SUGAR AND SPICE: DIABETES AND KETONES IN BIRDS

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INTRODUCTION

Diabetes is an uncommon disease of birds, and is a diagnostic challenge. Birds readily exhibit significant hyperglycaemia with stress, including handling and restraint for venepuncture. The renal threshold for glucose in birds is 33 mmol/L (Hochleithner, 1994), thus birds can have glucosuria with stress hyperglycaemia as well as diabetes, making glucosuria a non specific indicator of diabetes. Because of this, there is currently a need to document persistent hyperglycaemia and persistent glucosuria to make a diagnosis of diabetes in birds. Some authors have proposed values of serum glucose of >44 mmol/L and >55 mmol/L as diagnostic of diabetes mellitus (Fudge, 2000; Pilny, 2008).

Glycaemic control is a balance between the activity of glucagon and insulin. Glucagon is considered the principal director of carbohydrate metabolism in birds (Hazelwood, 1986). In the chicken pancreas there are twice as many alpha cells and half as many beta cells as in mammals (Murphy, 1992). As part of the promotion of increasing blood glucose levels, glucagon strongly promotes lipolysis.

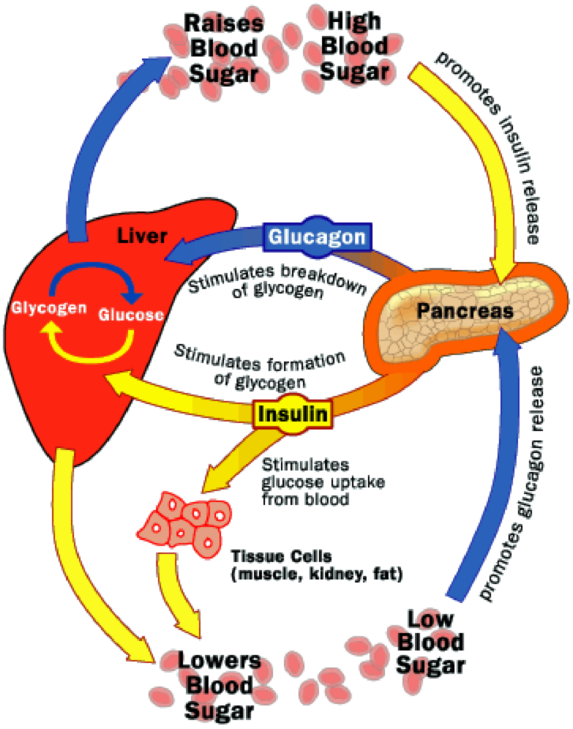

Image from http://health.howstuffworks.com/diseases-conditions/diabetes/diabetes1.htm

METHOD

Glucose and BOHB were assessed in 1505 avian samples submitted to a referral laboratory. A wide range of species was included in this study. The majority of samples were submitted in lithium heparin, eight cases were submitted as serum. Glucose and BOHB were analysed on an Olympus AU400 automated analyser. Glucose was analysed using an Olympus reagent by the hexokinase method. BOHB was analysed using a Randox reagent by the UV method, based on oxidation of BOHB to acetoacetate with associated reduction of NADH. These parameters were within internal and external QA/QC criteria throughout the study. The coefficient of variation of the glucose and BOHB assays during the study period were 8.0% and 8.1% respectively.

Birds were defined as hyperglycaemic when the measured glucose exceeded the reference interval held by the laboratory for that species. Data were analysed using the software package Graph Pad Prism 5. D'Agostino and Pearson tests were used to assess for normality. ANOVA with post test Dunn's testing was used to assess for difference between groups, followed by T tests. Correlation was assessed by Spearman analysis.

RESULTS

Of the 1505 samples, 1094 birds fell into 7 species (or groups of species) with a minimum of 50 accessions. These were budgerigars (Melopsittacus undulatus), cockatiels (Nymphicus hollandicus), sulphur crested cockatoos (Cacatua galerita), eclectus (Eclectus roratus), galahs (Eolophus roseicapillus), lorikeets (Lori sp) and macaws (Ara sp). A wide range of other birds including parrots, water birds, poultry, raptors, and ratites composed the remainder of the accessions.

Tables 1,2 and 3 display the glucose and BOHB values identified in 7 species and groups of species, carnivorous and piscivorous bird and the total data set of birds. The range of plasma / serum glucose values were similar to reported reference intervals in most species, but were higher in budgerigars, cockatiels and galahs. BOHB was significantly higher in galahs than all other species. BOHB was higher in budgerigars and sulphur crested cockatoos than in all other species excepting galahs. Carnivorous and piscivorous birds combined (32 carnivorous, 14 piscivorous) did not have significantly different serum BOHB concentration to other species.

72 birds (5% of cases) exhibited hyperglycaemia. 12 birds had glucose >44 mmol/L (1% of cases) and 5 birds had glucose >55 mol/L (0.3% of cases). Of 12 birds with hyperglycaemia potentially suggestive of diabetes (>44 mmol/L), none had elevated plasma BOHB. Glucose and BOHB showed poor correlation.

Table 1: Serum / plasma glucose and BOHB by species. Glucose and BOHB are in mmol/L.

Species	No.	Glucose (mean ± SD)	95% CI of mean	Glucose 95th interval	Glucose reference interval[2]	BOHB (mean ± SD)	95% CI of mean	BOHB 95th interval
Budgerigar	156	20.2 ± 9.5	18.7 - 21.7	3.8 - 50.9	12 - 25	0.9 ± 1.6[a]	0.6 – 1.2	0.1 – 4.0
Cockatiel	362	18.8 ± 8.6	17.9 - 19.7	7.2 - 42.1	13 - 25	0.8 ± 1.0	0.7 – 0.9	0.1 – 2.5
Sulphur crested cockatoo	124	16.7 ± 3.2	16.1 - 17.3	8.7 - 24.4	11 -23	1.2 ± 1.0[a]	1.0 – 1.4	0.2 – 3.6
Eclectus	140	15.2 ± 3.0	14.6 - 15.7	5.8 - 21.5	12 - 22	0.5 +/- 0.4	0.5 – 0.6	0.1 – 1.4
Galah	141	17.5 ± 4.7	16.7 - 18.3	8.4 - 34.7	11 - 21	2.3 +/- 2.0[b]	2.0 – 2.6	0.4 – 6.6
Lorikeet	100	15.9 ± 4.5	15.6 - 16.8	2.8 - 26.7	11 - 22	0.9 +/- 0.8	0.7 – 1.0	0.2 – 2.2
Macaw	71	15.4 ± 1.6	15.0 - 15.8	11.5 - 18.7	11 - 20	0.9 +/- 0.6	0.7 – 1.0	0.2 – 2.0
Carnivorous and piscivorous	46	14.4 ± 5.5	12.8 - 16.0	4.0 - 23.8		0.9 +/- 0.6	0.7 – 1.1	0.2 – 2.1
All birds	1505	16.7 ± 6.3	16.4 - 17.0	9.6 - 23.9		1.0 +/- 1.3	1.0 – 1.1	0.1 – 3.2

[a] Significantly higher than other species, but significantly lower than galahs

[b] Significantly higher than other species

Table 2: Serum / plasma BOHB by glycaemic status in species or species groups with >50 accessions. BOHB is in mmol/L.

Species	No.	Normoglycaemic (mean ± SD)	95% CI of mean	Normoglycaemic 95th interval	Hyperglycaemic (mean ± SD)	95% CI of mean	Hyperglycaemic 95th interval
Budgerigar	156	1.0 ± 1.8	0.7 - 1.3	0.1 - 4.2	0.5 +/- 0.5	0.2 - 0.8	0.1 - 1.7
Cockatiel	362	0.8 ± 1.0	0.7 - 0.9	0.1 - 2.6	0.5 +/- 0.4	0.4 - 0.7	0.1 - 1.3
SCC	124	1.2 ± 1.0	1.0 - 1.4	0.2 - 3.7	0.9 +/- 0.7	0.2 - 1.6	0.4 - 2.2
Eclectus	140	0.5 ± 0.4	0.4 - 0.6	0.1 - 1.4	n/a	n/a	n/a
Galah	141	2.2 ± 1.9	1.8 - 2.5	0.4 - 6.4	3.7 +/- 2.1	1.5 - 6.0	1.0 - 6.6
Lorikeet	100	0.9 ± 0.8	0.7 - 1.1	0.2 - 2.2	0.7 +/- 0.5	0.3 - 1.2	0.2 - 1.7
Macaw	71	0.9 ± 0.6	0.8 - 1.1	0.2 - 2.0	n/a	n/a	n/a

Table 3: BOHB by glycaemic status in species with >50 occurrences in this study. Glucose and BOHB are in mmol/L.

Glycaemic status	No	Glucose (mean ± SD)	95% CI of mean	BOHB (mean ± SD)	95% CI of mean	BOHB 95th interval
Normoglycaemic	1022	16.7 ± 3.3	16.5 - 16.9	1.0 ± 1.2	0.9 - 1.1	0.1 - 3.3
Hyperglycaemic	72	32.6 ± 16.5	28.6 - 36.7	0.9 ± 1.2	0.7 - 1.2	0.1 - 4.0
Glucose > 44 mmol/L	12	59.0 ± 21.5	45.3 - 73.7	0.9 ± 1.1	0.2 - 1.6	0.1 - 4.0
Glucose > 55 mmol/L	5	81.2 ± 18.1	58.7 - 103.6	0.6 ± 0.5	0.01 - 1.2	0.2 - 1.4

DISCUSSION

Diabetic birds have been reported to have ketonuria (Hochleithner, 1994), and rarely ketosis (Ganez et al., 2007; Desmarchelier and Langlois, 2008), however the latter has only been described in birds with concurrent hepatic or gastrointestinal disease. In the current study, BOHB was not elevated in hyperglycaemic birds or in birds with serum glucose concentrations suggestive of a diagnosis of diabetes mellitus. This is in contrast to reported diabetic macaws (Ganez et al., 2007), in which both ketosis and ketonuria were reported. Unfortunately, serum insulin and glucagon concentrations were not measured in these birds, and concurrent hepatic disease was present, which may have altered fat metabolism. BOHB was not re-evaluated once the diabetes mellitus was controlled.

Sitbon et al. (1980) reported elevated plasma BOHB values in experimentally induced acute diabetes mellitus in ducks and geese, with concurrently reduced insulin and glucagon, but BOHB became depressed below the reference interval with chronicity. This drop mirrored a drop in circulating free fatty acids and body weight and may reflect exhaustion of fat reserves, as birds in this study lost up to 66% of their body weight.

Ketosis was expected to be identified in the current study in at least some birds with hyperglycaemia consistent with diabetes. The lack of elevations even in birds with marked hyperglycaemia resulted in deeper evaluation of the published data of experimental and naturally occurring avian diabetes.

Previously published diabetes cases were searched, and insulin glucose molar ratios (I:G) were calculated for the cases in which adequate data was provided in the origin paper.

Two research papers were identified of experimental diabetes in birds (Karmann and Mialhe, 1976; Laurent et al., 1987). In both cases, diabetes was induced by subtotal pancreatectomy. In both cases, ketosis was induced. The I:G molar ratios were low even though absolute hormone values varied between the two species.

Table 4: Glucose and insulin relative concentrations and calculated I:G derived from published experimental diabetes cases

Species	Type of diabetes	Insulin	Glucagon	I:G molar ratio
Duck (Laurent et al., 1987)	Transient	Decreased	Normal	0.6
Goose (Karmann and Mialhe, 1976)	Permanent	Decreased	Increased	0.1 – 0.4
			Granivorous bird reference range	**1.3 – 2.0**

Table 5: Glucose and insulin relative concentrations and calculated I:G derived from published naturally occuring diabetes cases

Species	Type of diabetes	Insulin	Glucagon	I:G molar ratio
African grey (Candelleta et al., 1993)	Permanent	Decreased		
Amazon (Rae, 2000)	Permanent	Normal	Increased	<0.1
Cockatiel (Rae, 2000)	Permanent	Normal	Decreased	0.9
Macaw (Bonda, 1996)	Permanent	Normal	Increased	0.1 – 0.2
Macaw (Rae, 2000)	Permanent	Decreased		
Penguin (Pollock et al., 2001)	Permanent	Increased		
Toucan (Murphy, 1992)	Transient	Increased	Decreased	5.4
Toucan (Rae, 2000)	Permanent	Normal	Increased	<0.1
Toucan (Rae, 2000)	Permanent	Increased	Normal	0.5
Toucan (Kahler, 1994)	Permanent		Increased	
			Granivorous bird reference range	1.3 – 2.0

Naturally occurring cases (Murphy 1992; Candelleta et al., 1993; Kahler 1994; Bonda 1996; Rae 2000; Pollock et al., 2001) showed wide variation in absolute hormone values, however, in all cases but one, the I:G was significantly low. A single Toucan with an elevated I:G had apparently transient diabetes of unknown cause. This finding of low I:G regardless of the absolute concentrations of insulin and glucagon strengthens the concept of relative glucagon excess as the cause of diabetes in birds.

Glucagon excess would be expected to result in hyperglycaemia but also ketosis as a result of the strong lipolytic function of this hormone. It is known that BOHB is an important ketone resulting from lipolysis in birds, and yet, elevated BOHB was not identified in any hyperglycaemic bird in the current study. It is possible that the preservation of relatively normal, or even increased, levels of insulin in many natural avian diabetes cases counters glucagon's lipolytic function. If this were the case, avian diabetic cases with normal or elevated serum insulin levels would not be expected to exhibit ketosis, and only those with decreased insulin levels would be expected to become ketotic.

In only two case reports of naturally occurring diabetes was insulin reported to be low. In one of these, ketonuria was reported, supporting the requirement for absolute rather than just relative insulin deficiency for development of ketosis in birds.

Diagnostic implications of this study are:

- BOHB appears unreliable for differentiating stress hyperglycaemia and diabetes
    - Normal values do not exclude diabetes
    - However, elevated values are likely consistent with diabetic ketosis

- Measurement of insulin alone is unreliable for diagnosing diabetes in birds

- Determination of an I:G molar ratio is more reliable than absolute values of insulin and glucagon

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