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RESEARCH ARTICLE

Clinical findings of non-ketonuric versus ketonuric diabetic dogs: A retrospective study

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Abstract

Objective: This study aimed to compare the clinical findings of non-ketonuric (n=13) and ketonuric (n=21) diabetic dogs at their first presentation to the Veterinary Teaching Hospital, Khon Kaen University during January 2016-December 2018.

Materials and Methods: The medical records of diabetic dogs were reviewed for signalment and clinical findings regarding clinical presentation, hematology, serum biochemistry, urinalysis and measurement of serum canine pancreatic-specific lipase activity (SNAP cPL). Differences in clinical findings between non-ketonuric and ketonuric dogs were analyzed. Associations between ketonuric status and positive SNAP cPL were represented by the odds ratio with 95% confidence intervals.

Results: The diabetic dogs were mostly in the middle to old age groups. Both non-ketonuric dogs (13/34; 38.24%) and ketonuric dogs (21/34; 61.76%) were found. The degrees of ketonuria were 13/34 (38.24%) and 8/34 (23.53%) for mild (1+ to 2+) and moderate (3+) ketonuria respectively. Clinical presentations were polydipsia/polyphagia (PU/PD; 70.59%), weight loss (61.76%), cataract (47.06%), vomiting (32.35%), polyphagia (17.65%) and anorexia (8.82%). Clinical presentations did not differ between non-ketonuric and ketonuric dogs. Decrease in lymphocytes, likely reflecting stress, was significant in moderate ketonuria (p=0.03). A marked increased in ALP was a major clinical finding for diabetic dogs (26/27; 96.3%) but there was no significant difference between the non-ketonuric and the ketonuric group. Ketonuric dogs were significantly associated with a positive SNAP cPL (OR=13, 95% CI; 1.11 to 152.36, p=0.039).

Conclusion: Lymphopenia is likely more present in moderate ketonuria. The odds ratio of ketonuric diabetic dogs with a positive SNAP cPL was 13, compared to non-ketonuric dogs.

Keywords: Clinical finding, diabetes mellitus, dogs, ketonuria

Introduction

Diabetes mellitus (DM) is one of the common endocrine diseases in dogs that alter the metabolic state of the body. Multifactorial causes of DM in dogs such as genetic factors (Catchpole et al., 2013) and autoantibodies against β-cell components (Taplin and Barker, 2008) have been reported. Pancreatitis has also been shown to be an important disease concurrent with DM (Bostrom et al., 2013; Kasabalis et al., 2015). Dog breeds that are at high risk of developing DM include Samoyeds, Miniature Schnauzers, Miniature Poodles, Pugs and Toy Poodles (Hess et al., 2000a). Generally, fasting hyperglycemia and glucosuria with clinical signs such as polydipsia/polyuria (PU/PD), polyphagia and weight loss are clinical indicators of DM (Koenig, 2013). Because of insulin deficiency and stimulation of glucose counterregulatory hormones (glucagon, epinephrine, cortisol and growth hormone), ketone bodies (β-hydroxybutyrate, acetoacetate and acetone) may be produced excessively from lipolysis, causing keto(acido)sis in diabetic dogs (De Causmaecker et al., 2009; Koenig, 2013). In clinical practice, ketosis or ketonemia may be evaluated indirectly by measurement of ketone in the urine (ketonuria) using urine strip test. The nitroprusside urine strip test detects acetoacetate and acetone in the urine, but not β-hydroxybutyrate (Duarte et al., 2002). Subsequently, the association between ketonuria and the clinical consequences of diabetic dogs is questionable. Consequently, the present study aimed to examine the clinical findings of diabetic dogs with or without ketonuria at the first hospital presentation.

Material and methods

Medical records of the first hospital visit of dogs with fasting hyperglycemia and glucosuria during January 2016-December 2018 at the Veterinary Teaching Hospital, Khon Kaen University were reviewed for signalment and clinical findings, including clinical presentations, hematology, serum biochemistry, urinalysis and serum canine pancreatic lipase activity. The dogs in this report had no history of glucocorticoid treatment during the 6 months before DM diagnosis. Hematological values were determined by automated hematology analyzer (ABX Micros EVS 60, Horiba, Montpellier, France) and the differential white blood cell count was performed manually. Serum biochemical values including blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein and albumin were examined by automated chemistry analyzer (Olympus AU 400, Chema Diagnostica, Monsano, Italy). Blood glucose was measured by glucose meter (Onetouch, LifeScan, Inc., Zug, Switzerland). Measurement of semiquantitative serum canine pancreatic lipase was performed using SNAP cPL (IDEXX Laboratories, Inc., Maine, U.S.A.). A positive SNAP cPL result is considered to be when the colour intensity of the sample spot is darker than the colour intensity of the reference spot, which indicates that the quantitative serum cPL concentration is above 400 μg/L when measured by SPEC cPL (IDEXX Laboratories, Inc., Maine, U.S.A.) (Xenoulis and Steiner, 2016). If the colour intensity of the sample spot is either lighter than or equal to the colour intensity of the reference spot, which correlates with quantitative serum cPL, is 0-200 μg/L or 200-400 μg/L respectively when measured by SPEC cPL (Xenoulis and Steiner, 2016), the subject is considered to have a negative result in this study. Diabetic dogs with or without ketonuria were classified, and the degree of ketonuria was also subsequently classified by the results of the semiquantitative color change of the urine strip test (Uriscan; YD Diagnostics, Kyunggi-Do, Korea) as non-ketonuria (negative; <0.5 mmol/L), mild ketonuria (1+ to 2+; 1-5 mmol/L) and moderate ketonuria (3+; 10 mmol/L).

Statistical analysis

Clinical presentations of diabetic dogs were reported by number of dogs and percentages. Hematological and serum biochemical values were shown by mean±SEM. Category variables were compared between non-ketonuric and ketonuric dogs using the chi-squared test and Fisher's exact test. The clinical values between the degree of ketonuric groups were analyzed using one-way ANOVA and multiple comparison was performed using the Tukey test. Odds ratio (OR) between ketonuria and positive SNAP cPL was calculated and represented with their corresponding 95% confidence intervals (95% CI).

Results

None of the diabetic dogs were young (≤1 year). The age ranges were 1-3 year(s) (1/34; 2.94%), 4-6 years (12/34; 35.29%), 7-9 years (10/34; 2.94%) and ≥10 years (11/34; 32.35%). They were male (8/34; 23.53%), castrated male (8/34; 23.53%), female (8/34; 23.53%) and spayed

female (10/34; 29.41%). Breeds of dog were Poodle (18/34; 52.94%), Mixed breed (4/34; 11.76%), Chihuahua (3/34; 8.82%), Shi Tzu (3/34%; 8.82%), Miniature Pinscher (2/34; 5.88%), Cocker Spaniel, Pomeranian, Cavalier King Charles Spaniel and Labrador Retriever (each 1/34; 2.94%) (Table 1).

Diabetic dogs were 13 of 34 (38.24%) and 21 of 34 (61.76%) for non-ketonuria and ketonuria respectively; the degrees of ketonuria were 13 of 34 (38.24%) and 8 of 34 (23.53%) for mild and moderate ketonuria respectively. At clinical presentation (total=34 dogs), 24 dogs (70.59%) had polyuria and polydipsia (PU/PD), 21 dogs (61.76%) had weight loss, 16 dogs (47.06%) showed cataracts, 11 dogs (32.35%) had vomiting, 6 dogs (17.65%) showed polyphagia and 4 dogs (11.76%) exhibited anorexia at the first presentation. The clinical presentations had no significant difference between non-ketonuria and ketonuria (Table 2).

Averages of hematological values of diabetic dogs were within the reference interval (Table 3) and there was no difference between non-ketonuric and ketonuric dogs (data not shown). However, according to the degree of ketonuria classification, a decrease in lymphocytes was significantly present in the moderate ketonuric group ($p=0.03$) (Table 4). Lymphopenia, reflecting a stress leukogram manifested in 2 of 8 (25%), 0 of 13 (0%) and 5 of 8 (62.5%) while inflammatory leucogram presenting with leukocytosis and neutrophillia was found in 5 of 13 (38.46%), 6 of 13 (46.15%) and 3 of 8 (37.5%) in non-ketonuric, mildly and moderately ketonuric dogs respectively. Combined stress and inflammatory leucogram exhibited in 2 of 8 (25%) in moderately ketonuric dogs (data not shown). Means±SEM of hematological and serum biochemical values of non, mild and moderate ketonuria are shown in Table 4.

Concerning changes in serum creatinine, ALT and ALP had no difference between groups. Increased serum creatinine occurred in 4 of 34 (11.76%) and decreased serum creatinine in 5 of 34 (14.7%). A slight increase in ALT (25 of 34 dogs; 73.53%, mean±SEM 126.77±20.64, 143.77±30.02, 146.5±36.01 U/L in non-ketonuria, mild and moderate ketonuria respectively) and a marked increase in ALP (26 of 27 dogs; 96.3%, mean±SEM 561.70±144.08, 1029.44±544.5, 837.13±383.23 U/L in non-ketonuria, mild and moderate ketonuria respectively) were observed in diabetic dogs. Serum ALT and ALP activities had no significant differences between groups of dogs classified by degree of ketonuria. Means of total protein, globulin and albumin in diabetic dogs were within the reference interval. Increase in total protein, globulin and albumin was 7/16 (43.75%), 5/16 (31.25%) and 0/16 (0%) respectively. Only 3 dogs (18.75%) had hypoalbuminuria (Table 3).

Table 1. Signalment of 34 diabetic dogs

Signalments	No. of dogs (%) (n= 34)
Age	
≤1 y	0 (0%)
1-3 y	1 (2.94%)
4-6 y	12 (35.29%)
7-9 y	10 (29.41%)
≥10 y	11 (32.35%)
Gender	
Male	8 (23.53%)
Castrated male	8 (23.53%)
Female	8 (23.53%)
Sprayed female	10 (29.41%)
Breed	
Poodle	18 (52.94%)
Mixed breed	4 (11.76%)
Chihuahua	3 (8.82%)
Shi Tzu	3 (8.82%)
Miniature Pincher	2 (5.88%)
Cocker Spaniel, Pommeranian, Cavalier King Charles Spaniel, Labrador Retriever	each 1 (2.94%)

Signalments of 34 diabetic dogs are shown as number of dogs and percentages. Almost diabetic dogs were middle to old age. No difference of gender was found in this study. Small breed dogs had a high population of diabetes mellitus.

Positive SNAP cPL was detected in 17 of 22 dogs (77.27%) (4 dogs; 18.18% in non-ketonuria and 13 dogs; 59.09% in ketonuria). The odds ratio of diabetic dogs with ketonuria given a positive SNAP cPL was 13, compared to the non-ketonuria group (95% CI of 1.11 to 152.36), which showed a p-value of 0.039.

Discussion

Diabetic dogs were commonly in the middle to old age groups (³ 4 years) similarly to previous reports (Catchpole et al., 2005; Guptill et al., 2003). The number of female and male dogs with DM in this study was not different. The

Table 2. Clinical presentation of diabetic dogs with non-ketonuria and ketonuria

Clinical presentation	No. of dogs *(n=34)*	Non-ketonuria *(n=13)*	Ketonuria (*n=21*)	P-value
PU/PD	24 (70.59%)	9/13 (69.23%)	15/21 (71.42%)	0.89
Weight loss	21(6.176%)	7/13 (53.85%)	14/21 (66.67%)	0.46
Cataract	16 (47.06%)	8/13 (61.54%)	8/21 (38.1%)	0.18
Vomiting	11 (32.35%)	3/13 (23.08%)	8/21 (38.1%)	0.36
Polyphagia	6 (17.65%)	3/13 (23.08%)	3/21 (14.29%)	0.47
Anorexia	4 (11.76%)	0/13 (0%)	4/21 (19.05%)	0.09

Clinical presentations of diabetic dogs with non-ketonuria (n=13) and ketonuria (n=21) are shown as the number of dogs and percentages. The differences of clinical presentations between these two groups were calculated using chi-squared and Fisher's exact test, for which the non-ketonuric group was used as the control. PU/PD, weight loss, cataract, vomiting, polyphagia and anorexia were not significantly different between groups.

present study showed small breed dogs had a high population of diabetes mellitus.

PU/PD was a common presentation for diabetic dogs. Cataract, a chronic complication of diabetes, was likely a crucial presentation even at the first visit. Diabetic dogs with vomiting or polyphagia were occasionally found in the present study.

In this study, a decrease in lymphocytes was a significant hematological finding in moderately ketonuric dogs and is suggested to be involved with an increase in endogenous corticosteroid induced by stress. A decrease in the number of circulating lymphocytes induced by corticosteroid has been demonstrated. Corticosteroid induces apoptosis in lymphocytes (Distelhorst, 2002) and decreases the circulating lymphocytes recirculation from the lymphoid organs (Bloemena et al., 1990).

Decrease in serum creatinine can result from a reduction of body mass. Concerning concurrent kidney disease, an increase in both serum creatinine and BUN showed in 4 of 34 (3 in non-ketonuric and 1 in moderately ketonuric dogs) indicating an elevation of BUN in the non-ketonuric group.

For serum ALT activity, 6 of 10 dogs (60%) had returned to the reference interval over month(s) to a year. A persistent increase in ALP occurred in 12 of 19 dogs (63.16%), even when given insulin treatment for several months. An increase in ALP activity was a major clinical finding for dogs with DM. ALP isoenzymes have been found in the liver, kidney, placenta, bone and intestinal mucosa (Nagode et al., 1969). In dogs, ALP isoforms detected in serum include liver ALP (LALP), bone ALP (BALP) and corticosteroid-induced ALP (CALP) isoforms. Kidney and placenta isoforms are not normally detected in the serum of dogs, because of their short half-lives (Syakalima et al., 1997). A rise in serum ALP has 80% sensitivity and 50% specificity for diagnosing hepatobiliary disease (Center et al., 1992). Causes of increased total serum ALP could be primary hepatobiliary disease or systemic disorders causing reactive hepatopathy, or stress associated with acute or chronic illness. Fatty hepatic change or hepatic lipidosis (hepatocellular steatosis) has been found in 70% of diabetic dogs at necropsy (Hess et al., 2000b). Vacuolar hepatopathy exhibiting mixed cytoplasmic glycogen accumulation within hepatocytes caused by steroid-induced hepathopathy and hepatic lipidosis has been demonstrated in a dog with type 1 insulin-dependent diabetes mellitus secondary to hyperadrenocorticism (Carloni et al., 2017). Hyperadrenocorticism concurrent with DM has been demonstrated at 13.61 and 23% (Hess et al., 2000b; Miceli et al., 2017). Exogenous corticosteroid can result in a marked increase in serum LALP and CALP caused by hepatocyte swelling and intrahepatic cholestasis due to glycogen deposition in the hepatocytes (Sanecki et al., 1987). In conclusion, increased serum ALP activity in diabetic dogs might result from hepatic lipidosis and stress induced endogenous steroid-hepathopathy, if other causes such as hyperadrenocorticism and extrahepatic cholestasis including bile duct obstruction or biliary diseases are ruled out.

Table 3. Hematological and serum biochemical values of diabetic dogs

Variables	Reference interval	No. of dogs	Mean±SEM	Normal	Increase	Decrease
PCV (%)	37-55	34	43.01±1.59	25	1	8
RBC (x10^6/L)	5.5-8.5	29	6.49±0.30	19	1	8
Hb (g/dL)	12-17.99	27	14.77±0.61	19	3	5
WBC (10^9/L)	6.0-17.0	34	16.28±1.44	21	13	0
Band (109/L)	0-0.3	29	52.55±31.09	27	2	0
Neutrophil (10^9/L)	3.0-11.8	29	11.25±1.03	20	9	0
Lymphocyte (10^9/L)	1.0-4.8	29	1.74±0.21	21	7	1
Monocyte (10^9/L)	0.15-1.35	29	0.95±0.22	14	8	7
Eosinophil (10^9/L)	0.1-1.25	29	0.42±0.093	20	2	7
Basophil (10^9/L)	Rare	29	0.004±0.004	28	1	0
Platelet (10^9/L)	180-500	19	397.35±35.38	14	3	2
Glucose (mg/dL)	66-102	34	446.76±21.14	0	34	0
Creatinine (mg/dL)	0.34-1.02	34	0.98±0.25	25	4	5
BUN (mg/dL)	4.76-20.72	22	45.27±11.14	10	12	0
ALT (U/L)	15-60	34	137.91±15.86	9	25	0
ALP (U/L)	20-60	27	799.22±215.14	1	26	0
Total protein (mg%)	5.8-7.3	16	7.77±0.31	9	7	0
Globulin (mg%)	2.1-5.0	16	2.28±0.63	11	5	0
Albumin (mg%)	2.7-3.7	16	3.08±0.14	13	0	3

Hematological and serum biochemical values of diabetic dogs are shown as mean±SEM. Numbers of dogs with normal, increased and decreased from the reference interval are shown. Means of hematological values were within reference interval. Apart from hyperglycemia, means of BUN, ALT, ALP and total protein rose above the reference interval. A marked increase in ALP was an essential clinical finding in diabetic dogs. Hematological and biochemical reference values (Jain, 1993), (Hill and Warman, 2011)

The hyperproteinemia found in this study might reflect dehydration status or concurrent chronic diseases. The cause of hypoalbuminemia is often multifactorial such as hepatic disease, kidney disease, protein-losing gastroenteropathy, inflammation or chronic malnutrition (Throop et al., 2004). One of 3 diabetic dogs with hypoalbuminemia had accompanying kidney disease. Although increases in ALT and ALP activity have been found associated with hepatobiliary disease in diabetic dogs, a low percentage of diabetic dogs with hypoalbuminemia (3 of 16; 18.75%) was found. It did not markedly affect hepatic function in the context of albumin production for most diabetic dogs.

In the present study, ketonuric dogs were likely to have positive SNAP cPL activity. In a previous report, sensitivities and specificities of SNAP cPL for diagnosing acute pancreatitis, with ranges between 91.5-94.1% and 71.1-77.5% respectively, have been demonstrated (McCord et al., 2012). Dogs with acute pancreatitis concurrent with DM have been reported at 13 and 30% (Hess et al., 2000b; Kasabalis et al., 2015). Acute pancreatitis has been reported to be one important concurrent disease of DM. Profoundly, the clinical diagnosis of acute pancreatitis requires the combination of clinical signs, serum cPL concentration, abdominal ultrasound and histological findings. In the present study, abdominal imaging was examined to support the diagnosis of acute pancreatitis in some dogs. A positive SNAP cPL test was compatible with the abnor-

Table 4. Hematological and serum biochemical values of diabetic dogs with non-ketonuria, mild and moderate ketonuria

Variables	n	Non-ketonuria	n	Mild ketonuria (1+ to 2+)	n	Moderate ketonuria (3+)	P value
		Mean±SEM		Mean±SEM		Mean±SEM	
Hematocrit (%)	13	44.81±3.11	13	41.00±2.17	8	43.37±2.73	1
RBC ($x10^6$/L)	10	6.88±0.76	13	6.41±0.30	8	6.24±0.48	0.7
Hb (g/dL)	11	15.59±1.29	10	14.08±0.80	8	14.71±0.88	0.58
WBC (10^9/L)	13	19.16±3.10	13	15.34±1.71	8	13.13±1.84	0.25
Band (10^9/L)	8	0.009±0.009	13	0.065±0.05	8	0.075±0.075	0.59
Neutrophil (10^9/L)	8	10.51±2.12	13	12.08±1.57	8	9.88±1.91	0.59
Lymphocyte (10^9/L)	8	2.01±0.52	13	$2.14±0.26^b$	8	$0.91±0.18^a$	0.03
Monocyte (10^9/L)	8	1.19±0.43	13	0.45±0.19	8	1.61±0.61	1
Eosinophil (10^9/L)	8	0.513±0.16	13	0.57±0.16	8	0.082±0.065	0.07
Basophil (10^9/L)	8	0	13	0.01±0.01	8	0.00	0.56
Platelet (10^9/L)	6	366.33±4.17	6	371.67±69.37	7	445.86±69.96	ND
Glucose (mg/dL)	13	480.38±43.48	13	415.23±22.61	8	443.38±42.04	0.42
Creatinine (mg/dL)	13	1.47±0.56	13	0.40±0.05	8	1.14±0.48	0.16
BUN (mg/dL)	6	$91.08±29.52^b$	9	$14.77±2.69^a$	7	45.23±15.21	0.01
ALT (U/dL)	13	126.77±20.64	13	143.77±30.02	8	146.5±36.01	0.86
ALP (U/dL)	10	561.70±144.08	9	1029.44±544.5	8	837.13±383.23	0.67
Total protein (g%)	5	8.48±0.74	7	7.56±0.43	4	7.25±0.27	ND
Globulin (g%)	5	2.16±1.34	7	2.37±0.89	4	2.31±1.09	ND
Albumin (g%)	5	2.86±0.33	7	3.16±0.21	4	3.2±0.11	ND

Hematological and serum biochemical values of diabetic dogs with non, mild and moderate ketonuria are shown as mean±SEM. The difference of means among groups was analyzed by one-way ANOVA and multiple comparisons were analyzed by the Tukey test. The difference of superscripts in each row indicates statistical significance ($p<0.05$). A decrease in lymphocytes, likely reflecting a stress leukogram, was found in moderate ketonuria (3+ ketone in urine detected by urine strip test) and was significant when compared with mild ketonuria (1+ to 2+ ketone in urine), with p values of 0.03. Blood glucose, creatinine, ALT and ALP activity were not significantly different between groups, except BUN which was significantly found to increase in non-ketonuria when compared with mild ketonuria ($p=0.01$). The increase of BUN seen in this group was found to be associated with concurrent kidney disease in 3 non-ketonuric dogs. ND; not determined

Table 5. Association between diabetic dogs with ketonuria and positive SNAP cPL test

SNAP cPL test	Non-ketonuria (*n=8*)	Ketonuria (*n=14*)	Odds ratio	95% CI	P value
Positive	4	13	13	1.11-152.36	0.039
Negative	4	1			

A positive SNAP cPL is considered to be when the sample spot is darker than the reference spot, which indicates the serum cPL concentration is above 400 µg/L while a negative result is considered to be when the sample spot is either ligher than or equal to the reference spot, which indicate the serum cPL concentration is less than 400 µg/L. Association between diabetic dogs with ketonuria and the positive SNAP cPL test was analyzed using chi-squared and Fisher's exact test, for which the non-ketonuria group was used as the control. The odds ratio of diabetic dogs with ketonuria with a positive SNAP cPL test was 13 compared to the non-ketonuria group (95% CI of 1.11 to 152.36), which showed a p-value of 0.039.

malities of pancreatic ultrasonographic findings in 4 out of 5 dogs (80%). According to the SNAP cPL test, dogs suspected of having pancreatitis should be confirmed by a combination of abdominal ultrasound and histological diagnosis.

Conclusion

In summary, a stress leukogram presented with lymphopenia is likely more present in moderately ketonuric dogs. Apart from hyperglycemia and glucosuria, markedly increased serum ALP activity is an essential clinical finding in diabetic dogs, but there was no difference between non-ketonuric and ketonuric diabetic dogs. The odds ratio between ketonuric diabetic dogs and positive SNAP cPL test was significant. An indirect estimate of ketosis using ketonuria and the degree of ketonuria might be used as a beginning factor for the prediction of concurrent suspicious pancreatitis and chronic stress respectively in some diabetic dogs.

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Conflict of interest

The authors declare no conflicts of interest.

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