fulfillment of the Wild Animal Health MSc degree at the Royal Veterinary College and the Zoological Society of London.

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